Tetrahedron Vol. 43, No. 20, pp. 4699 to 4723, 1987
Printed in Great Britain.

0040-4020/87 $3.00+.00

EXPERIMENTAL STUDIES OF THE ANOMERIC EFFECT.

PART I. 2-SUBSTITUTED TETRAHYDROPYRANS.

HAROLD BOOTH, KHEDHAIR A. KHEDHAIR
AND SIMON A. READSHAW

Department of Chemistry, University of Nottingham,
Nottingham, NG7 2RD, U.K.

(*Received in UK* 31 *July* 1987)

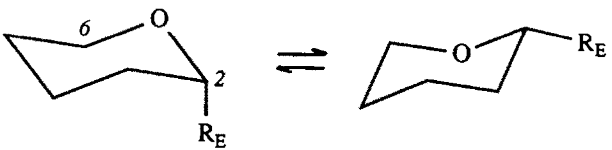
Abstract - Variable temperature ^1H and ^{13}C n.m.r. studies in $CFCl_3/CDCl_3$ of equilibria in 2-substituted- and 2-substituted-4-methyl-tetrahydropyrans have given conformational enthalpy differences and conformational entropy differences for chloro, methoxy, hydroxy and methylamino substituents. For $\Delta H^o_{a\rightarrow e}$, the values obtained, in kcal mol^{-1}, were 1.67 (Cl), 0.03 (OCH_3), -0.63 (OH) and -1.75 ($NHCH_3$); for $\Delta S^o_{a\rightarrow e}$ the values obtained, in cal K^{-1} mol^{-1} were -1.69 (Cl), -2.52 (OCH_3), -2.50 (OH) and -0.60 ($NHCH_3$). The trend in ΔH^o values confirms the importance of antiperiplanar n-σ* stabilisation as a contributor to the explanation of the anomeric effect, and supports a suggestion that endo- and exo-anomeric effects which occur in the same conformation are competitive.

A variable temperature ^{13}C n.m.r. study of ($\underline{Me}$-$^{13}\underline{C}$)-4-methyltetrahydropyran in CD_2Cl_2 has given a conformational enthalpy difference ($\Delta H^o_{a\rightarrow e}$) of -1.86 kcal mol^{-1} and a conformational entropy difference ($\Delta S^o_{a\rightarrow e}$) of -0.07 cal K^{-1} mol^{-1} for a methyl substituent at the 4-position of a tetrahydropyran.

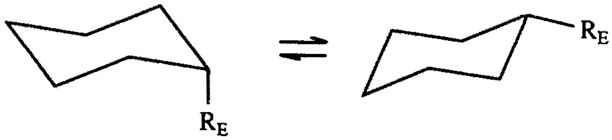
Introduction

The unexpected preference for the axial conformation (1) of tetrahydropyrans (1 $\rightleftarrows$ 2) substituted at the 2 position by an electronegative group R_E was described by Lemieux and Chu[1] as the "anomeric effect".[2,3,4.] The equilibria in the corresponding cyclohexanes (3 $\rightleftarrows$ 4) favours the equatorial conformation (4). Quantitatively, the anomeric effect has been defined[5,6] as $\Delta G^o_{1\rightarrow 2} - \Delta G^o_{3\rightarrow 4}$.

In non-polar solvents the position of equilibrium (3 $\rightleftarrows$ 4) is largely determined by the severe 1,3-syn-axial repulsions ("steric effects") present in (3), whereas the position of equilibrium in (1 $\rightleftarrows$ 2) is generally considered to involve both steric effects and polar effects. As C-O bonds are shorter than C-C bonds, tetrahydropyrans are expected to be slightly puckered (relative to cyclohexanes) in the region C6-O-C2. It follows that syn-axial repulsions in (1) should be more severe than in (3). In agreement, alkyl groups have a much stronger

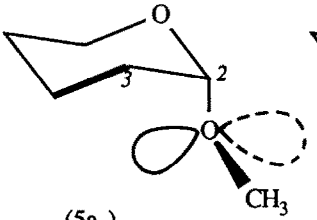


(1) (2)

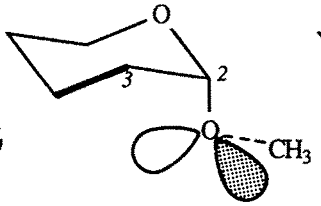


(3) (4)

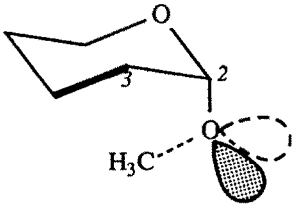
preference for the equatorial orientation when substituted at position 2 of a tetrahydropyran than when substituted in cyclohexane.[7] It is obviously difficult to determine the purely steric interactions of electronegative groups in (1). R.W. Franck[8] has attempted to predict such interactions from an apparently linear correlation of $\Delta G^{\circ}_{1\rightarrow2}$ values with $\Delta G^{\circ}_{3\rightarrow4}$ values, the plotted values relating to substituents (e.g. alkyl) which are <u>not</u> expected to show anomeric effects. However, since conformational entropy differences have been found to be significant,[9,10] any correlation involving temperature - dependent ΔG° values (rather than ΔH° values) is clearly unsatisfactory.



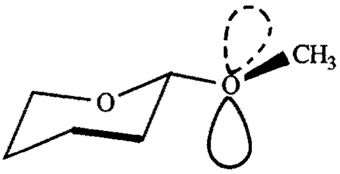
(5a$_1$)



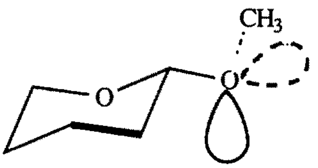
(5a$_2$)



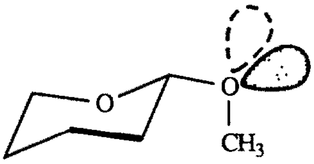
(5a$_3$)



(6e$_1$)



(6e$_2$)

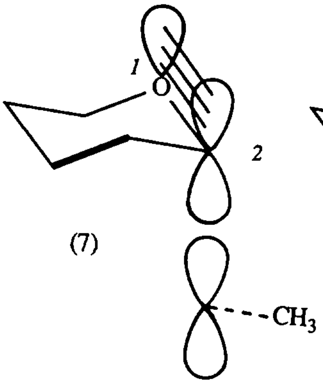


(6e$_3$)

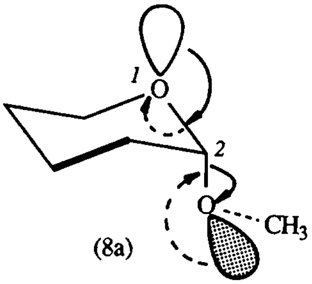
When the electronegative substituent is OCH_3, the axial ($5a_1 \rightleftarrows 5a_2 \rightleftarrows 5a_3$) and equatorial ($6e_1 \rightleftarrows 6e_2 \rightleftarrows 6e_3$) conformations can each assume three staggered conformations with respect to rotation about the <u>exo</u>cyclic C_2-O bond. The <u>exo</u>-anomeric effect, as originally defined by R.U. Lemieux,[11,12] describes the preference shown by axial and equatorial conformations for rotamers ($5a_2$) and

($6e_2$), respectively, in which the bonds are staggered, and the O-CH_3 bond lies anti-coplanar to the C_2-C_3 bond. Convincing evidence for the dominance of conformations ($5a_2$) and ($6e_2$) in the *crystalline* state has been provided by X-ray crystallography and neutron diffraction,[2,4,13,14] although a recent survey has highlighted the wide variation in torsion angle ϕ (exo) (77±19°).[15] Evidence for a similar situation in *solution* has been lacking until recently,[10,16] although early n.m.r. studies[12,17,18] of methyl hexopyranosides revealed ^3J ($\underline{C}H_3OC\underline{H}$) values which were too small (cf.[19-22]) to signify appreciable proportions of conformations $5a_3$ and $6e_3$. Rotamer $6e_3$ occurs in the *crystalline* state of some β-glycopyranosides,[23] and its occurrence in *solution*, (albeit as a minor component, to judge from measurements[16] of coupling constants), has now been established through n.O.e. experiments on simple 2-methoxytetrahydropyrans.[16] Indirect support for the *exo*-anomeric effect in solution has been provided through the success of hard sphere calculations, with inclusion of the *exo*-anomeric effect, in predicting for glycosides those conformational preferences which are indicated by experimental data, particularly data derived from n.m.r. spectra.[12,24-26] It is obvious that the *exo*-anomeric effect must itself contribute to the anomeric effect. Although it is possible to explain the *exo*-anomeric effect solely in terms of steric effects, it is generally believed that polar and stereoelectronic effects (which are not necessarily independent) must also be involved.[11,27]

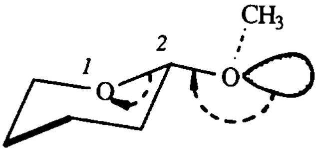
Several explanations have been advanced to account for the anomeric effect. The higher energy of the equatorial conformation ($6e_1 \rightleftarrows 6e_2 \rightleftarrows 6e_3$), relative to the axial conformation ($5a_1 \rightleftarrows 5a_2 \rightleftarrows 5a_3$), has been variously ascribed (a), to the relatively greater electrostatic repulsions between electron pairs of the ring oxygen atom and the exocyclic C_2-O bond,[28] (b) to the relatively greater dipolar interactions between the C_6-O bond and the exocyclic C_2-O bond,[1] and (c) to the greater number of syn-axial 1,3-repulsions between lone pair orbitals on the two oxygen atoms ("rabbit ear effects").[29,30] The equatorial conformation is also expected to have a higher overall dipole moment[27] and should therefore be disfavoured in a non-polar solvent. The sensitivity of the equilibrium ($1 \rightleftarrows 2$; R_E=OCH_3) to solvent polarity is well established.[2,11] The explanation of the anomeric effect due to Altona[27,31,32] has gained much support recently and invokes a stabilising overlap of lone pair orbital on ring oxygen (the *donor* atom) with the antibonding orbital of the exocyclic C_2-O bond (the *acceptor* bond). This n-σ^* stabilisation has been supported by calculations[33,34] and has been generalised by Epiotis.[35] Maximum stabilisation is achieved when the lone pair orbital of the best donor atom is antiperiplanar to the best acceptor bond, i.e. the bond with the lowest energy antibonding orbital. This overlap is shown in (7), for example, and is conveniently abbreviated to the *full* arrows in (8a). Significantly, the stereochemical requirement for overlap involving a lone pair orbital of ring oxygen occurs only in axial conformations, and is therefore satisfied in (8a) and not in (8e). Since in (8a) the donor atom is the endocyclic oxygen, we have recently[10] described this stabilisation as the "*endo*-anomeric effect" [*full* arrows in (8a)]. The great merit of the Altona explanation is its applicability also to the *exo*-anomeric effect. In the *exo*-anomeric effect, shown in both (8a) and (8e) by *dotted* arrows, the donor atom is the exocyclic oxygen atom, a lone pair orbital of which can overlap with the antibonding orbital of the C_2-O bond within the ring. In this case the stereochemical requirement for orbital overlap is satisfied for equatorial rotamers ($6e_2$) and ($6e_3$), *and* for axial rotamers ($5a_2$) and ($5a_3$). However, rotamers ($6e_3$) and ($5a_3$) are disfavoured on steric grounds. The predicted dominance of rotamers ($5a_2$) and ($6e_2$) is thus in perfect accord with the *exo*-anomeric effect as originally defined.



