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EXPERIMENTAL STUDIES OF THE ANOMERIC EFFECT. PART IV[1]. CONFORMATIONAL EQUILIBRIA DUE TO RING INVERSION IN TETRAHYDROPYRANS SUBSTITUTED AT POSITION 2 BY THE GROUPS ETHOXY, 2'-FLUOROETHOXY, 2',2,'-DIFLUOROETHOXY, AND 2',2',2'-TRIFLUOROETHOXY

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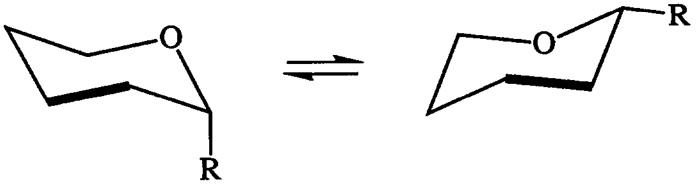
Abstract - Equilibrium constants (K) for ring inversion equilibria in 2-(RO)-tetrahydropyrans (R=Et, CH_2CH_2F, CH_2CHF_2, CH_2CF_3) have been determined from ^{13}C nmr spectra recorded at 145-160K in CD_2Cl_2 and $CFCl_3/CDCl_3$ (85/15 by volume). Additional values of K were obtained at 250-270K from the acid-catalysed equilibration of cis- and trans-2-(RO)-4-methyl tetrahydropyran (R as above). Plots of lnK against T^{-1} gave values for $\Delta H°_{a\to e}$ of -0.26, -0.12, -0.05 and 0.13 kcal mol^{-1} for R=Et, CH_2CH_2F, CH_2CHF_2 and CH_2CF_3, respectively, in CD_2Cl_2. The corresponding values of $\Delta H°_{a\to e}$ for $CFCl_3/CDCl_3$ as solvent were -0.58, -0.15, -0.07 and 0.21 kcal mol^{-1}, respectively. The derived $\Delta S°_{a\to e}$ values were -2.33 , -2.22, -2.25 and -2.24 cal $K^{-1}mol^{-1}$, respectively, in CD_2Cl_2 and -4.65, -3.37, -3.30 and -3.03 cal $K^{-1}mol^{-1}$, respectively, in $CFCl_3/CDCl_3$.

The trends in $\Delta H°$ values are attributed to modifications of anti-periplanar n-σ* stabilisation (itself partly responsible for endo- and exo- anomeric effects) which occur as the number of electronegative fluorine substituents increases. For all substituents, axial conformations are the most abundant in the temperature range 120K-∞. However, this finding is a consequence of the higher entropy of axial conformations; in at least two cases (R=Et and CH_2CH_2F) it is the equatorial conformation which has the lower enthalpy. The results confirm the importance of studying conformational equilibria over a wide range of temperature.

The positions of equilibria ($1 \rightleftharpoons 2$) in tetrahydropyrans substituted at position 2 by electronegative substituents R is dependent on both steric effects and polar effects, of which the latter are expected to be sensitive to the nature of the solvent. Although 'polar effects' include dipole – dipole interactions and destabilising lone pair - lone pair repulsions, a more important effect is believed to be a stabilising overlap of heteroatom lone pair with the antibonding orbital of an antiperiplanar



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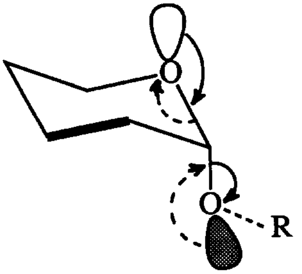
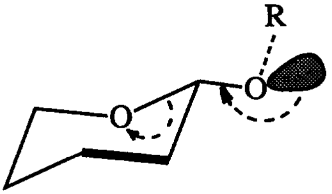
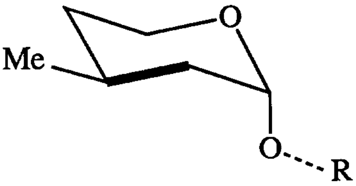


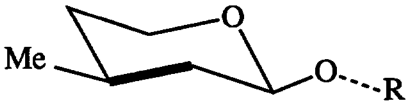
(3; R = CH_2CH_3)
(5; R = CH_2CH_2F)
(7; R = CH_2CHF_2)
(9; R = CH_2CF_3)



(4; R = CH_2CH_3)
(6; R = CH_2CH_2F)
(8; R = CH_2CHF_2)
(10; R = CH_2CF_3)



(11; R = CH_2CH_3)
(13; R = CH_2CH_2F)
(15; R = CH_2CHF_2)
(17; R = CH_2CF_3)



(12; R = CH_2CH_3)
(14; R = CH_2CH_2F)
(16; R = CH_2CHF_2)
(18; R = CH_2CF_3)

C-heteroatom bond.[2] In the specific case of the equatorial conformation (4) of a 2-ethoxytetrahydropyran ($3 \rightleftharpoons 4$), the rotamer illustrated is the preferred rotamer,[1] and is stabilised only by an exo-anomeric effect (broken curved arrows). In the preferred rotamer (3) of the axial conformation, the exo-anomeric effect[3] is now in competition with an endo-anomeric effect[3] (solid curved arrows). The relative magnitudes of the endo- and exo-anomeric effects are not known at present. Experimental work designed to probe the proposed theory was described earlier[4] and support for the theory was derived from determinations at variable temperature of the conformational equilibria in tetrahydropyrans substituted at 2 by the groups Cl, OMe and NHMe[4]. Unfortunately these substituents differ not only in electronegativity but also in their steric effects.

In the present investigation we have studied a group of 2-substituted tetrahydropyrans ($1 \rightleftharpoons 2$) in which R is ethoxy, 2'-fluorethoxy, 2',2',-difluoroethoxy, and 2',2',2',-trifluoroethoxy. In this series, steric effects are essentially constant and equilibrium constants are expected to depend very largely on polar effects related to the degree of substitution of hydrogen by fluorine. As the number of electron-attracting fluorine atoms is increased, the increase in the endo-anomeric effect is accompanied by a decrease in the exo-anomeric effect, thus leading us to expect a gradually increasing preference, in $\Delta H°$ terms, for the axial conformation. Two relatively non-polar solvents were employed: CD_2Cl_2 (ε8.9) and a mixture of 85% (by volume) $CFCl_3$(ε2.3) and 15% $CDCl_3$(ε4.8).

The required compounds ($3 \rightleftharpoons 4$), ($5 \rightleftharpoons 6$), ($7 \rightleftharpoons 8$) and ($9 \rightleftharpoons 10$), and their conformationally homogeneous 4-methyl derivatives (11—18), were synthesised by standard methods (see Experimental). ^{1}H nmr spectra details are reported in the Experimental section. ^{13}C nmr chemical shifts, summarised in Table I (CD_2Cl_2 as solvent) were recorded for 2-substituted tetrahydropyrans at room temperature and also at 145-160K, where slow ring inversion allows the observation of both axial and equatorial conformations. The ^{13}C chemical shifts for $CFCl_3$/$CDCl_3$ as solvent are summarised in Table 2. Carbon-fluorine coupling constants are assembled in Table 3. In the ^{13}C nmr spectrum of 2-ethoxytetrahydropyran ($3 \rightleftharpoons 4$) at 294K, the signals for 6-C and 1'-C were close in shift, but a ID INADEQUATE experiment allowed definite assignments; the relevant values of ($^1J_{CC}$)are given as footnotes in Table 1. ^{19}F nmr spectra were recorded for the fluorine-containing tetrahydropyrans, but temperatures around 150K failed to give complete separation of ^{19}F signals due to axial and equatorial conformations.

Analysis of the ^{13}C nmr spectra at one or two temperatures in the range 145-160K was carried out by repeated integration, giving equilibrium constants K(=e/a) which are reported in the Experimental section. Below

155K, the number of temperatures at which equilibrium constants could be determined accurately was limited by the onset of severe line broadening, particularly for solutions in $CFCl_3/CDCl_3$.

Table 1 Carbon-13 chemical shifts (δ ppm from Me_4Si) at 62.9MHz for 2-substituted tetrahydropyrans in CD_2Cl_2

Compound	T/K	2-C	3-C	4-C	5-C	6-C	1'-C	2'-C
$3 \rightleftharpoons 4$	294	99.06[a]	31.41[b]	20.18[c]	26.16[d]	62.50[e]	63.04[f]	15.42[f]
3	156	96.93	30.30	18.28	25.80	59.73	62.61	15.69
4	156	102.34	31.96	22.82	25.80	66.64	64.43	15.69
$5 \rightleftharpoons 6$	294	99.47	31.07	19.87	25.99	62.51	66.89	83.56
5	150	96.82	29.82	17.90	25.51	69.77	65.93	83.91
6	150	102.05	31.52	22.48	25.51	66.58	67.66	83.91
$7 \rightleftharpoons 8$	294	99.94	30.81	19.63	25.85	62.65	67.19	115.47
7	160	97.47	26.67	17.71	25.38	60.07	65-68[g]	115.1
8	160	102.89	31.24	22.36	25.38	← 65-68[g] →		115.1
$9 \rightleftharpoons 10$	294	99.22	30.40	19.09	25.70	62.31	64.43	124.91
9	152	97.24	29.42	17.61	25.32	60.41	63.31	124.75
10	152	102.26	31.22	22.32	25.32	66.94	h	124.75

a $^1J_{cc}$ 43.33 Hz

b $^1J_{cc}$ 43.32, 32.78 Hz

c $^1J_{cc}$ 32.78 Hz

d $^1J_{cc}$ 35.04, 32.78 Hz

e $^1J_{cc}$ 35.41 Hz

f $^1J_{cc}$ 38.81 Hz

g not resolved

h not seen clearly

Table 2 Carbon-13 chemical shifts (δ/ppm from Me_4Si) at 62.91 MHz for 2-substituted tetrahydropyrans in $CFCl_3/CDCl_3$(85/15, v/v).