(7)



(8a)



(8e)

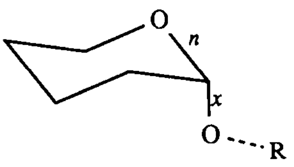
The foregoing theory forms the basis for the following propositions (cf.[10]):

(1) the anomeric effect, when defined in terms of the equilibrium ($1 \rightleftarrows 2$), must involve both endo- and exo- anomeric effects. For the reasons stated, the axial and equatorial conformations of a 2-alkoxytetrahydropyran are assumed to exist very largely as rotamers ($5a_2$) and ($6e_2$), respectively.

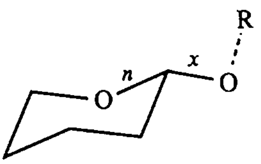
(2) the axial conformation ($5a_2$) of a 2-alkoxytetrahydropyran involves both endo- and exo-anomeric effects, as in (8a). An equatorial conformation ($6e_2$) involves only the exo-anomeric effect, as in (8e).

(3) following Lemieux,[36] it is proposed that endo- and exo- anomeric effects are in competition in the axial conformation ($5a_2$). Hitherto it has been assumed that the two effects are supportive.[37] Opposition of endo- and exo-anomeric effects can be understood in terms of the bond shortening which is expected to accompany orbital overlap; it is reasonable to assume that there is a limit to which both endo- and exo- C_2-O bonds in (8a) can be shortened simultaneously.

The propositions just outlined are supported by bond lengths, determined by X-ray or neutron diffraction. In the first place the suggested theory correctly predicts that for a fixed substituent (e.g. OR) in (9a) and (9e), the exo-bond C_2-O (x) will be shorter in (9e) than in (9a), and that the endo-bond C_2-O (n) will be longer in (9e) than in (9a).[2,14] Secondly, the theory correctly predicts, for variable R in both (9a) and (9e), that the exo-bond (x) will decrease, and the endo-bond (n) will increase, with decreasing electronegativity of R.[14]



(9a)

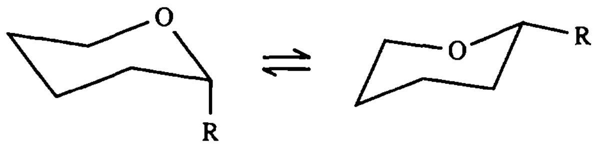


(9e)

Finally (and significantly), since the decrease in electronegativity of R will cause an increase in the exo-anomeric effect and, simultaneously, a decrease in the endo- anomeric effect, the theory of endo/exo competition in (9a) correctly predicts that the plots of bond length n and x against electronegativity of R will be steeper for (9a) than for (9e).[14]

Results and Discussion

The present investigation seeks to determine the origin or origins of the anomeric effect by determining, in a relatively non-polar solvent, the position of equilibrium ($1 \rightleftharpoons 2$) in tetrahydropyrans substituted by electronegative groups OCH_3, OH, $NHCH_3$ and Cl. The required compounds, and their 4-methyl derivatives, were synthesised by literature methods requiring no comment (see Experimental). Previous work in this area has generally involved the determination of equilibrium constants (K) at a single temperature, yielding only $\Delta G^o_{1\rightarrow2}$ values. However, it is the conformational enthalpy difference $\Delta H^o_{1\rightarrow2}$ which is most easily correlated with intramolecular steric and polar effects. The determination of ΔH^o values requires the measurement of K at several temperatures over as wide a range of temperature as is possible. In spite of early warnings[38] and several observations,[39,40,41] the assumption persists that conformational entropy differences ΔS^o are negligible. Detailed arguments continue to be made on the basis of parameters obtained from single temperature observations.[42]



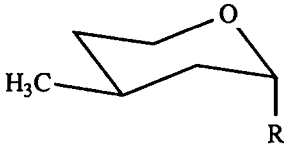
(10; R = OCH_3) (11; R = OCH_3)
(12; R = OH) (13; R = OH)
(14; R = $NHCH_3$) (15; R = $NHCH_3$)
(16; R = Cl) (17; R = Cl)

The room-temperature equilibrium in 2-methoxytetrahydropyran ($10 \rightleftarrows 11$) has been studied by several teams, who determined equilibrium constants in a variety of solvents using vicinal ^1H : ^1H coupling constants,[11,27,43] optical rotation,[11] and ^1H chemical shifts.[5,44] In our experiments, the ^{13}C n.m.r. spectrum of ($10 \rightleftarrows 11$) was studied in the range 143-165 K, where relatively slow ring inversion allows observation of signals for both (10) and (11) (cf. preliminary report[9]). The relatively non-polar solvent used was a mixture of 85% $CFCl_3$ (dielectric constant $\varepsilon 2.28$) and 15% $CDCl_3$ ($\varepsilon 4.81$), by volume. Five of the six carbon atoms gave well spaced signals for (10) and (11), 5-C being the exception. Chemical shifts are given in Table 1. Calculated shifts were obtained using published shifts for tetrahydropyran,[45,46] together with substitutent shift parameters for a methoxy group in methoxycyclohexane.[47] Analysis of the spectra by repeated instrumental integration and/or hand planimetry gave equilibrium constants in the range 0.248-0.260 for e/a (=11/10) at four temperatures (see Experimental). Canadian workers[48] had measured an equilibrium constant of 0.67 at 160 K in the slightly more polar solvent of $CHFCl_2$ ($\varepsilon 5.34$). The range of temperature over which equilibrium constants were determined is too small to allow even moderately accurate values of ΔH^o and ΔS^o to be determined. Accurate measurements below 143 K were frustrated by signal broadening; signal broadening above 165 K, due to an increased rate of ring inversion, caused overlap of signals to be integrated.

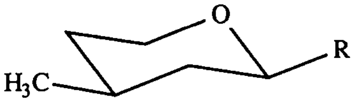
Table 1. Carbon-13 chemical shifts (δ/ppm from Me_4Si) for 2-methoxytetrahydropyran (10 $\rightleftarrows$ 11) in $CFCl_3/CDCl_3$ (85/15 v/v).

	(10 $\rightleftarrows$ 11)	(10)	(10)	(11)	(11)
T/K	275	143	a	143	a
carbon					
2	99.52	97.66	116.5	102.97	121.7
3	30.72	29.60	30.0	31.35	32.1
4	19.35	17.64	17.5	22.23	21.8
5	25.87	25.18	26.8	25.18	26.2
6	61.29	59.31	62.5	66.30	66.8
MeO	54.67	54.60	-	56.42	-

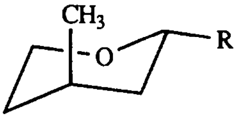
a calculated (see discussion)



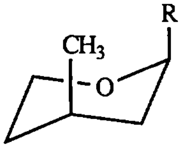
(18; R = OCH_3)
(22; R = OH)
(26; R = $NHCH_3$)
(30; R = Cl)



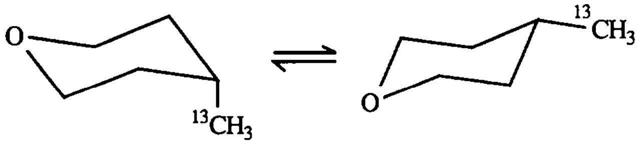
(19; R = OCH_3)
(23; R = OH)
(27; R = $NHCH_3$)
(31; R = Cl)



(20; R = OCH_3)
(24; R = OH)
(28; R = $NHCH_3$)
(32; R = Cl)



(21; R = OCH_3)
(25; R = OH)
(29; R = $NHCH_3$)
(33; R = Cl)



(34) (35)

In order to extend the temperature range of measurements, the acid-catalysed equilibration (18 ⇄ 19) of trans- and cis-2-methoxy-4-methyltetrahydropyran was studied at 245 K and 273 K (see Experimental), following the classic work of Bishop and Cooper,[49] and Anderson and Sepp.[5,44] The synthesis of 2-methoxy-4-methyltetrahydropyran followed the work of Parham and Holmquist,[50] except that the hydrogenation of cis- and trans-2-butoxy-4-methyl-3,4-dihydropyran was carried out at room temperature and atmospheric pressure in MeOH. The use of Pd/C as catalyst caused remarkable stereoselectivity, giving cis-2-butoxy-4-methyltetrahydropyran and unaltered trans-2-butoxy-4-methyldihydropyran. The cis-dihydropyran is expected to occur in a half-chair conformation with substituents equatorial and quasi-equatorial, leaving the C=C relatively unhindered. The trans-isomer, on the other hand, must hold one of the substituents axial, thus offering some resistance to the catalyst. When the catalyst was Adam's PtO_2, both isomers were smoothly hydrogenated to the corresponding tetrahydropyrans. The final mixture of trans- and cis-2-methoxy-4-methyltetrahydropyrans was separated by preparative gas liquid chromatography. The ^{1}H n.m.r. parameters of the trans (18)- and cis (19)-isomers are reported in Tables 2 and 3 respectively; assignments were confirmed by 2D COSY experiments. The analysis of equilibrated mixtures of trans- and cis-2-methoxy-4-methyltetrahydropyrans assumes that only conformations (18) and (19) need be considered, in which case the position of equilibrium (18 ⇄ 19), due to acid catalysed equilibration, is almost identical to that in (10 ⇄ 11), due to ring inversion. The cis-conformation (21) can safely be ignored, due to the severe syn-axial Me/OMe repulsions. The proportion of trans- conformation (20) in the equilibrium (18 ⇄ 20), at any temperature, will be determined at a first approximation, by the difference in ΔG^{o} values, at that temperature, of the two

Table 2. ^{1}H nmr data (400 MHz, 297 K) for trans-2-methoxy-4-methyltetrahydropyran (18) in CD_2Cl_2.

Chemical Shifts (δ/ppm)

2-H	4.64	$5\text{-}H_a$	1.23
$3\text{-}H_e$	1.67[a]	$6\text{-}H_e$	3.53
$3\text{-}H_a$	1.24	$6\text{-}H_a$	3.70
$4\text{-}H_a$	1.88	MeO	3.30
$5\text{-}H_e$	1.52[a]	MeC	0.87

Coupling Constants (Hz)

$^{2}J_{3e3a}$	13.3	$^{3}J_{4a5e}$	c
$^{2}J_{5e5a}$	13.1	$^{3}J_{4a5a}$	c
$^{2}J_{6e6a}$	11.2	$^{3}J_{5e6e}$	1.8
$^{3}J_{2e3e}$	b	$^{3}J_{5e6a}$	2.4
$^{3}J_{2e3a}$	b	$^{3}J_{5a6e}$	4.8
$^{3}J_{3e4a}$	c	$^{3}J_{5a6a}$	12.6
$^{3}J_{3a4a}$	c	$^{3}J_{4aCH_3}$	6.63

[a] although a COSY experiment proved 3e and 5e to be coupled, the complexity of the signals prevented extraction of $^{4}J_{3e5e}$

[b] 2-H is an apparent doublet, separation 3.1 Hz.

[c] not seen clearly.

Table 3. ^1H nmr data (400 MHz, 297 K) for cis- 2-methoxy-4-methyltetrahydropyran (19) in $CFCl_3/CDCl_3$ (85/15 v/v).

Chemical Shifts (δ/ppm)

2-H	4.21	5-H_a	1.20
3-H_e	1.76[a]	6-H_e	4.00
3-H_a	1.08	6-H_a	3.40
4-H_a	1.64	MeO	3.45
5-H_e	1.49[a]	MeC	0.98

Coupling Constants (Hz)

$^2J_{3e3a}$	12.6	$^3J_{4a5e}$	b
$^2J_{5e5a}$	13.2	$^3J_{4a5a}$	11.8
$^2J_{6e6a}$	11.7	$^3J_{5e6e}$	1.9
$^3J_{2a3e}$	2.1	$^3J_{5e6a}$	2.4
$^3J_{2a3a}$	9.2	$^3J_{5a6e}$	4.6
$^3J_{3e4a}$	b	$^3J_{5a6a}$	12.0
$^3J_{3a4a}$	12.0	$^3J_{4aCH_3}$	6.58

[a] although a COSY experiment proved 3e and 5e to be coupled, the complexity of the signals prevented extraction of $^4J_{3e5e}$.