Compound	T/K	2-C	3-C	4-C	5-C	6-C	1'-C	2'-C
$3 \rightleftharpoons 4$	270	98.21	30.94	19.55	25.95	61.45	62.65	15.33
3	155	96.54	29.86	17.83	25.37	59.37	62.26	15.35
4	155	101.95	31.56	22.45	25.37	66.40	64.30	15.35
$5 \rightleftharpoons 6$	270	98.52	30.57	19.16	25.77	61.39	66.47	82.63
5	154	96.68	29.53	17.56	25.20	59.51	65.73	82.71
6	154	102.03	31.26	22.16	25.20	66.52	67.44	82.71
$7 \rightleftharpoons 8$	270	98.96	30.34	18.96	25.61	61.53	66.91	114.17
7	152	97.22	29.36	17.39	25.06	59.77	65.84	114.22
8	152	102.77	31.37	22.52	25.06	$\leftarrow$ 65.4-66.3[a] $\rightarrow$		114.22
$9 \rightleftharpoons 10$	270	98.36	30.05	18.52	25.58	61.31	64.12	124.49
9	155	96.98	29.28	17.32	25.11	60.01	63.31	124.17
10	155	102[b]	31[b]	22[b]	25[b]	66[b]	c	124[b]

a not resolved

b broad signal

c not seen clearly

Table 3 Carbon-fluorine coupling constants (±0.6Hz) in 2'-fluoroethoxy-, 2',2'-difluoroethoxy- and 2',2',2'-trifluoroethoxy-tetrahydropyrans.

Solvent	CD_2Cl_2			$CFCl_3/CDCl_3$		
Compound	T/K	$^1J_{CF}$	$^2J_{CF}$	T/K	$^1J_{CF}$	$^2J_{CF}$
$5 \rightleftharpoons 6$	294	167.9	20.5	270	170.3	19.8
5	150	166.4	17.4	154	169.3	16.8
6	150	166.4	16.5	154	169.3	a
$7 \rightleftharpoons 8$	294	240.1	28.0	270	240.6	28.7
7	160	239.3	a	152	240.1	28.6
8	160	239.3	a	152	240.1	a
$9 \rightleftharpoons 10$	294	277.9	34.2	270	277.3	34.8
9	152	278.7	33.2	155	277.4	33.6
10	152	278.7	b	155	c	c

a not resolved

b not clear due to signal overlap

c not clear due to poor signal to noise

Values of equilibrium constants at 2 or 3 temperatures in the range 250-27 also reported in the Experimental section, were obtained by analysis of the mixtures of (11) and (12) produced by the acid-catalysed equilibrium of 2-ethoxy-4-methyltetrahydropyran in both CD_2Cl_2 and $CFCl_3/CDCl_3$. The corresponding equilibrium constants for (13 ⇌ 14), (15 ⇌ 16) and (17 ⇌ 18) were similarly obtained, and the equilibrium constants from the equilibration experiments were combined with those from the low temperature studies to derive the thermodynamic parameters for (1 ⇌ 2). It was assumed, as before (see ref.4, p.4705), that the ring-inverted conformations of (11)-(18) are insignificantly populated at 240-280K. The values of $\Delta H°_{1 \rightarrow 2}$ ($= \Delta H°_{a \rightarrow e}$) and $\Delta S°_{1 \rightarrow 2}$ ($= \Delta S°_{a \rightarrow e}$) for the equilibria (1 ⇌ 2; R=OEt, OCH_2CH_2F, OCH_2CHF_2 and OCH_2CF_3) were derived from the plots of lnK against T^{-1} and are assembled in Table 4.

Table 4 Thermodynamic Parameters for (1 ⇌ 2) ($\Delta H°$ in kcal mol^{-1}; $\Delta S°$ in cal K^{-1} mol^{-1}).

R	CD_2Cl_2		$CFCl_3/CDCl_3$	
	$\Delta H°_{1 \rightarrow 2}$	$\Delta S°_{1 \rightarrow 2}$	$\Delta H°_{1 \rightarrow 2}$	$\Delta S°_{1 \rightarrow 2}$
OCH_2CH_3	-0.26(±0.03)	-2.33(±0.08)	-0.58 (±0.03)	-4.65(±0.15)
OCH_2CH_2F	-0.12(±0.03)	-2.22(±0.16)	-0.15(±0.02)	-3.37(±0.09)
OCH_2CHF_2	-0.05(±0.04)	-2.25(±0.21)	-0.07(±0.03)	-3.30(±0.15)
OCH_2CF_3	0.13(±0.03)	-2.24(±0.14)	0.21(±0.03)	-3.03(±0.15)

The change in $\Delta H°_{1 \rightarrow 2}$ with alteration in fluorine substitution is small when error limits are taken into account. However, for both solvents used, the trend in $\Delta H°_{1 \rightarrow 2}$ along the series (3 ⇌ 4) to (9 ⇌ 10) is unmistakable. The gradually increasing stability of the axial conformation (1), in $\Delta H°$ terms, as the number of fluorine atoms increases, is exactly in line with the earlier prediction (see above) based on a consideration of endo- and exo-anomeric effects. It is significant that at all reasonable temperatures the four molecules examined give equilibria which are clearly biased in favour of the axial conformation; nevertheless, 3 of the molecules (R=OEt, OCH_2CH_2F, OCH_2CHF_2) favour the equatorial conformation in $\Delta H°$ terms. In these examples, the entropy term is crucial and serves to warn us that the measurement of a conformational equilibrium at a single temperature is often misleading. For a given substituent, $\Delta H°_{1 \rightarrow 2}$ is only slightly affected by change of solvent from CD_2Cl_2 to $CFCl_3/CDCl_3$; the decrease in dielectric constant which accompanies this change is possibly too small to promote a significant change in $\Delta H°$.

For all substituents, $\Delta S°_{1\rightarrow 2}$ values are negative, i.e. equatorial conformations have lower entropy than the corresponding axial conformations. This finding contrasts with the situation for ethyl and isopropyl substituents in cyclohexanes, where it is the axial conformations which have the lower entropies.[5,6] However, it is significant that the careful measurements of Binsch and coworkers[7] showed that the equatorial conformation of trideuteromethoxycyclohexane has lower entropy than its axial counterpart.

As shown in Table 4, there is a significant decrease in $\Delta S°_{1\rightarrow 2}$, for all substituents, on changing the solvent from CD_2Cl_2 to $CFCl_3/CDCl_3$. Further studies are in progress to decide whether this movement is caused by a relatively stronger complexation of the oxygen atom(s) of the equatorial conformation with $CDCl_3$, which is a more powerful donor of D^+ than CD_2Cl_2 (cf[8,9]).

EXPERIMENTAL

General - see Part 1[4]

2,2-Difluoroethanol - To 2,2-difluoroacetic acid (5.0g, 52mmol), dissolved in ether (30 cm^3), was added borane methyl sulphide (6 cm^3, 62 mmol), dropwise over 1 hour, at room temperature, with stirring. When addition was complete, stirring was continued for 4 hours. The mixture was treated cautiously with water (6 cm^3) and filtered, after which the precipitate was washed with ether. The combined filtrates were dried ($MgSO_4$), filtered and fractionally distilled, giving 2,2-difluoroethanol (2.34g, 55%) as a colourless liquid, b.p. 92-5° at 760 mm Hg (lit,[10] 92-94°). The ^1H nmr spectrum (90 MHz, $CDCl_3$) showed signals at δ 5.87 (tt, $^2J_{HF}$ 57Hz, $^3J_{HH}$ 4 Hz; CHF_2), 4.78(td, $^3J_{HF}$ 14.5 Hz, $^3J_{HH}$ 4 Hz; OCH_2) and 3.65 (s;OH).

2-(2'-Fluoroethoxy)tetrahydropyran - To 3,4-dihydro-2H-pyran (3.20g) was added concentrated hydrochloric acid (0.05 cm^3), followed by 2-fluoroethanol (2.40g), when the mixture spontaneously came to the boil. The mixture was allowed to stand for 3 hours, treated with KOH pellets (1g) poured into water (15 cm^3) and extracted with ether (3x20 cm^3). The combined ether extracts were dried ($MgSO_4$), filtered and distilled, giving 2-(2'-fluoroethoxy)-tetrahydropyran (2.87g, 52%) as a colourless liquid, b.p. 74-75° at 25 mm Hg (Found: M^+ 148.0885.$C_7H_{13}O_2F$ requires 148.0898). The ^1H nmr spectrum (250 MHz, $CDCl_3$) showed signals at δ4.72 (partly resolved t, $w_{\frac{1}{2}}$ 6Hz; 2-H), 4.62 (dt, $^2H_{HF}$ 48 Hz, $^3J_{HH}$ 8.5 Hz; CH_2F), 4.3-4.4 (m; both of 1'-H and both of 6-H), 2.05-1.40 (m; 3,4,5-H). ^{13}C nmr spectral data are summarised in Tables 1 and 2. The ^{19}F nmr spectrum (235.4 MHz; $CFCl_3/CDCl_3$) gave a triplet ($^2J_{HF}\sim$ 48 Hz) of triplets (mean $^3J_{HF}\sim$ 29 Hz) at 223.54 ppm upfield from $CFCl_3$.