[b] not seen clearly.

monosubstituted tetrahydropyrans substituted by CH_3 at position 4 and by OCH_3 at position 2. Now ^1H band width measurements[11] had indicated a preference of a 2-OCH_3 group for the axial orientation equivalent to about 0.8 kcal.mol^{-1} at 300 K. Moreover, ^{13}C measurements on several substituted tetrahydropyrans[7] at 173-183 K showed that a 4-CH_3 group prefers the equatorial orientation to the extent of 1.95 kcal mol^{-1}. If a conformational entropy difference (ΔS^o) of zero is assumed for the ring inversion of 4-methyltetrahydropyran, then the assumption that (20) has an insignificant population, at 240-280 K, is completely justified. Furthermore, a preliminary report[10] of the present work employed the literature value of ΔG^o (Me) [$\simeq \Delta H^o$ (Me)] to evaluate ΔH^o and ΔS^o for the ring inversion in 2-methylaminotetrahydropyran. However, the published value of ΔG^o (Me) in 4-methyltetrahydropyran was based on measurements of equilibria in one monosubstituted and three disubstituted tetrahydropyrans,[7] with the usual assumption of additivity of ΔG^o values. Consequently, it was desirable to determine ΔG^o (Me) by a direct method and to extend measurements over a range of temperature to confirm that ΔS^o (Me) was, indeed, zero.

[Me-^{13}C]-4-methyltetrahydropyran (34 $\rightleftarrows$ 35) was synthesised from tetrahydropyran-4-one by sequential reactions of addition (using ^{13}C-MeMgI from ^{13}C-enriched iodomethane), dehydration ($KHSO_4$) and catalytic hydrogenation (Pd/C) The equilibrium (34 $\rightleftarrows$ 35) was studied in CD_2Cl_2 by direct integration of the methyl carbon signals in the ^{13}C n.m.r. spectrum recorded at 5 temperatures in the range 145-160 K (see Experimental). At 145 K the ^{13}C chemical shifts of carbons in axial and equatorial methyl groups were 16.73 and 22.75 ppm, respectively, and the measured equilibrium constants (e/a) varied from 348 (at 160 K) to 584 (at 145 K).

In addition, a line-broadening ^{13}C n.m.r. study (cf.[51,52]) in the temperature range 185-220 K showed that the maximum broadness ($W_{\frac{1}{2}}$) of the methyl carbon signal was 4.25 Hz at 206 K, giving an equilibrium constant (e/a) of 87.9 and incidentally, an activation energy $\Delta G^{*}_{35\to34}$ of 10.55 kcal mol^{-1}. The best-fit straight line of lnK against T^{-1} gave $\Delta H^{o}_{34\to35}$ as -1.86 kcal mol^{-1} and $\Delta S^{o}_{34\to35}$ as -0.07 cal K^{-1} mol^{-1}. Evidently there is a slightly greater preference (in ΔH^{o} terms) for a methyl group to be oriented equatorial in the 4 position of a tetrahydropyran ring than in the cyclohexane ring, where $\Delta H^{o}_{a\to e}$ (Me) was found to be -1.75 kcal mol^{-1}.[53] In 4-methyltetrahydropyran, $\Delta G^{o}_{34\to35}$ is calculated to be -1.85 kcal mol^{-1} at 173 K and -1.84 kcal mol^{-1} at 298 K. Although these values are in reasonable agreement with Eliel's value of 1.95 kcal mol^{-1} at 173-183 K, the discrepancy has significant consequences for the study of 2-methylamino-4-methyltetrahydropyran, where 3 of the 4 data points are sensitive to the value of $\Delta H^{o}_{a\to e}$(Me) (see later). However, in the case of 2-methoxy-4-methyltetrahydropyran, the assumption that conformation (20) has a negligible population at 250-280 K is now seen to be completely justified.

Equilibrium constants for (10 ⇄ 11) and (18 ⇄ 19) are summarised in the Experimental section, together with the derived thermodynamic parameters ΔH^{o} (OCH_3) and $\Delta S^{o}_{a\to e}$ (OCH_3). The conformational enthalpy difference of 0.03 kcal mol^{-1} may be compared with the published[41] value of -0.71 kcal mol^{-1} for methoxycyclohexane in $CFCl_3$. Neglecting the slight difference in solvent, the "anomeric effect $\Delta\Delta H^{o}$" is calculated to be 0.74 kcal mol^{-1}.

The position of equilibrium in (10 ⇄ 11) is virtually independent of temperature and represents approximately 78% axial and 22% equatorial conformations. As ΔH^{o} is approximately zero, the conformational free energy difference ΔG^{o} is largely determined by the $T\Delta S^{o}$ term, a result not previously recorded and one which has not been anticipated by semiempirical calculations.[54,55] It must be emphasised, however, that specific effects due to the solvent (85% $CFCl_3$, 15% $CDCl_3$ by volume) remain to be investigated. The conformational entropy difference ΔS^{o} is surprisingly large; moreover, it is the axial conformation which has the greater entropy, a result which recalls the similar finding for the conformational equilibrium in methoxycyclohexane.[41] Our findings have been supported by a recently reported[56] investigation of solvent effects on (10 ⇄ 11); in $CDCl_3$ Praly and Lemieux found $\Delta H^{o}_{10\to11}$ to be -0.2 kcal mol^{-1} and $\Delta S^{o}_{10\to11}$ to be -2.0 cal K^{-1} mol^{-1}.

The conformational equilibrium in 2-hydroxytetrahydropyran (12 ⇄ 13) was also studied by direct integration of the ^{13}C n.m.r. spectra recorded at 169 K and 172 K, and by analysis of the acid-catalysed equilibrium (22 ⇄ 23) of cis- and trans-2-hydroxy-4-methyltetrahydropyran. Although 2-hydroxytetrahydropyran occurs as an equilibrium mixture of cyclic hemiacetal and open chain aldehyde (5-hydroxypentanal), the proportion of latter is only 5-6% at room temperature and decreases rapidly on lowering the temperature.[57,58] The ^{13}C n.m.r. spectra at 283 K and 169 K of 2-hydroxytetrahydropyran in $CFCl_3/CDCl_3$ showed no signal for an aldehyde carbon.

The low temperature ^{13}C n.m.r. spectrum of a 1.5 M solution of (12 ⇄ 13) in $CFCl_3/CDCl_3$, studied at 169 K and 172 K, showed signals for both (12) and (13), and accurate integration was based on the pairs of well separated signals assigned to 2-C and 6-C. Signal assignments (Table 4) relied on reported[47] chemical shift parameters for equatorial and axial hydroxy groups attached to cyclohexane; however, as with the corresponding methoxytetrahydropyran, discrepancies between calculated and observed shifts were considerable for the anomeric carbons (2-C). The equilibrium constant (e/a) of 1.96-2.01 determined at 169 K and 172 K in $CFCl_3/CDCl_3$, may be compared with the values of between 1.56 and 3.0, determined at

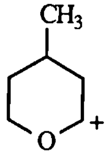
Table 4. Carbon-13 chemical shifts (δ/ppm from Me_4Si) for 2-hydroxytetrahydropyran ($12 \rightleftarrows 13$) in $CFCl_3/CDCl_3$, (85/15 v/v).

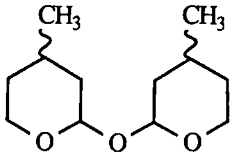
	($12 \rightleftarrows 13$)	(12)	(12)	(13)	(13)
T/K	275	169	a	169	a
carbon					
2	94.11	90.83	107.7	96.22	112.9
3	31.83	30.20	32.9	32.36	35.4
4	20.28	17.27	16.9	22.33	21.5
5	25.35	24.96	26.3	24.96	25.4
6	63.35	59.57	61.9	66.51	66.5

[a] calculated (see discussion)

temperatures between 233 K and 403 K in CS_2, using measurements of ^1H band widths in n.m.r. spectra.[59]

The equilibration of (22) and (23) in $CFCl_3/CDCl_3$ was a relatively slow process involving bond fission, and required at least 30 days for completion at 250-270 K. It is likely that equilibration occurs partly through an intermediate open-chain aldehyde (cf. glucose) and partly through an intermediate carbocation (36) (cf. methyl glucopyranoside[60]).


(36)


(37)

In both cases, reaction of the intermediate with 2-hydroxytetrahydropyran can give rise to the bicyclic ether (37). Samples of the equilibrium mixture of (22) and (23) showed a peak in the mass spectrum at m/e corresponding to (37). Further, the anomeric region of the ^1H n.m.r. spectrum of the equilibrium mixture included the 2 signals assigned to 2-H in (22) and (23), and 8 additional minor signals, comprising 4 broadened singlets (characteristic of a trans-relationship of exo-C_2-O and C_4-Me) and 4 double doublets (characteristic of a cis-relationship of exo-C_2O and C_4-Me). The 4 racemic (cis-cis, trans-trans, cis-trans I and cis-trans II) and 2 meso (cis-cis) and trans-trans) modifications of (37) are expected to show a maximum of 4 broadened singlets and 4 double doublets in the region δ4.3 to δ5.4. Fortunately, in the spectrum at 250 MHz, none of the additional signals overlapped with the signals at δ5.26 and δ4.66 which were required to be integrated in the assessment of the equilibrium ($22 \rightleftarrows 23$). As with the related 2-methoxy-4-methyltetrahydropyran, the proportion of diaxial conformation (25) in the equilibrium ($23 \rightleftarrows 25$) may be neglected. The belief that (24) may be neglected in the equilibrium ($22 \rightleftarrows 24$) rests on the finding,[59] based on ^1H band-width measurements, that $\Delta G^o_{a\to e}$ for OH in 2-hydroxytetrahydropyran was -0.34 kcal mol^{-1} at 273 K and -0.21 kcal mol^{-1} at 233 K in the non-polar solvent CS_2. Consequently [$\Delta G^o_{a\to e}$(Me) - $\Delta G^o_{a\to e}$(OH)] varies from -1.52 kcal mol^{-1} at 273 K to -1.65 kcal mol^{-1} at 233 K; clearly the population of (24) is not significant at 250 K and 270 K.

The equilibrium constants obtained in the present studies of ($12 \rightleftarrows 13$) and ($22 \rightleftarrows 23$) are given in the Experimental section, along with the derived values for $\Delta H^o_{a\to e}$ and $\Delta S^o_{a\to e}$. Although the axial conformation is favoured by entropy, it is the equatorial conformation (13) which is preferred in terms of enthalpy. However, since the published value[61] for $\Delta H^o_{a\rightarrow e}$ in cyclohexanol (in isooctane) is -1.24 kcal mol^{-1}, the "anomeric effect $\Delta\Delta H^o$" is calculated to be 0.61 kcal mol^{-1}.

Tesse and coworkers[62] suggested that the methylamino group in 2-methylaminotetrahydropyran had a strong preference for the equatorial orientation because the 2-H signals of this molecule (14 ⇄ 15) and of cis-2-methylamino-4-methyltetrahydropyran (27) had identical chemical shifts (δ3.95) in CCl_4. Moreover, Barbry and coworkers[63] used ^1H band widths to calculate an equilibrium constant of 0.54 for (28)/(26) in the ring inversion equilibrium of trans-2-methylamino-4-methyltetrahydropyran, thus confirming the strong tendency of 2-methylamino to be equatorial, at least in ΔG^o terms. In the present study, three methods were used to measure the position of equilibrium in (14 ⇄ 15).