2-(2',2'-Difluoroethoxy)tetrahydropyran - The reaction of 2,2-difluoroethanol (1.97g) with 3,4-dihydro-2H-pyran (2.02g) was carried out as described in the preceding preparation. The product, 2-(2',2'-difluoroethoxy) tetrahydropyran (1.91g, 48%) was a colourless liquid, b.p. 62-66° at 19 mm Hg (Found: M^+ 166.0791. $C_7H_{12}O_2F_2$ requires M 166.0804). The ^1H nmr spectrum (250 MHz, $CDCl_3$) showed signals at δ 5.94 (tdd, $^2J_{HF}$ 55.7 Hz, doublet separations 3.6 Hz and 4.9 Hz; CHF_2), 4.69 (partly resolved t, $w_{\frac{1}{2}}$ 6.2 Hz; 2-H), 3.88(ddt; $^2J_{H_AH_B}$ 11.70 Hz, $^3J_{H_AH}$ 3.65 Hz, $^3J_{H_BH}$ 15.15 Hz; H_A of OCH_AH_B), 3.69 (ddt; $^2J_{H_AH_B}$ 11.70 Hz, $^3J_{H_BH}$ 4.89 Hz, $^3J_{H_BF}$ 13.16 JHz; H_B of OCH_AH_B), 3.85 (td; one of 6-H), 3.54 (ddt; one of 6-H) and 1.90-1.48 (m; 3,4,5-H). ^{13}C nmr data are summarised in Tables 1 and 2. The ^{19}F nmr spectrum (235.4 MHz; $CFCl_3/CDCl_3$) showed a doublet ($^2J_{HF}$ 55.9 Hz) of triplets (mean $^3J_{HF}$ 14.0 Hz) at 125.42 ppm upfield from $CFCl_3$.

2-(2',2',2'-Trifluoroethoxy)tetrahydropyran - The reaction of 2,2,2-trifluoroethanol (7.21g) with 3,4-dihydro-2H-pyran (5.67g) was carried out as described in the preceding preparation. The products, 2-(2',2',2'-trifluoroethoxy)tetrahydropyran (7.04g, 57%) was a colourless liquid, b.p. 44° at 25 mm Hg (lit,[11] 141-143° at 760 mmHg) (Found: M^+ 184.0693, Calc. for $C_7H_{11}O_2F_3$: 184.0711). The ^1H nmr spectrum (250 MHz, $CDCl_3$) showed signals at δ 4.76 (partly resolved t, $w_{\frac{1}{2}}$ 6.0 Hz; 2-H), 4.01 (dq, $^2J_{H_AH_B}$ 12.30 Hz, $^3J_{H_AF}$ 9.0 Hz; H_A of OCH_AH_B), 3.86(dq $^2J_{H_AH_B}$ 12.30 Hz, $^3J_{H_BF}$ 8.7 Hz; H_B of OCH_AH_B), 3.83 (dt; one of 6-H), 3.57 (dm; one of 6-H) and 1.95-1.45 (m; 3,4,5-H). ^{13}C nmr data are given in Tables 1 and 2. The ^{19}F nmr spectrum (235.4 MHz; $CFCl_3/CDCl_3$) showed a triplet (mean $^3J_{HF}$ 8.9 Hz) at 74.9 ppm upfield from $CFCl_3$.

2-Ethoxytetrahydropyran - Using the general method described above, ethanol (4.62g) and 3,4-dihydro-2H-pyran (8.40g) gave 2-ethoxytetrahydropyran (7.41g, 57%) as a colourless liquid, b.p.47-49° at 23 mm Hg (lit,[12] 146° at 760 mm Hg) (Found: M^+ 130.0977. Calc. for $C_7H_{14}O_2$:130.0994). The ^1H nmr spectrum (250 MHz, $CDCl_3$) showed signals at δ4.59 (partly resolved t, $w_{\frac{1}{2}}$ 7 Hz; 2-H), 3.81 (dq, $^2J_{H_AH_B}$ 9.65 Hz, $^3J_{H_AH}$ 7.10 Hz; H_A of OCH_AH_B), 3.47 (dq, $^2J_{H_AH_B}$ 9.65 Hz, $^3J_{H_BH}$ 7.05 Hz; H_B of OCH_AH_B), 3.93-3.84 (m; one of 6-H), 3.55-3.48 (m; one of 6-H), 1.91-1.44 (m; 3,4,5-H) and 1.23 (t; $^3J_{HH}$ 7.1 Hz; CH_3). ^{13}C nmr data are assembled in Tables 1 and 2.

cis-and trans-2-(2'-Fluoroethoxy)-4-methyltetrahydropyran - The reaction of 4-methyl-3,4-dihydro-2H-pyran[4] (2.01g) with 2-fluoroethanol (1.31g) was carried out by the general method described above. The product was cis-*and* trans-2-(2'-*fluoroethoxy*)-4-*methyltetrahydropyran* (2.33g, 70%, a colourless liquid, b.p. 68-72° at 11 mm Hg (Found: $[M-1]^+$ 161.0955. $C_8H_{15}O_2F$ requires [M-1] 161.0978). The ^1H nmr spectrum (250 MHz, $CDCl_3$) showed signals for the *cis*-isomer at δ 4.56 (dt, $^2J_{HF}$ 47.7 Hz, triplet separations 2.55 Hz; CH_2F), 4.40 (dd, $^3J_{2a3a}$ 9.30 Hz, $^3J_{2a3e}$ 2.14 Hz; 2-H), 4.01 (ddd, $^2J_{6e6a}$ 11.66 Hz, $^3J_{6e5a}$ 4.63 Hz, $^3J_{6e5e}$ 1.88 Hz; 6-H_e), 4.03-3.78 (qdt, $^2J_{H_AH_B}$ 12.2 Hz, $^3J_{H_AF}$ 33.4 Hz, $^3J_{H_BF}$ 25.4 Hz, $^3J_{H_AH}$ 3.8 Hz, $^3J_{H_BH}$ 3.0 Hz; H_A and H_B of O-CH_AH_B), 3.43 (td, $^3J_{6a5e}$ 2.4 Hz, [$^2J_{6a6e}$ + $^3J_{6a5a}$] 23.7 Hz; 6-H_a), 1.90-1.82(dm; 3-H_e), 1.78-1.62 (m; 4-H), 1.50-1.47 (dm; 5-H_e), 1.38-1.06 (m; 3-H_a and 5-H_a) and 0.97 (d, ^3J 6.55 Hz; 4-Me). Signals for the *trans*-isomer appeared at δ4.85 (partly resolved d, $w_{\frac{1}{2}}$ 6.5 Hz; 2-H), 4.58 (dt, $^2J_{HF}$ 47.8 Hz, triplet separations 4.25 Hz; CH_2F), 3.88 (ddt, $^2J_{H_AH_B}$ 12.4 Hz, $^3J_{H_AF}$ 31.9 Hz, $^3J_{H_AH}$ 4.0 Hz; H_A of OCH_AH_B), 3.66 (ddt, $^2J_{H_AH_B}$ 12.4 Hz, $^3J_{H_BF}$ 28.4 Hz, $^3J_{H_BH}$ 4.5 Hz; H_B of OCH_AH_B), 3.78 (td, $^3J_{6a5e}$ 2.3 Hz, [$^2J_{6a6e}$ + $^3J_{6a5a}$] 24.0 Hz; 6-Ha, 3.59 (ddd, $^2J_{6a6e}$ 11.0 Hz, $^3J_{6e5a}$ 4.7 Hz, $^3J_{6e5e}$ 1.6 Hz; 6-H_e), 2.05-1.91(m; 4-H), 1.77 (dm, $^2J_{3e3a}$ 13.4 Hz; 3-H_e), 1.56 (dm, $^2J_{5e5a}$ 13.0 Hz; 5-H_e), 1.38-1.06 (m; 3-H_a and 5-H_a), and 0.89 (d, ^3J 6.61 Hz; 4-Me).

cis-*and* trans-2-(2',2'-*Difluoroethoxy*)-4-*methyltetrahydropyran* - The reaction of 4-methyl-3,4-dihydro-2H-pyran (2.21g) and 2,2-difluoroethanol (1.85g) (see above for method) gave a mixture of *cis*- and *trans*-2(2',2'-*difluoroethoxy*)-4-*methyltetrahydropyran* (2.41g, 59%), a colourless liquid with b.p. 70-74° at 19 mmHg (Found: M^+ 181.1023. $C_8H_{14}O_2F_2$ requires M 181.1041). The ^1H nmr spectrum (250 MHz, $CDCl_3$) gave signals for the *cis*-isomer at δ5.92 (tt, $^2J_{HF}$ 55.7 Hz, small separations 4.25 Hz; CHF_2), 4.40 (dd, $^3J_{2a3a}$ 9.24 Hz, $^3J_{2a3e}$ 2.22 Hz; 2-H), 4.01 (ddd, $^2J_{6e6a}$ 11.8 Hz, $^3J_{6e5a}$ 4.8 Hz, $^3J_{6e5e}$ 1.8 Hz; 6-H_e), 3.95-3.60 (m; H_A and H_B of OCH_AH_B), 3.43 (td, $^3J_{6a5e}$ 2.43 Hz, $^2J_{6a6e}$ + $^3J_{6a5a}$ 23.7 Hz; 6-H_a), 1.84-1.82 (dm; 3-H_e), 1.72-1.63 (m; 4-H), 1.51-1.47 (m; 5-H_e), 1.2-1.0 (m; 3-H_a and 5-H_a), and 0.98 (d, ^3J 6.57 Hz; 4-Me). The *trans*-isomer revealed signals at δ5.91 (tt, $^2J_{HF}$ 55.7 Hz, small separations 4.2 Hz; CHF_2), 4.85 (partly resolved d, $w_{\frac{1}{2}}$ 6.7 Hz; 2-H), 3.82 (ddt, $^2J_{H_AH_B}$ 11.7 Hz, $^3J_{H_AH}$ 3.7