In the first method, trans-2-methylamino-4-methyltetrahydropyran (26 ⇄ 28) was analysed at 174 K by ^{13}C n.m.r. spectroscopy. The experiment was complicated by the presence of the cis-isomer (27). No attempt was made to separate the isomers as it had been demonstrated that equilibration of isomers commenced immediately a solution of the mixed isomers had been prepared in $CDCl_3$, or $CFCl_3$ containing $CDCl_3$, possibly due to traces of HCl (or DCl) in the $CDCl_3$. At 174 K, each carbon of the trans-isomer (26 ⇄ 28) was expected to show a pair of signals corresponding to the two conformations; in the event, only one pair of signals, at 57.7 and 61.4 ppm, assigned to 6-C, were clearly seen (Table 5). This was due partly to interference from signals due to the cis- isomer (27) and partly due to the fact that several carbon atoms of (26) and (28) have identical, or nearly identical chemical shifts. The signal at 17.5 ppm, which could be assigned with confidence to the carbon of the axial methyl in (28), had an area identical to that of the signal at 61.4 ppm. Consequently, the latter signal was assigned to 6-C in (28), the 57.7 signal representing 6-C in (26). The derived equilibrium constant of 0.578 (= 28/26) was converted into a $\Delta G^o_{26\rightarrow 28}$ value, from which (assuming additivity of ΔG^o values) was calculated $\Delta G^o_{a\rightarrow e}$ (NHMe) and hence a value for the equilibrium constant (15/14) at 174 K. (see Experimental).

Table 5. Carbon-13 chemical shifts (δ/ppm from Me_4Si) for cis-(27)- and trans-(26 ⇄ 28)-2-methylamino-4-methyltetrahydropyran in $CFCl_3/CDCl_3$ (85/15 v/v).

	(27)	(27)	(26 ⇄ 28)	(26)	(28)
T/K	275	174	275	174	174
carbon					
2	89.05	89.03	84.26	84.30	84.30
3	40.83	40.95	38.14	38.06	38.06
4	30.28	30.32	24.87	a	a
5	34.11	34.00	33.04	a	a
6	65.57	66.03	58.60	57.7	61.4
MeN	31.49	32.34	31.26	31.7	31.7
MeC	21.71	22.28	20.37	a	17.5

a not seen clearly

Table 6 Carbon-13 Chemical Shifts (δ/ppm from Me_4Si) for 2-methylamino-tetrahydropyran (14 $\rightleftharpoons$ 15) in $CFCl_3/CDCl_3$ (85/15 v/v) at 275 K.

carbon	2	3	4	5	6	MeN
shift	89.7	32.8	23.8	26.1	66.6	32.0

The <u>second</u> method involved a line-broadening study of the ^{13}C n.m.r. spectrum of 2-methylaminotetrahydropyran itself (14 $\rightleftharpoons$ 15). The method required values for the chemical shifts of 6-C in conformations (14) and (15). The necessary shifts were easily calculated from the 6-C shifts observed at 174 K in (26), (27) and (28) (see Table 5). The γ-substituent ^{13}C shift parameters for a 4-methyl group in a tetrahydropyran are known[46] to be +0.2 ppm (equatorial Me) and −5.6 ppm (axial Me). Consequently, 6-C is expected to have a chemical shift of 57.5 ppm in (14), 66.4 ± 0.6 ppm in (15). The ^{13}C nmr spectrum of (14 $\rightleftharpoons$ 15) in $CFCl_3/CDCl_3$ (85/15) reveals the expected six signals at 273 K (Table 6), and no additional signals were detected at temperatures down to 160 K. However, a study of the signals in the range 160-210 K showed significant broadening of all signals except those assigned to 5-C and $N\text{-}CH_3$. A line-broadening study concentrated on the 6-C signal, which is expected to show exceptional broadening owing to the large chemical shift difference (8.9 ± 0.6 ppm, see above) between its environments in (14) and (15). Careful measurements gave an equilibrium constant of 74.2 (= 15/14) at 191 K. The <u>third</u> method of investigation involved a study of the equilibrium between <u>cis</u>- and <u>trans</u>-2-methylamino-4-methyltetrahydropyran. Whereas the <u>cis</u>-isomer (27 $\rightleftharpoons$ 29) is undoubtedly confined to conformation (27), it is clear from the earlier analysis of the <u>trans</u>-isomer at 174 K that in this case both conformation (26) and its ring inverted conformation (28) must be considered. In fact, direct integration of the ^1H nmr spectrum of the equilibrium mixture of <u>cis</u>- and <u>trans</u>- isomers only gives an equilibrium constant equal to [27]/[26+28]. Nevertheless, the required equilibrium constant 27/26, which approximates to 15/14, is readily calculated in the following way:

$$\begin{tikzcd}(26) \arrow[r, shift left] \arrow[dr, shift left] & (27) \arrow[l, shift left] \\ & (28) \arrow[ul, shift left]\end{tikzcd}$$

$$\text{Let } K = [27]/[26 + 28]$$

$$K_1 = 27/26$$

$$\text{and } K_2 = 28/26$$

$$\text{Then } K_1 = K(1+K_2) \tag{1}$$

$$\text{and } -RT\ln(K+KK_2) = \Delta G^o_{a\to e}(NHMe) \tag{2}$$

Also

$$-RT\ln K_2 = \Delta G^o_{a\to e}(NHMe) - [\Delta H^o_{a\to e}(Me) - T\Delta S^o_{a\to e}(Me)] \tag{3}$$

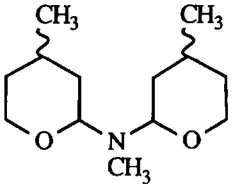
(2) and (3) give

$$RT\ln[(K+KK_2)/K_2] = -\Delta H^o_{a\to e}(Me) + T\Delta S^o_{a\to e}(Me)$$

This may be transformed into

$$K_2 = K/\{e^{[1860/RT - 0.07/R]} - K\}$$

since we have earlier determined $\Delta H^{o}_{a\rightarrow e}$(Me) to be -1.86 kcal mol^{-1} and $S^{o}_{a\rightarrow e}$(Me) to be -0.07 cal K^{-1} mol^{-1}. Thus measurement of K at any temperature yields K_2, and hence K_1 from equation (1).



(38)

The long period (> 4 weeks) required for the attainment of equilibrium of cis- and trans-isomers caused a build-up of impurities. Equilibrated mixtures were thought to contain small proportions of bicyclic amines of structure (38), and the mass spectrum included a small peak at the m/e value corresponding to the molecular mass of (38). The equilibrium constants determined from studies on ($26 \rightleftarrows 28$), ($14 \rightleftarrows 15$) and ($26 \rightleftarrows 27 \rightleftarrows 28$) are listed in the Experimental section, along with the derived values for $\Delta H^{o}_{a\rightarrow e}$ (NHMe) and $\Delta S^{o}_{a\rightarrow e}$ (NHMe). The fact that these values are significantly different from those published in the preliminary report[10] is due entirely to the use of new thermodynamic parameters for 4-methyltetrahydropyran (see earlier). In ΔH^{o} terms, a 2-methylamino group in a tetrahydropyran has a strong preference for the equatorial orientation, as in (15). However, the negative $\Delta H^{o}_{a\rightarrow e}$ ensures that the proportion of axial conformation (14) will increase at higher temperatures. Since $\Delta H^{o}_{a\rightarrow e}$ in N-methylcyclohexylamine[10] is -1.78 kcal mol^{-1}, the "anomeric effect $\Delta\Delta H^{o}$" is, in this case, not significant. However, room temperature $\Delta G^{o}_{a\rightarrow e}$ values for 2-methylaminotetrahydropyran (-1.58 kcal mol^{-1}) and N-methylcyclohexylamine (-1.17 kcal mol^{-1}) differ substantially, and proportions of conformations will vary accordingly. For example, at 300 K the proportion of axial conformation is 6.6% (K = 14.15) in 2-methylaminotetrahydropyran, as against 12.3% (K = 7.12) in N-methylcyclohexylamine; only at temperatures below about 20 K does the tetrahydropyran have the greater percentage of axial conformation.

Attention was next turned to 2-chlorotetrahydropyran ($16 \rightleftarrows 17$) which was prepared by reaction of anhydrous hydrogen chloride with dihydropyran, and which was found to be stable for periods of up to 4 weeks if stored at 250 K. Early work[64] using ^{1}H n.m.r. band-widths, in comparison with band-widths of model compounds, indicated a very strong preference for the axial conformation (16) at room temperature. In the present investigation, the ^{13}C n.m.r. spectrum of 2-chlorotetrahydropyran was studied at room temperature and at temperatures down to 143 K. Although two very weak signals, not seen at 270 K, were observed at 143 K, they could not be assigned with certainty to carbon atoms in the minor conformation (17). Consequently, the equilibrium mixture ($30 \rightleftarrows 31$) of trans- and cis-2-chloro-4-methyltetrahydropyran in $CDCl_3$ was studied at variable temperature, as in the classical work of Anderson and Sepp,[65] who analysed the neat liquid at four temperatures in the range 313 to 378 K. Conformation (33) need not be considered, and in this instance the population of (32) is insignificant, as the 2-chloro and 4-methyl substituents strongly prefer the axial and equatorial orientations, respectively. Therefore the position of equilibrium in ($30 \rightleftarrows 31$) is likely to be close to that in ($16 \rightleftarrows 17$). The equilibration of (30) and (31) occurs rapidly, even in the absence of acid. At least two mechanisms are possible. Hydrolysis of the C-Cl bond by traces of water will liberate protons; protonation of the ring oxygen then encourages endocyclic fission of the C_2-O bond. However, exocyclic fission of the C_2-Cl bond, giving a stabilised carbocation, may occur without the intervention of protons.

Table 7. ^1H nmr data (250 MHz, 294 K) for 2-chloro-4-methyltetrahydropyran (<u>trans</u>, unless stated otherwise) in $CDCl_3$.

Chemical shifts (δ/ppm)

2-H	6.32	$5-H_e$	1.66
2-H	5.49[a]	$5-H_a$	1.36
$3-H_e$	2.02	$6-H_e$	3.82
$3-H_a$	1.63	$6-H_a$	4.06
$4-H_a$	2.2	Me	0.95

Coupling constants (Hz)

$^2J_{3e3a}$	14.0	$^3J_{2a3a}$	8.70[a]
$^2J_{5e5a}$	12.0	$^3J_{2a3e}$	2.75[a]
$^2J_{6e6a}$	11.6	$^3J_{5e6e}$	1.5
$^3J_{2e3a}$	3.3	$^3J_{5a6e}$	4.9
$^3J_{2e3e}$	0.7	$^3J_{5a6a}$	12.5
$^3J_{4aCH_3}$	6.6		

[a] <u>cis</u>-isomer

The fast equilibration of (30) and (31) allowed the variable temperature study to be carried out in the n.m.r. probe (<u>see Experimental</u>). The ^1H n.m.r. parameters of <u>cis</u>- and <u>trans</u>-2-chloro-4-methyltetrahydropyrans are summarised in Table 7. Isomer ratios were readily measured by integration of the 2-H signals, and equilibrium constants at 8 temperatures in the range 253 to 324 K are listed in the Experimental section. The hand-drawn plot of lnK against T^{-1} gave $\Delta H^o_{a\rightarrow e}$ as 1.67 kcal mol^{-1} and $\Delta S^o_{a\rightarrow e}$ as -1.69 cal K^{-1} mol^{-1}. In ΔH^o terms, the chlorine atom in 2-chlorotetrahydropyran has a marked preference for the axial orientation. The published value[41] for $\Delta H^o_{a\rightarrow e}$ in chlorocyclohexane (in $CFCl_3$) is -0.45 kcal mol^{-1}, giving an "anomeric effect $\Delta\Delta H^o$" of 2.12 kcal mol^{-1}. In 2-chlorotetrahydropyran ($16 \rightleftarrows 17$), the population of the minor equatorial conformation (17) will increase at elevated temperatures, but will never attain parity with that of the axial conformation (16), as the latter has the higher entropy. At reduced temperatures, the axial conformation is dominant; the ΔH^o and ΔS^o values allow a calculated equilibrium constant K (= e/a) at 150 K of about (1/800), thus explaining the difficulty in observing signals due to the minor conformation in the lower temperature ^{13}C n.m.r. spectrum.

Theoretical implications of Results

The experimentally determined thermodynamic parameters ΔH^o and ΔS^o, together with room temperature ΔG^o values, for the equilibrium ($1 \rightleftarrows 2$), are assembled in Table 8. The trend in the $\Delta H^o_{a\rightarrow e}$ values in the Table lends support to the Altona theory of antiperiplanar n-σ* stabilisation, modified by the competition between <u>endo</u>- and <u>exo</u>-anomeric effects in the axial conformation [see (8a)] and (8e)]. In general, and neglecting for the moment steric factors, any change of the

2-substituent which causes an increase in the exo-anomeric effect will favour, in ΔH^o terms, the equatorial conformation because the effect is not modified by an opposing endo-anomeric effect; conversely, any decrease in the exo-anomeric effect will favour the axial conformation. An exception to these generalisations would arise in the rare instance of a ring heteroatom which is such a poor donor that the endo-anomeric effect is insignificant. Since the magnitude of exo- and endo-anomeric effects are unknown, further generalisations are not warranted at present.

Table 8. Thermodynamic Parameters[a] for ($1 \rightleftarrows 2$) (ΔH^o and ΔG^o in kcal mol^{-1}; ΔS^o in cal K^{-1} mol^{-1}).

R_E	$\Delta H^o_{1\to2}$ (error)	$\Delta S^o_{1\to2}$ (error)	$\Delta G^o_{1\to2}$ (300 K)
Cl[b]	1.67 (±0.26)	-1.69 (±0.90)	2.18
OCH_3[c]	0.03 (±0.06)	-2.52 (±0.43)	0.79
OH[c]	-0.63 (±0.07)	-2.50 (±0.30)	0.12
$NHCH_3$[c]	-1.75 (±0.10)	-0.60 (±0.40)	-1.57

[a] from hand plots of lnK against T^{-1}; see experimental for parameters from computer plots.

[b] solvent $CDCl_3$

[c] solvent $CFCl_3/CDCl_3$ (85/15 v/v)

The following arguments involve a comparison of ΔH^o values for 2-chloro-, 2-methoxy- and 2-methylamino-tetrahydropyrans. This series represents a sequence in which an increase in donor power of the heteroatom is accompanied by a decrease in acceptor power of the C-heteroatom bond. For 2-chlorotetrahydropyran, in which chlorine is a weak donor and the C-Cl bond a strong acceptor, a weak exo-anomeric effect is allied to a strong endo-anomeric effect, leading to a marked preference for the axial conformation, as observed. This tendency is accentuated by the weak syn-axial steric repulsions arising from a relatively long C-Cl bond in the axial orientation. The change from 2-chlorotetrahydropyran to 2-methoxytetrahydropyran is expected to cause a weakening of the endo-anomeric effect and a strengthening of the exo-anomeric effect. Thus the theory predicts an increase in preference for the equatorial conformation, in ΔH^o terms, as observed. Finally, the change from 2-methoxytetrahydropyran to 2-methylaminotetrahydropyran is accompanied by a further weakening of the endo-anomeric effect, and a further strengthening of the exo-anomeric effect. An increased preference for the equatorial conformation, in ΔH^o terms, is therefore expected, and the data of Table 8 confirm this prediction. The predicted trend is almost certainly augmented as a result of the more severe syn-axial repulsions suffered by an axial NHMe, compared to axial OMe.

The position of 2-hydroxytetrahydropyran in the series under discussion is difficult to rationalise. There is a parallel situation in the related cyclohexane series, where cyclohexanol shows a stronger preference, in ΔH^o terms, for the equatorial orientation than methoxycyclohexane, a result not anticipated on steric grounds. Thus $\Delta H^o_{a\to e}$ is -0.71 kcal mol^{-1} for methoxycyclohexane in $CFCl_3$[41] and -1.21 kcal mol^{-1} for cyclohexanol in isooctane.[61] The change $OCH_3 \to OH$ would be expected to reduce the electron donor power of oxygen, thereby weakening the exo-anomeric effect in 2-substituted tetrahydropyran and leading to a greater preference, in ΔH^o terms, for the axial conformation. However, in both tetrahydropyrans and cyclohexanes, the intermolecular H-bonding, which is possible only for a hydroxy substituent, should be more effective for an equatorial substituent than for a sterically hindered axial substituent,[66] thus increasing the preference for the equatorial conformation.

This work is being extended by a study of the effect of solvents on the conformational equilibria in 2-substituted tetrahydropyrans.

EXPERIMENTAL

General - Mass spectra were recorded on either a VG Micromass 70E (7070E) or an A.E.I. MS902 spectrometer. Analytical g.l.c. employed a Pye Series 104 instrument; preparative g.l.c. used a Varian Aerograph Autoprep Model A-700.

^1H n.m.r. spectra were recorded on a Perkin-Elmer R.32 spectrometer (90 MHz) at 305 K, a Bruker WP80 PFT spectrometer (80 MHz) at 294 K, a Bruker WM250 PFT spectrometer (250 MHz) at 294 K and on a Bruker AM400 PFT spectrometer (400 MHz) at 297 K, unless stated otherwise.

^{13}C n.m.r. spectra were recorded on a Bruker WM250 PFT spectrometer (62.9 MHz) or a Bruker AM400 PFT spectrometer (100.6 MHz) at the stated temperature.

The parameters used for $^1H/^1H$ COSY 90 experiments at 400 MHz were as follows: F_2 spectral width 4201.68 Hz; F_1 spectral width ± 2100.84 Hz; number of data points 2048 in t_2 and, after zero filling, 2048 in t_1. The recycle delay was 1.5s and the initial evolution time was 0.1 ms. with increments of 0.238 ms. The number of FIDs was 256 or 512, with 8 scans per FID. Sine bell weighting was used in both dimensions and the matrix was symmetrised after transformation.

The thermocouple reading of the Bruker WM250 spectrometer was found to be accurate to ± 2K in the range 230-325 K when checked against a standard methanol sample, and to be accurate to ±0.5 K, over the range 145-294 K when checked against a gold/gold-doped iron thermocouple.

The following abbreviations are employed in descriptions of n.m.r. spectra: s (singlet); bs (broad singlet); d (doublet); t (triplet); q (quartet); dd (doublet of doublets), etc.; m (multiplet), a (axial), e (equatorial). Unless stated otherwise, ^1H n.m.r. spectra are analysed by a first-order method and therefore most reported coupling constants are approximate.

2-Methoxytetrahydropyran. - Following the general procedure of Woods and Kramer,[67] 3,4-dihydro-2H-pyran (6.21 g.) was converted into 2-methoxytetrahydropyran (6.15 g, 71.7%), a colourless liquid, b.p. 126-127°/760 mm Hg (lit.,[67,68] 125° and 128-9°, respectively). The ^1H n.m.r. spectrum (250 MHz, $CDCl_3$) showed signals at δ4.50 (apparent t; width 6.5 Hz; 2-H), 3.80-3.90 (m; one of 6-H), 3.45-3.56 (q; one of 6-H), 3.38 (s, OCH_3) and 1.48-1.86 (m; 3,4,5-H).

cis- and trans-2-n-Butoxy-4-methyl-3,4-dihydro-2H-pyran. - Following the literature,[50] a mixture of freshly distilled crotonaldehyde (50.07 g.) and n-butyl vinyl ether (71.59 g.) gave a mixture of 60% cis- and 40% trans-2n-butoxy-4-methyl-3,4-dihydro-2H-pyran (72-80 g.), b.p. 82-88°/16-17 mm Hg (lit.,[50] 76-82°)/14-15 mm Hg). The infrared spectrum (liquid film) included ν_{max} at 1645 cm^{-1} (C=C str.) and 3060 cm^{-1} (C-H str.). The ^1H n.m.r. spectrum (250 MHz, $CDCl_3$) showed signals for the cis-isomer at δ 6.23 (dd, $^3J_{5,6}$ 6.15 Hz, $^4J_{4,6}$2.15 Hz; 6-H), 4.89 (dd, $^3J_{2,3a}$ 8.5 Hz, $^3J_{2,3e}$ 2.20 Hz, 2-H), 4.55 (ddd, $^3J_{5,6}$ 6.15 Hz, $^3J_{4,5}$ 2.30 Hz, $^4J_{3,5}$ 1.40 Hz; 5-H), 3.95-3.40 (m; OCH_2), 2.45-2.35 (m, 4-H), 2.0 (m; 3-H), 1.65-1.35 (m; CH_2CH_2 of Bu), 1.03 (d, ^3J 7.10 Hz; 4-Me) and 0.925 (t, ^3J 7.25 Hz, Me of Bu). The *trans*-isomer showed signals at δ 6.17 (dd, $^3J_{5,6}$ 6.30 Hz, $^4J_{4,6}$ 2.30 Hz; 6-H), 4.97 (t, $^3J_{2,3e}$ 2.90 Hz, $^3J_{2,3a}$ 2.90 Hz; 2-H), 4.64 (ddd, $^3J_{5,6}$ 6.30 Hz, $^3J_{4,5}$ 2.10 Hz; $^4J_{3,5}$ 1.60 Hz; 5-H), 3.95-3.40 (m; OCH_2), 2.45-2.35 (m; 4-H), 1.90 (m; 3-H), 1.65-1.35 (m; CH_2CH_2 of Bu), 1.00 (d, ^3J 7.25 Hz; 4-Me) and 0.916 (t, ^3J 7.30 Hz; Me of Bu).

cis- *and* trans-2-n-*Butoxy*-4-*methyltetrahydropyran*. - The foregoing mixture (17 g.) of dihydropyrans, dissolved in methanol (100 cm^3) containing Adam's PtO_2 catalyst (1.7 g.), was hydrogenated at 293 K and 760 mm Hg. The uptake of hydrogen was 2460 cm^3 (theory 2404 cm^3). The usual method of working up gave, after distillation, a mixture of 65% *cis*- and ∿35% *trans*-2-n-butoxy-4-methyltetrahydropyran (14.3 g., 83%), b.p. 90-92°/16 mm Hg (lit.,[49] 79-86°/4-5 mm Hg). The ^1H n.m.r. spectrum (250 MHz, $CDCl_3$) showed signals for the *cis*-isomer at δ 4.32 (dd, $^3J_{2a3a}$ 9.3 Hz, $^3J_{2a3e}$ 2.1 Hz; 2-H), 3.99 (ddd, $^2J_{6e6a}$ 11.7 Hz, $^3J_{6e5a}$ 4.5 Hz, $^3J_{6e5e}$ 1.8 Hz; 6-H_e), 3.86 (td, $^2J_{AB}$ 10.2 Hz, ^3J 7.0 Hz; OCH_A of OBu), 3.45-3.25 (m; OCH_B of OBu and 6-H_a), 2.02-1.02 (m; CH_2CH_2 of Bu and 3,4,5-H), 0.96 (d, ^3J 6.6 Hz; 4-Me) and 0.92 (t, ^3J 7.2 Hz; Me of Bu). The *trans*-isomer showed signals at δ 4.77 (unresolved m, $W_{\frac{1}{2}}$ 6.8 Hz; 2-H), 3.76 (td, $^2J_{6e6a}$ 11.6 Hz, $^3J_{6a5a}$ 11.6 Hz, $^3J_{6a5e}$ 1.8 Hz; 6-H_a), 3.66 (td, $^2J_{AB}$ 12.2 Hz, ^3J 6.8 Hz; OCH_A of OBu) 3.55 (dm, $^2J_{6e6a}$ ∿11.3 Hz; 6-H_e), 3.45-3.25 (m; OCH_B of OBu), 2.02-1.02 (m; CH_2CH_2 of Bu and 3,4,5-H), 0.88 (d, ^3J 6.6 Hz; 4-Me) and 0.93 (t, ^3J 7.3 Hz; Me of Bu).