Hz, $^3J_{H_AF}$ 14.9 Hz; H_A of OCH_AH_B), 3.66 (ddt, $^2J_{H_AH_B}$ 11.7 Hz, $^3J_{H_BH}$ 4.6 Hz, $^3J_{H_BF}$ 13.6 Hz; H_B of OCH_AH_B), 3.76 (td, $^3J_{6a5e}$ 2.6 Hz, $^2J_{6a6e}$ + $^3J_{6a5a}$ 23.9 Hz; 6-H_a), 3.62 (ddd, $^2J_{6e6a}$ 11.1 Hz, $^3J_{6e5a}$ 5.0 Hz, $^3J_{6e5e}$ 1.7 Hz; 6-H_e), 2.05-1.85 (m; 4-H), 1.77 (dm, $^2J_{3e3a}$ 13.5 Hz; 3-H_e), 1.57 (dm, $^2J_{5e5a}$ 12.6 Hz; 5-H_e), 1.30 (td, $^3J_{3a2e}$ 3.5 Hz, $^2J_{3e3a}$ + $^3J_{3a4a}$ 25.8 Hz; 3-H_a), 1.29 (qd, $^3J_{5a6e}$ 4.8 Hz, $^2J_{5a5e}$ + $^3J_{5a6a}$ + $^3J_{5a4a}$ 37.7 Hz; 5-H_a) and 0.90 (d, ^3J 6.56 Hz; 4-Me).

cis-*and* trans-2-(2',2',2'-*Trifluoroethoxy*)-4-*methyltetrahydropyran* - The reaction of 4-methyl-3,4-dihydro-2H-pyran (3.01g) with 2,2,2-trifluoroethanol (3.22g) (see above for method) gave a mixture of *cis*- and *trans*-2-(2',2',2',-trifluoroethoxy)-4-methyltetrahydropyran (4.05g, 67%), a colourless liquid with b.p. 52-6° at 19 mm Hg (Found: M^+ 198.0843. $C_8H_{13}O_2F_3$ requires M 198.0867). Separation of the mixture by preparative gas liquid chromatography employed a 12' x 3/8" aluminium column packed with 20% carbowax 20M on 60/70 mesh chromosorb W (7.5% KOH) at a column temperature of 70°. The fraction with retention volume 869 cm^3 was the *trans*-isomer (Found: C, 48.60; H,6.85. $C_8H_{13}O_2F_3$ requires C, 48.48; H, 6.61%). The fraction with retention volume 1350 cm^3 was the *cis*-isomer (Found: C,48.32; H,6.72. $C_8H_{13}O_2F_3$ requires C,48.48; H,6.61%).

The ^1H nmr spectrum (250 MHz, $CDCl_3$) of the *cis*-isomer showed signals at δ 4.46 (dd, $^3J_{2a3a}$ 9.08 Hz, $^3J_{2a3e}$ 2.31 Hz; 2-H), 4.02 (ddd, $^2J_{6e6a}$ 11.7 Hz, $^3J_{6e5a}$ 4.7 Hz, $^3J_{6e5e}$ 2.2 Hz; 6-H_e), 4.11 (dq, $^2J_{H_AH_B}$ 12.45 Hz, $^3J_{H_AF}$ 9.0 Hz; H_A of OCH_AH_B), 3.92 (dq, $^2J_{H_AH_B}$ 12.45 Hz, $^3J_{H_{BF}}$ 8.7 Hz; H_B of OCH_AH_B), 3.44 (td, $^3J_{6a5e}$ 2.5 Hz, $^2J_{6a6e}$ + $^3J_{6a5a}$ 23.5 Hz; 6-H_a) 1.88 (dm, $^2J_{3e3a}$ 12.8 Hz; 3-H_e), 1.76-1.60 (m; 4-H), 1.53 (dm, $^2J_{5e5a}$ 13.4 Hz; 5-H_e), 1.22 (qd, $^3J_{5a6e}$ 4.6 Hz, $^2J_{5a5e}$ + $^3J_{5a6a}$ + $^3J_{5a4a}$ 36.2 Hz; 5-H_a), 1.15 (td, $^3J_{3a2a}$ 9.16 Hz, $^3J_{3a3e}$ + $^3J_{3a4a}$ 24.4 Hz; 3-H_a) and 0.99 (d, ^3J6.53 Hz; 4-Me).

Determination of Thermodynamic Parameters

See Part 1[4]

Data Treatment

Data treatment employed computer-drawn plots of lnK against T^{-1}.