4-*Methyl*-3,4-*dihydro*-2H-*pyran*. - A mixture (7.2 g.) of *cis*- and *trans*-2-n-butoxy-4-methyltetrahydropyran was treated with P_2O_5 according to the published method[49] for 3-methyl-2,3-dihydrofuran, except that two treatments with sodium were required to remove butanol. A final distillation from sodium gave 4-methyl-3,4-dihydro-2H-pyran (2.8 g., 68.3%) as a colourless liquid b.p. 100-101° (lit.[49] 101-101.5°). The infrared spectrum (liquid film) included ν_{max} at 3060 cm^{-1} (C-H str.) and 1640 cm^{-1} (C=C str.). The ^1H n.m.r. spectrum (250 MHz, $CDCl_3$) showed signals at δ 6.31 (dd, $J_{5,6}$ 6.2 Hz, $^4J_{4,6}$ 2.0 Hz; 6-H), 4.56 (ddd, $^3J_{5,6}$ 6.2 Hz, $^3J_{4,5}$ 3.0 Hz, $^4J_{3,5}$ 1.0 Hz; 5-H), 3.85-4.05 (m; 2-H), 2.20-2.30 (m; 4-H), 1.35-1.65 and 1.85-1.95 (m; 3-H) and 1.00 (d, ^3J 7.0 Hz; 4-Me).

cis- *and* trans-2-*Methoxy*-4-*methyltetrahydropyran*. - 4-Methyl-3,4-dihydro-2H-pyran (6.51 g.) was treated with methanol (2.14 g.) by the method of Woods and Kramer,[66] giving a mixture (6.06 g., 70.2%) of *cis*- and *trans*-2-methoxy-4-methyltetrahydropyran, b.p. 138-142° and 44-48°/20 mm Hg (lit.[5,6] 35-45°/10 mm Hg and 54-55°/28 mm Hg, respectively). The isomers were separated preparatively by glc on a 10' x 1/4" aluminium column packed with 20% Carbowax 20M on Chromosorb W. The column temperature was 60° and the isomers had retention volumes of 720 cm^3 (*trans*) and 1368 cm^3 (*cis*). The ^1H n.m.r. spectral details are summarised in Tables 2 and 3.

2-*Hydroxytetrahydropyran* - 3,4-Dihydro-2H-pyran (8.4 g.) was converted by the reported method[68] into 2-hydroxytetrahydropyran (7.24 g., 70.9%), b.p. 78-80°/19 mm Hg (lit.[68] 62-66°/9-10 mm Hg). The ^1H n.m.r. spectrum (90 MHz, $CDCl_3$) at 308 K showed a weak signal at δ 9.87 (s; CHO), in addition to signals at δ 4.95 (bs; 2-H), 3.93-4.22 (m; one of 6-H), 3.41-3.75 (m; one of 6-H), and 1.33-2.11 (m; 3,4,5-H). ^{13}C n.m.r. data are given in Table 4.

cis- *and* trans-2-*Hydroxy*-4-*methyltetrahydropyran*. - 4-Methyl-3,4-dihydro-2H-pyran (5.8 g.) was converted by the foregoing method into a mixture (4.65 g., 67.8%) of *cis*- and *trans*-2-hydroxy-4-methyltetrahydropyran, b.p. 84-90°/20-22 mm Hg (lit.[5] 75-80°/5 mm Hg). The ^1H n.m.r. spectrum (250 MHz, $CDCl_3$) included signals for the *cis*-isomer at δ4.66 (dd, $^3J_{2a3a}$ 9.5 Hz, $^3J_{2a3e}$ 2.2 Hz; 2-H), 4.00-4.06 (m; 6-H_e), 3.55-3.68 (m; 6-H_a), 1.03-2.11 (m; 3,4,5-H and OH), and 0.97 or 0.91 (d; ^3J 6.5 Hz; 4-Me). The *trans*-isomer showed signals at δ5.26 (bs; 2-H), 3.96-3.98 (m; 6-H_e), 3.48 (td, $^2J_{6e6a}$ 12.0 Hz, $^3J_{5a6a}$ 12.0 Hz, $^3J_{5e6a}$ 2.3 Hz; 6-H_a), 1.03-2.11 (m; 3,4,5-H and OH) and 0.91 or 0.97 (d; ^3J 6.5 Hz; 4-Me).

2-*Methylaminotetrahydropyran*. - Using the published method,[69] 2-hydroxytetrahydropyran was converted into 2-methylaminotetrahydropyran (3.6 g., 67.8%), b.p. 54°/22 mm Hg (lit.,[69] 56°/20 mm Hg). The ^1H n.m.r. spectrum (400 MHz, $CDCl_3$) showed signals at δ3.95 (dq, $^2J_{6e6a}$ 11.5 Hz; 6-H_e), 3.87 (dd, $^3J_{2a3a}$ 9.80 Hz, $^3J_{2a3e}$ 1.95 Hz; 2-H), 3.44 (m; 6-H_a), 2.49 (s; NMe), 1.83 (m; 4-H_e), 1.77 (dm, $^2J_{3e3a}$ 12.5 Hz; 3-H_e); 1.52-1.54 (m; 5-H_a), 1.48-1.51 (m; 4-H_a and 5-H_e), and 1.27 (m; 3-H_a). Assignments were confirmed by $^1H/^1H$ COSY Experiments which also demonstrated long-range coupling between 4-H_e and 6-H_e. The ^{13}C n.m.r. spectral data for 2-methylaminotetrahydropyran are summarised in Table 6.

cis- and trans-2-*Methylamino*-4-*methyltetrahydropyran*. - Using the reported method,[61] a mixture (4.3 g.) of *cis*- and *trans*-2-hydroxy-4-methyltetrahydropyran was converted into *cis*- and *trans*-2-methylamino-4-methyltetrahydropyran (2.64 g., 55.2%), b.p. 52-54°/19 mm Hg (lit.,[61]/18 mm Hg). The ^1H n.m.r. spectrum (400 MHz, $CDCl_3$) showed signals for the *cis*-isomer at δ3.98 (ddd, $^2J_{6e6a}$ 11.6 Hz, $^3J_{5a6e}$ 4.6 Hz,$^3J_{5e6e}$ 1.4 Hz,; 6-H_e), 3.84 (dd, $^3J_{2a3a}$ 10.3 Hz, $^3J_{2a3e}$ 1.9 Hz, 2-H), 3.42 (td, $^2J_{6e6a}$ 12 Hz, $^3J_{5a6a}$ 12 Hz, $^3J_{5e6a}$ 2.2 Hz; 6-H_a), 2.51 (s; NMe), 1.78 (dm, $^2J_{3e3a}$ 12.6 Hz; 3-H_e), 1.71 (s; NH), 1.57-1.76 (m; 4-H), 1.51 (dm, $^2J_{5e5a}$ 13.2 Hz; 5-H_e), 1.14 (qd, $^2J_{5e5a}$ 12.5 Hz, $^3J_{5a6a}$ 12.5 Hz, $^3J_{4a5a}$ 12.5 Hz, $^3J_{5a6e}$ 4.6 Hz; 5-H_a), 0.94 (d; J 6.5 Hz; CMe) and 0.82-1.02 (m; 3-H_a). Signals for the *trans*-isomer (minor component) were seen at δ4.33 (t, $^3J_{2,3} + {}^3J_{2,3'} =$ 8.5 Hz; 2-H), 3.6-3.75 (m; 6-H_e and 6-H_a), 2.45 (s; NMe) and 0.97 (d, J 6.7 Hz; CMe).

2-*Chlorotetrahydropyran*. - 3,4-Dihydro-2H-pyran (8.4 g.) was converted by the published method[63] into 2-chlorotetrahydropyran (7.1 g., 59%), b.p. 44-45°/15 mm Hg (lit.,[63] 35-36°/12 mm Hg). The ^1H n.m.r. spectrum (250 MHz, $CDCl_3$) showed signals at δ6.28 (m, $W_{\frac{1}{2}}$ 4.8 Hz; 2-H), 3.98-4.17 (tm, J 11.5 Hz; 6-H_a), 3.72-3.80 (dm, ^2J 11.5 Hz, 6-H_e), 1.54-2.20 (m; 3,4,5-H). The ^{13}C n.m.r. spectrum (62.90 MHz, $CFCl_3/CDCl_3$ 85/15) showed signals at δ95.00 (2-C), 62.07 (6-C), 34.66 (3-C), 25.21 (5-C) and 17.43 (4-C).

cis- *and* trans-2-*Chloro*-4-*methyltetrahydropyran*. - The published method[63] for 2-chlorotetrahydropyran was used to convert 4-methyl-3,4-dihydro-2H-pyran (6.3 g.) into a mixture (5.5 g., 63.6%) of *cis*- and *trans*-2-chloro-4-methyltetrahydropyran, b.p. 57-59°/24 mm Hg (lit.,[64] 41-42°/5 mm Hg). The ^1H n.m.r. data are summarised in Table 7.

4-*Methyltetrahydropyran*-4-*ol*. (cf.[45]). - A solution of methylmagnesium iodide in dry ether (25 cm^3), prepared from magnesium turnings (0.33 g.) and iodomethane (2.03 g.), was added to a stirred solution of tetrahydropyran-4-one (1.09 g.) in dry ether (25 cm^3). The mixture was stirred during 16 hr., quenched with ice-cold saturated ammonium chloride solution (15 cm^3) and separated into aqueous and ethereal phases. The aqueous phase was extracted with ether (2 x 40 cm^3) and the combined ether fractions were dried (K_2CO_3). Removal of ether gave crude 4-methyltetrahydropyran-4-ol (1.08 g., 85%). The ^{1}H n.m.r. spectrum (90 MHz, $CDCl_3$) showed signals at δ3.96-3.61 (m; 2,6-H), 1.90 (s; OH), 1.98-1.39 (m; 3,5-H) and 1.29 (s; Me). The infrared spectrum (liquid film) included the expected peak at 3420 cm^{-1} (O-H str.) and a weak peak at 1710 cm^{-1} (C=O str.) due to starting material.

[Me-^{13}C]-Methyltetrahydropyran-4-ol. - The foregoing reaction was repeated using tetrahydropyran-4-one (2.09 g.) and [^{13}C]methylmagnesium iodide prepared from magnesium turnings (0.63 g.) and [^{13}C]iodomethane (4 g., 90.5 ^{13}C atom %). The product was crude [Me-^{13}C]-4-methyltetrahydropyran-4-ol (2.02 g., 82.6%), a colourless oil. The ^{1}H n.m.r. spectrum (90 MHz, $CDCl_3$) included signals at δ1.28 (d, $^1J_{CH}$ 125.0 Hz; 4-^{13}-CH_3) and 1.28 (s; 4-$^{12}CH_3$).

4-Methyltetrahydropyran. - A mixture of crude 4-methyltetrahydropyran-4-ol (1.08 g.) and potassium hydrogen sulphate (1 g.) was heated in a bulb-tube for 1 h. at 140° and then at 150° under distillation conditions. Crude 4-methyl-5,6-dihydro-2H-pyran (0.52 g., 57%) was collected over anhydrous potassium carbonate. The infrared spectrum (liquid film) included ν_{max} at 3030 cm^{-1} (=C-H str.), 1680 cm^{-1} (C=C str.) and 3450 cm^{-1} (O-H str., very weak). The ^{1}H n.m.r. spectrum (90 MHz, $CDCl_3$) showed signals at δ5.34 (m; 3-H), 4.00 (m; 2-H), 3.69 (t; 6-H), 1.96 (m; 5-H) and 1.63 (d, $^4J \sim 1$ Hz; 4-Me). Weak signals at δ4.65 (=CH_2) and 2.18 (3,5-H) were probably due to traces of 4-methylenetetrahydropyran. The foregoing product (0.45 g.) was hydrogenated over 10% palladised charcoal (0.04 g.) at room temp. and atm. pressure during 3 hr., when 110 cm^{-3} H_2 (1.01 mole) were absorbed. The crude 4-methyltetrahydropyran (0.34 g., 74%) was separated by pipette from spent catalyst and purified by g.l.c. using a 10' x 1/4" aluminium column packed with 30% SE30 on silanised 60/80 Chromosorb W. The column temperature was 35° and the retention volume was 1152 cm^3. The ^{1}H n.m.r. spectrum (250 MHz, CD_2Cl_2) showed signals at δ3.87 (dm, $^2J \sim 11$ Hz; 2,6-H_e), 3.32 (td, ^2J 11 Hz, $^3J_{aa}$ 12.5 Hz, $^3J_{ae}$ 2 Hz; 2,6-H_a), 1.14-1.57 (m; 3,4,5-H) and 0.93 (d, ^3J 6.13 Hz; CH_3). The ^{13}C n.m.r. spectrum (62.90 MHz, $CDCl_3$) showed signals at δ68.11 (2,6-C), 35.06 (3,5-C), 30.03 (4-C) and 22.24 (CH_3).

[Me-^{13}C]-4-Methyltetrahydropyran. - The foregoing reactions were repeated, starting with [Me-^{13}C]-4-methyltetrahydropyran-4-ol (1.60 g.). The intermediate [Me-^{13}C]-4-methyl-5,6-dihydro-2H-pyran (0.76 g., 56.1%) gave a ^{1}H n.m.r. spectrum (90 MHz; $CDCl_3$) showing signals at δ5.40 (m; 3-H), 4.05 (m; 2-H), 3.74 (t; 6-H), 1.96 (m; 5-H), 1.70 (d, $^1J_{CH}$ 124 Hz; 4-^{13}C) and 1.70 (s; 4-$^{12}CH_3$). Hydrogenation of the above (0.70 g.) gave crude [Me-^{13}C]-4-methyltetrahydropyran (0.52 g., 74%), which was purified by g.l.c. using a 25' x 5/8" aluminium column packed with 15% silicone oil on 60/80 Diatomite CAW/DMC. The column temperature was 35° and the retention volume was 3072 cm^3. The pure liquid gave M^+ 101.0922 ($^{13}C^{12}C_5H_{12}O$ requires M^+ 101.0922). The ^{1}H n.m.r. spectrum included signals at 0.93 (d, $^3J_{HH}$ 6.13 Hz; 4-$^{12}CH_3$) and 0.92 (dd, $^3J_{HH}$ 6.14 Hz, $^1J_{CH}$ 124.51 Hz; 4-$^{13}CH_3$). The ^{13}C n.m.r. spectrum (62.90 MHz, CD_2Cl_2, 294 K) showed signals at δ68.31 (d, $^3J_{CC}$ 4.26 Hz; 2,6-C), 35.54 (d, $^2J_{CC}$ 0.81 Hz; 3,5-C), 30.49 (d, $^1J_{CC}$ 36.06 Hz; 4-C) and 22.41 (s; CH_3). The ^{13}C n.m.r. spectrum at 160 K showed signals for the major conformation (Me equatorial) at δ68.23 (d, ^3J 3.42 Hz; 2,6-C), 34.87 (bs; 3,5-C), 30.12 (d, ^1J 36.26 Hz; 4-C) and 22.74 (s; CH_3). The minor conformation (Me axial) showed a signal at δ16.75 (s; CH_3).

Determination of Thermodynamic Parameters

(a) Direct Determination of Equilibrium Constants at 140-175 K.

The precautions necessary to obtain quantitative assessment of ^{13}C n.m.r. spectra have been described earlier.[70] Equilibrium constants were determined from careful and repeated measurements of the relative areas of signals due to structurally identical carbons in the two conformations. Portions of spectra were expanded to 5 or 10 Hz/cm prior to instrumental integration and/or hand planimetry. Measurements were repeated at least 5 times and the results were averaged.

(b) Acid-catalysed equilibration of 2-substituted-4-methyltetrahydropyrans.

To a mixture of $CFCl_3/CDCl_3$ (85/15, v/v) (10 cm^3) contained in a graduated flask was added the tetrahydropyran (0.25 g.) and 4-methylbenzenesulphonic acid (0.01 g.). The firmly stoppered flask was stored in a cold room maintained at 273 K. An identical mixture was stored in a graduated flask in a freezer maintained at 245 K. At intervals during 3 months a portion (about 1 cm^3) of the solution was removed, quenched by addition of anhydrous sodium carbonate (0.10 g.) and filtered. The cis/trans composition of the filtrate was determined by careful and repeated integration of the signals due to 2-H protons ("anomeric") in the ^1H n.m.r. spectrum recorded at 250 MHz. The results were averaged. Mixtures of cis- and trans-2-chloro-4-methyltetrahydropyran underwent spontaneous equilibration and were analysed (via integration of their 2-H signals in the ^1H n.m.r. spectrum) in the n.m.r. probe set at temperatures between 253 K and 324 K. Samples for temperatures between 290 and 324 K were equilibrated in the probe for 1 hour; samples for temperatures between 260 and 290 K were equilibrated in the probe for 1½ hours. The sample for 253 K was allowed to equilibrate overnight in a freezer at 252 K before transfer to the probe set at 253 K.

(c) Equilibrium constants from line-broadening experiments.

^{13}C n.m.r. spectra were recorded over 10,000 Hz, using 32 K or 64 K data points, at a series of temperatures in the range (normally 165-215 K) which included the maximum line-broadening for all the carbon signals. The free induction decays were transformed without prior line-broadening and the half-intensity widths ($W_{\frac{1}{2}}$) of each signal, including that of the reference TMS (W_o) were measured on portions of spectra expanded to 1,2 or 5 Hz/cm. For each signal, a plot of ($W_{\frac{1}{2}}-W_o$) against temperature gave a parabola, from which both the maximum broadness, and the corresponding temperature, were obtained. Proportions of conformations were calculated by application of one of the two Sorensen equations,[50] chosen as to whether the approximate equilibrium constant was greater or less than 10.

Data Treatment

The foregoing methods gave averaged values (K) of the equilibrium constants as a function of temperature (T). The data were then treated in two ways.

Method (A). Hand-drawn plots were made of lnK against T^{-1} and the best straight line was drawn by eye. Since $\ln K = -\Delta H^o/RT+\Delta S^o/R$, the slope gives ΔH^o and the intercept gives ΔS^o.

In methods (a) and (b) (see above), the r.m.s. deviations from measurements of steps in repeated integral traces and/or repeated planimeter readings on signals were translated into maximum and minimum values for K. In method (c), estimates were made of the maximum and minimum values for $W_{\frac{1}{2}}$ and W_o, and extremes of $(W_{\frac{1}{2}}-W_o)$ were separately plotted against temperature. The (two) resulting parabola gave maximum and minimum possible values for maximum $(W_{\frac{1}{2}}-W_o)$, and hence maximum and minimum values for K.

Maximum and minimum values for K, taken in conjunction with maximum and minimum values for T, allowed two 'extreme' straight lines to be drawn in the plot of lnK against T^{-1}; from these were obtained the errors in ΔH^o and ΔS^o.

Method (B). The best-fit straight lines for the plot of lnK against T^{-1} was obtained using a linear regression program on a Commodore CBM model 4032 computer. The program gave values for ΔH^o and ΔS^o, together with standard errors in ΔH^o and ΔS^o.

1. [Me-^{13}C]-4-Methyltetrahydropyran (34 $\rightleftarrows$ 35) in CD_2Cl_2.

Equilibrium constant K = 35/34 = e/a

T/K	145[a]	148[a]	152[a]	156[a]	160[a]	206[b]
K	584.2	525.0	454.3	403.7	348.2	87.86

[a] by direct integration

[b] from line broadening study, in which the maximum $(W_{\frac{1}{2}}-W_o)$ for the CH_3 carbon was 4.25 Hz.

The best-fit straight line given by the linear regression program [method (B)] produced $\Delta H^o_{a\rightarrow e}$ as -1.86 ± 0.05 kcal mol^{-1} and $\Delta S^o_{a\rightarrow e}$ as -0.07 ± 0.32 cal K^{-1} mol^{-1}.

2. (a) 2-Methoxytetrahydropyran (10 $\rightleftarrows$ 11) in $CFCl_3/CDCl_3$.

Equilibrium constant K = 11/10 = e/a

T/K	143	150	160	165
K	0.257	0.260	0.257	0.248

(b) cis- and trans-2-methoxy-4-methyltetrahydropyran (18 $\rightleftarrows$ 19) in $CFCl_3/CDCl_3$.

Equilibrium constant K = 19/18 = e/a

T/K	245	273
K	0.266	0.263

Treatment (A) gave $\Delta H^o_{a\rightarrow e}$ (OCH_3) as 0.03 ± 0.06 kcal mol^{-1}
and $\Delta S^o_{a\rightarrow e}$ (OCH_3) as -2.52 ± 0.43 cal K^{-1} mol^{-1};

Treatment (B) gave $\Delta H^o_{a\rightarrow e}$ (OCH_3) as 0.03 ± 0.01 kcal mol^{-1}
and $\Delta S^o_{a\rightarrow e}$ (OCH_3) as -2.51 ± 0.09 cal K^{-1} mol^{-1}.

3. (a) 2-Hydroxytetrahydropyran (12 $\rightleftarrows$ 13) in $CFCl_3/CDCl_3$

Equilibrium constant K = 13/12 = e/a

T/K	169	172
K	1.957	2.008

(b) cis- *and* trans-2-*hydroxy*-4-*methyltetrahydropyran* (22 $\rightleftarrows$ 23) *in* *$CFCl_3/CDCl_3$*.

Equilibrium constant K = 23/22 = e/a

T/K	250	270
K	1.05	0.98

Treatment (A) gave $\Delta H^o_{a\rightarrow e}$ (OH) as $-0.63\underline{+}0.07$ kcal mol^{-1}
and $\Delta S^o_{a\rightarrow e}$ (OH) as $-2.50\underline{+}0.30$ cal K^{-1} mol^{-1}

Treatment (B) gave $\Delta H^o_{a\rightarrow e}$ (OH) as $-0.66\underline{+}0.08$ kcal mol^{-1}
and $\Delta S^o_{a\rightarrow e}$ (OH) as $-2.50\underline{+}0.40$ cal K^{-1} mol^{-1}.

4. (a) trans-2-*Methylamino*-4-*methyltetrahydropyran* (26 $\rightleftarrows$ 28) *in $CFCl_3/CDCl_3$*. The areas of 6-C signals at 61.4 ppm and 57.7 ppm gave 28/26 = 0.578 at 174 K, equivalent to a $\Delta G^o_{26\rightarrow 28}$ value of 0.19 kcal mol^{-1}. Since $\Delta G^o_{a\rightarrow e}$ (Me) is −1.85 kcal mol^{-1} at 174 K, it follows that $\Delta G^o_{14\rightarrow 15}(NHCH_3)$ is −1.66 kcal mol^{-1}, equivalent to K = 15/14 = 121.7 at 174 K.