1. (a) 2-Ethoxytetrahydropyran ($3 \rightleftharpoons 4$).

equilibrium constant K = 4/3 = e/a

solvent	CD_2Cl_2		$CFCl_3/CDCl_3$
T/K	151	156	155
K	0.728	0.720	0.642

(b) cis-and trans-2-Ethoxy-4-methyltetrahydropyran ($11 \rightleftharpoons 12$)

equilibrium constant K = 12/11 = e/a

solvent	CD_2Cl_2			$CFCl_3/CDCl_3$		
T/K	251	255	270	251	255	270
K	0.510	0.508	0.516	0.309	0.293	0.296

For CD_2Cl_2,

data treatment gave $\Delta H°_{1\to2}(OCH_2CH_3)$ as -0.26 ± 0.03 kcal mol^{-1} and $\Delta S°_{1\to2}(OCH_2CH_3)$ as -2.33 ± 0.08 cal K^{-1} mol^{-1}.

For $CFCl_3/CDCl_3$,

data treatment gave $\Delta H°_{1\to2}(OCH_2CH_3)$ as -0.58 ± 0.03 kcal mol^{-1} and $\Delta S°_{1\to2}(OCH_2CH_3)$ as -4.65 ± 0.15 cal K^{-1} mol^{-1}.

2. (a) 2-(2'-Fluoroethoxy)tetrahydropyran($5 \rightleftharpoons 6$).

equilibrium constant K = 6/5 = e/a

solvent	CD_2Cl_2		$CFCl_3/CDCl_3$
T/K	150	155	154
K	0.484	0.487	0.302

(b) cis and trans-2-(2'-fluoroethoxy)-4-methyltetrahydropyran($13 \rightleftharpoons 14$)

equilibrium constant K = 14/13 = e/a

solvent	CD_2Cl_2		$CFCl_3/CDCl_3$	
T/K	255	270	251	270
K	0.396	0.425	0.245	0.247

For CD_2Cl_2

data treatment gave $\Delta H°_{1\rightarrow 2}(OCH_2CH_2F)$ as -0.12 ± 0.03 kcal mol^{-1} and $\Delta S°_{1\rightarrow 2}(OCH_2CH_2F)$ as -2.22 ± 0.16 cal K^{-1} mol^{-1}.

For $CFCl_3/CDCl_3$

data treatment gave $\Delta H°_{1\rightarrow 2}(OCH_2CH_2F)$ as -0.15 ± 0.02 kcal mol^{-1} and $\Delta S°_{1\rightarrow 2}(OCH_2CH_2F)$ as -3.37 ± 0.09 cal K^{-1} mol^{-1}.

3. (a) 2-(2',2'-Difluoroethoxy)tetrahydropyran(7 $\rightleftharpoons$ 8).

equilibrium constant K = 8/7 = e/a

solvent	CD_2Cl_2	$CFCl_3/CDCl_3$
T/K	160	152
K	0.377	0.243

(b) <u>cis</u> and <u>trans</u>-2-(2',2'-Difluoroethoxy)-4-methyltetrahydropyran(15 $\rightleftharpoons$ 16)

equilibrium constant K = 16/15 = e/a

solvent	CD_2Cl_2		$CFCl_3/CDCl_3$		
T/K	255	270	251	255	270
K	0.344	0.364	0.215	0.214	0.227

For CD_2Cl_2

data treatment gave $\Delta H°_{1\rightarrow 2}(OCH_2CHF_2)$ as -0.05 ± 0.04 kcal mol^{-1} and $\Delta S°_{1\rightarrow 2}(OCH_2CHF_2)$ as -2.25 ± 0.21 cal K^{-1} mol^{-1}.

For $CFCl_3/CDCl_3$

data treatment gave $\Delta H°_{1\rightarrow 2}(OCH_2CHF_2)$ as -0.07 ± 0.03 kcal mol^{-1} and $\Delta S°_{1\rightarrow 2}(OCH_2CHF_2)$ as -3.30 ± 0.15 cal K^{-1} mol^{-1}.

4. (a) 2-(2',2',2-Trifluoroethoxy)tetrahydropyran($9 \rightleftharpoons 10$)

equilibrium constant K = 10/9 = e/a

solvent	CD_2Cl_2			$CFCl_3/CDCl_3$
T/K	147	150	152	155
K	0.197	0.211	0.214	0.109

(b) <u>cis</u> and <u>trans</u>-2-(2',2',2'-Trifluoroethoxy)-4-methyltetrahydropyran ($17 \rightleftharpoons 18$)

equilibrium constant K = 18/17 = e/a

solvent	CD_2Cl_2			$CFCl_3/CDCl_3$		
T/K	251	255	270	251	255	270
K	0.244	0.238	0.266	0.140	0.138	0.152

For CD_2Cl_2

data treatment gave $\Delta H°_{1\to2}(OCH_2CF_3)$ as 0.13 ± 0.03 kcal mol^{-1} and $\Delta S°_{1\to2}(OCH_2CF_3)$ as -2.24 ± 0.14 cal K^{-1} mol^{-1}.

For $CFCl_3/CDCl_3$

data treatment gave $\Delta H°_{1\to2}(OCH_2CF_3)$ as 0.21 ± 0.03 kcal mol^{-1} and $\Delta S°_{1\to2}(OCH_2CF_3)$ as -3.03 ± 0.15 cal K^{-1} mol^{-1}.

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