(b) 2-*Methylaminotetrahydropyran* (14 $\rightleftarrows$ 15) *in $CFCl_3/CDCl_3$*. From a line-broadening study of the ^{13}C signals of (14 $\rightleftarrows$ 15) in the range 160-210 K, the maximum $(W_{\frac{1}{2}}-W_o)$ value for 6-C was 7.50 Hz at 191 K. The accurate Sorensen equation[51] then gave 15/14 = 74.2 at 191 K.

(c) cis- *and* trans-2-*Methylamino*-4-*methyltetrahydropyran* (26 $\rightleftarrows$ 27 $\rightleftarrows$ 28) *in* *$CFCl_3/CDCl_3$*.

Observed K = cis/trans = 27/(26+28)

Direct integration on samples equilibrated for > 60 days at 250 K and 270 K gave values of K from which values of K_2 and K_1 were calculated by the method described in the discussion.

Summary:-

Equilibrium Constant	250 K	270 K
K = 27/(26+28)	15.12	12.36
K_2 = 28/26	0.589	0.665
K_1 = 27/26 $\simeq$ 15/14	24.02	20.59

Method (A) gave $\Delta H^o_{a\rightarrow e}$ $(NHCH_3)$ = $-1.75\underline{+}0.10$ kcal mol^{-1}
and $\Delta S^o_{a\rightarrow e}$ $(NHCH_3)$ = $-0.60\underline{+}0.40$ cal K^{-1} mol^{-1}

Method (B) gave $\Delta H^o_{a\rightarrow e}$ $(NHCH_3)$ = $-1.75\underline{+}0.07$ kcal mol^{-1}
and $\Delta S^o_{a\rightarrow e}$ $(NHCH_3)$ = $-0.57\underline{+}0.33$ cal K^{-1} mol^{-1}

5. cis- and trans-2-Chloro-4-methyltetrahydropyran ($30 \rightleftarrows 31$) in $CDCl_3$.

Equilibrium constant K = cis/trans = 31/30

T/K	253	267	276.5	293.5	296.5	307	316	324
10^{-2} K	1.538	1.729	1.990	2.480	2.591	2.835	2.925	3.093

Method (A) gave $\Delta H^o_{a\rightarrow e}$ (Cl) = 1.67 ± 0.26 kcal mol^{-1}
and $\Delta S^o_{a\rightarrow e}$ (Cl) = -1.69 ± 0.90 cal K^{-1} mol^{-1}

Method (B) gave $\Delta H^o_{a\rightarrow e}$ (Cl) = 1.71 ± 0.09 kcal mol^{-1}
and $\Delta S^o_{a\rightarrow e}$ (Cl) = -1.59 ± 0.30 cal K^{-1} mol^{-1}

Acknowledgements: We are grateful to Professor R.W. Franck for a valuable suggestion. We thank the S.E.R.C. for the award of a studentship to S.A.R. and the University of Salah Al-deen for the award of a scholarship to K.A.K. We thank R.U. Lemieux for stimulating discussions.

REFERENCES

1. R.U. Lemieux and N.J. Chu, Abstracts, 133rd Meeting of the American Chemical Society, San Francisco, April 1958, 31N; R.U. Lemieux, in 'Molecular Rearrangements' Part 2, ed. P.de Mayo, Interscience, New York, 1964.
2. A.J. Kirby, 'The Anomeric Effect and Related Stereoelectronic Effects at Oxygen', Springer, Berlin, 1983.
3. P. Deslongchamps, 'Stereoelectronic Effects in Organic Chemistry', Pergamon Press, Oxford, 1983.
4. W.A. Szarek and D. Horton (eds.), 'Anomeric Effect, Origin and Consequences', American Chemical Society, Washington, 1979 (ACS Symposium Series No.87).
5. C.B. Anderson and D.T. Sepp, Tetrahedron, 1968, 24, 1707.
6. E.L. Eliel and C.A. Giza, J.Org.Chem., 1968, 33, 3754.
7. E.L. Eliel, K.D. Hargrave, K.M. Pietrusiewicz and M. Manoharan, J.Am.Chem.Soc., 1982, 104, 3635.
8. R.W. Franck, Tetrahedron, 1983, 39, 3251.
9. H. Booth, T.B. Grindley and K.A. Khedhair, J.Chem.Soc., Chem.Commun., 1982, 1047.
10. H. Booth and K.A. Khedhair, J.Chem.Soc., Chem.Commun., 1985, 467.
11. R.U. Lemieux, A.A. Pavia, J.-C. Martin and K.A. Watanabe, Can.J.Chem., 1969, 47, 4427.
12. R.U. Lemieux and S. Koto, Tetrahedron, 1974, 30, 1933.
13. G.A. Jeffrey and R. Taylor, J.Comput.Chem., 1980, 1, 99 and references therein.
14. A.J. Briggs, R. Glenn, P.G. Jones, A.J. Kirby and P. Ramaswamy, J.Am.Chem. Soc., 1984, 106, 6200, and references therein.
15. A. Cosse-Barbi and J.E. Dubois, J.Am.Chem.Soc., 1987, 109, 1503.
16. H. Booth, K.A. Khedhair and S.A. Readshaw, to be published.
17. R.U. Lemieux, Ann.N.Y. Acad.Sci., 1973, 222, 915.
18. R.U. Lemieux and J.-C. Martin, Carbohydrate Research, 1970, 13, 139.
19. P.E. Hansen, Prog.Nucl.Magn.Reson.Spectrosc., 1981, 14, 175.
20. J.L. Marshall, 'Carbon-Carbon and Carbon-Proton NMR Couplings,' Verlag Chemie Internat., Florida, 1983.

21. A.H. Haines and M.S. Shandiz, J.Chem.Soc., Perkin Trans.I, 1981, 1671.
22. V.A. Chertkov and N.M. Sergeyev, J.Am.Chem.Soc., 1977, 99, 6750.
23. B. Fuchs, L. Schleifer and E. Tartakovsky, Nouveau Journal de Chimie, 1984, 8, 275.
24. R.U. Lemieux, K. Bock, L.T.J. Delbaere, S. Koto and V.S. Rao, Canad.J.Chem., 1980, 58, 631.
25. H. Thogersen, R.U. Lemieux, K. Bock and B. Meyer, Canad.J.Chem., 1982, 60, 44.
26. K. Bock, Pure Applied Chem., 1983, 55, 605.
27. A.J. de Hoog, H.R. Buys, C. Altona and E. Havinga, Tetrahedron, 1969, 25, 3365.
28. J.T. Edward, Chem. and Ind., 1955, 1102.
29. M.A. Kabayama and D. Patterson, Can.J.Chem., 1958, 36, 563.
30. R.O. Hutchins, L.D. Kopp and E.L. Eliel, J.Am.Chem.Soc., 1968, 90, 7174.
31. C. Altona, Ph.D. dissertation, Leiden, 1964.
32. C. Romers, C. Altona, H.R. Buys and E. Havinga, Top.Stereochemistry, 1969, 69, 1.
33. S. Wolfe, M.-H. Whangbo and D.J. Mitchell, Carbohydrate Research, 1979, 69, 1.
34. S. David, O. Eisenstein, W.J. Hehre, L. Salem and R. Hoffmann, J.Am.Chem.Soc., 1973, 95, 3806.
35. N.D. Epiotis, R.L. Yates, J.R. Larson, C.R. Kirmaier and F. Bernardi, J.Am.Chem.Soc., 1977, 99, 8379.
36. R.U. Lemieux, Personal communication, June 1983.
37. cf. P. Deslongchamps, D.D. Rowan, N. Pothier, T. Sauve and J.K. Saunders, Can.J.Chem., 1981, 59, 1105.
38. F.R. Jensen and C.H. Bushweller, Adv.Alicyclic Chem., 1971, 3, 139.
39. J.C. Celotti, J. Reisse and G. Chiurdoglu, Tetrahedron, 1966, 22, 2249.
40. G.W. Buchanan and A.R. McCanville, Can.J.Chem., 1972, 50, 1965.
41. D. Hofner, S.A. Lesko and G. Binsch, Org.Magn.Reson., 1978, 11, 179.
42. e.g. B. Fuchs, A. Ellencweig, E. Tartakovsky and P. Aped, Angew.Chem. Int.Ed., 1986, 25, 287; P. Aped, Y. Apelvig, A. Ellencweig, B. Fuchs, I. Goldberg, M. Karni and E. Tartakovsky, J.Am.Chem.Soc., 1987, 109, 1486; E. Giralt, M.A. Pericas and A. Riera, Tetrahedron, 1983, 39, 3959; M.A. Pericas, A. Riera and Giralt, Tetrahedron, 1985, 41, 3785.
43. G.O. Pierson and O.A. Runquist, J.Org.Chem., 1968, 33, 2572.
44. C.B. Anderson and D.T. Sepp, Chem. and Ind., 1964, 2054.
45. A.J. de Hoog, Org.Magn.Reson., 1974, 6, 233.
46. E.L. Eliel, M. Manoharan, K.M. Pietrusiewicz and K.D. Hargrave, Org. Magn.Reson., 1983, 21, 94.
47. F.W. Wehrli and T. Wirthlin, "Interpretation of Carbon-13 NMR Spectra," Heyden, London, 1976.
48. N. Pothier, D.D. Rowan, P. Deslongchamps and J.K. Saunders, Can.J.Chem., 1981, 59, 1132.
49. C.T. Bishop and F.P. Cooper, Can.J.Chem., 1962, 40, 224.
50. W.E. Parham and H.E. Holmquist, J.Am.Chem.Soc., 1951, 73, 913.
51. N. Okazawa and T.S. Sorensen, Can.J.Chem., 1978, 56, 2737.
52. F.A.L. Anet and V.J. Basus, J.Magn.Reson., 1978, 22, 339.
53. H. Booth and J.R. Everett, J.Chem.Soc., Perkin Trans.II, 1980, 255.
54. I. Tvaroska and T. Kozar, Theor.Chim.Acta, 1979, 53, 9; J.Am.Chem.Soc., 1980, 102, 6929; Carbohydrate Research, 1981, 90, 173.
55. N.L. Allinger and D.Y. Chung, J.Am.Chem.Soc., 1976, 98, 6798.

56. J.-P. Praly and R.U. Lemieux, Can.J.Chem., 1987, 65, 213.

57. L.E. Schniepp and H.H. Geller, J.Am.Chem.Soc., 1946, 68, 1646.

58. C.D. Hurd and W.H. Saunders, Jnr., J.Am.Chem.Soc., 1952, 74, 5324.

59. A. El-Kafrawy and R. Perraud, Compt.Rend.Acad.Sci.Ser.C, 1975, 280, 1219.

60. B. Capon and D. Thacker, J.Chem.Soc., (B), 1967, 1010.

61. J. Reisse, J.C. Celotti, D. Zimmermann and G. Chiurdoglu, Tetrahedron Letters, 1964, 2145.

62. J. Tesse, C. Glacet and D. Couturier, Compt.Rend.Acad.Sci.Ser.C, 1975, 280, 1525.

63. D. Barbry, D. Couturier and G. Ricart, J.Chem.Soc., Perkin Trans.II, 1982, 249.

64. G.E. Booth and R.J. Ouellette, J.Org.Chem., 1966, 31, 544.

65. C.B. Anderson and D.T. Sepp, J.Org.Chem., 1967, 32, 607.

66. H.-J. Schneider and V. Hoppen, Tetrahedron Letters, 1974, 579.

67. G.F. Woods and D.N. Kramer, J.Am.Chem.Soc., 1947, 69, 2246.

68. R. Paul, Compt.Rend.Acad.Sci., 1933, 197, 1652.

69. G.F. Woods, Org.Synth., 1947, 27, 43.

70. C. Glacet and D. Veron, Bull.Soc.Chim.Fr., 1965, 1789.

71. H. Booth and M.L. Jozefowicz, J.Chem.Soc., Perkin Trans.II, 1976, 895.