# *endo*-Anomeric and *exo*-Anomeric Effects in 2-Substituted Tetrahydropyrans

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Determinations by variable temperature $^{13}C$ and/or $^{1}H$ n.m.r. spectroscopy of equilibrium constants for inversion of 2-substituted tetrahydropyrans and comparisons with substituted cyclohexanes have given 'anomeric effects ($\Delta\Delta H°$)' of +2.12, +0.75, +0.61, and −0.33 kcal mol$^{-1}$ (1 cal = 4.184 J) for substituents Cl, OMe, OH, and NHMe respectively; this sequence confirms the importance of antiperiplanar n-σ* stabilisation but supports the suggestion that *endo*-anomeric and *exo*-anomeric effects which occur in the same conformation are competitive.

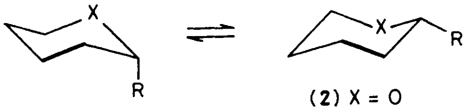
Although the anomeric effect[1,2] has generally[1—5] been evaluated as $(\Delta G°_{1\rightarrow2} - \Delta G°_{3\rightarrow4})$ there are advantages in using $\Delta H°$ values in order to eliminate temperature-dependent entropy-based contributions. We now report 'anomeric effects ($\Delta\Delta H°$)' for substituents Cl, OMe, and OH and a '*reverse* anomeric effect ($\Delta\Delta H°$)' for the substituent NHMe.

Equilibrium constants $K$ for (**1**⇌**2**) and (**3**⇌**4**) were determined as indicated in footnotes to Table 1, which summarises the values of $\Delta H°_{1\rightarrow2}$ and $\Delta S°_{1\rightarrow2}$ obtained from plots of ln $K$ against $T^{-1}$. In enthalpy terms, only 2-chlorotetrahydropyran favours the axial conformation. The 'anomeric effects ($\Delta\Delta H°$)' for each substituent were deduced from values of $\Delta H°_{1\rightarrow2}$ and $\Delta H°_{3\rightarrow4}$. It is realised that such anomeric effects inevitably include differences in steric effects as between cyclohexanes and tetrahydropyrans, differences which are difficult to evaluate.[9] Nevertheless, the trend in $\Delta\Delta H°$ values for Cl, OMe, OH, and NHMe supports the current view that a significant source of both anomeric and

**Table 1.** Thermodynamic parameters[a] for (**1**⇌**2**) and (**3**⇌**4**) ($\Delta H°$/kcal mol$^{-1}$; $\Delta S°$/cal K$^{-1}$ mol$^{-1}$).

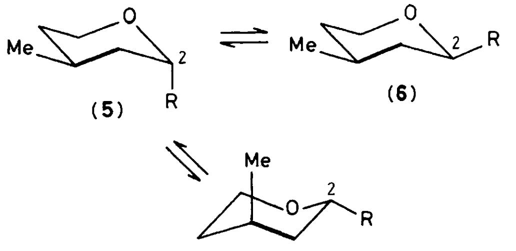
|  | (**1**⇌**2**) |  | (**3**⇌**4**) |  | Anomeric effect, |
|---|---|---|---|---|---|
| R | $\Delta H°_{1\rightarrow2}$ | $\Delta S°_{1\rightarrow2}$ | $\Delta H°_{3\rightarrow4}$ | $\Delta S°_{3\rightarrow4}$ | $\Delta\Delta H°$ |
| Cl | 1.67[b,d] | −1.69[b,d] | −0.45[i] | 0.32[i] | 2.12 |
| OMe | 0.04[c,e] | −2.5[c,e] | −0.71[i] | −0.42[i] | 0.75 |
| OH | −0.63[c,f] | −2.5[c,f] | −1.24[j] | −1.21[j] | 0.61 |
| NHMe | −2.11[c,g] | −2.2[c,g] | −1.78[c,h] | −2.02[c,h] | −0.33 |

[a] This work, unless stated otherwise; 1 cal = 4.184 J. [b] Solvent $CDCl_3$. [c] Solvent $CFCl_3$–$CDCl_3$ (85:15 v/v). [d] From (**5**⇌**6**) using $^{1}H$ n.m.r. (253—325 K). [e] Ref. 6. [f] From (**1**⇌**2**) using $^{13}C$ n.m.r. (169—172 K) and acid-catalysed (**5**⇌**6**) using $^{1}H$ n.m.r. (250, 270 K). [g] From (**1**⇌**2**) using $^{13}C$ n.m.r. line-broadening[8] (180—210 K), from (**5**⇌**7**) using $^{13}C$ n.m.r. integration (174 K) and from (**5**⇌**6**⇌**7**) using $^{1}H$ n.m.r. (250, 270 K), taking 1.95 kcal mol$^{-1}$ for $\Delta G°$(4-Me).[7] [h] From (**3**⇌**4**) using $^{13}C$ n.m.r. integration (180 K) and $^{13}C$ n.m.r. line-broadening (190—230 K). [i] Solvent $CFCl_3$.[14] [j] Solvent iso-octane.[15]



**(1)** X = O
**(3)** X = CH$_2$

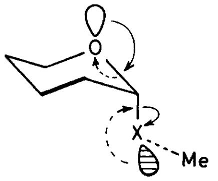
**(2)** X = O
**(4)** X = CH$_2$



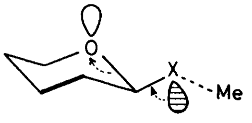
**(5)**

**(6)**

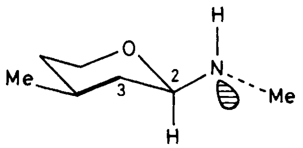
**(7)**



**(8)** X = O
**(9)** X = NH



**(10)** X = O
**(11)** X = NH



**(12)**

*exo*-anomeric[10] effects is a stabilisation due to an antiperiplanar n-σ* interaction of the heteroatom lone pair with the antibonding orbital of the C heteroatom bond.[1,2,5] However, it is impossible at present to exclude contributions arising from dipole–dipole interactions and lone pair–lone pair repulsions.

The NHMe group has a small *reverse* anomeric effect, since 2-methylaminotetrahydropyran has a stronger preference than methylaminocyclohexane for the *equatorial* conformation. This finding recalls a similar conclusion drawn for aminomethanol from *ab initio* calculations,[5] but is contrary to the prediction[9] based on a linear correlation of $\Delta G°$ values in 2-substituted tetrahydropyrans with those in the related cyclohexanes. Franck's prediction relies on a value for $\Delta G°_{1\rightarrow 2}$ (NHMe) deduced from the work of Tesse, Glacet, and Couturier[11] who found that 2-methylamino-4-methyltetrahydropyran contained 85% *cis*- and 15% *trans*-isomers at room temperature in CCl$_4$. It was apparently assumed by Franck that the *trans*-isomer ($\mathbf{5}\rightleftharpoons\mathbf{7}$) existed entirely in conformation (**5**), although Barbry *et al.*[12] had estimated the position of equilibrium in ($\mathbf{5}\rightleftharpoons\mathbf{7}$) by measurement of proton band-widths for the mixture and for model compounds.

The pronounced change (~ 2 kcal mol$^{-1}$) in $\Delta H°$ when OMe is changed to NHMe is interesting and cannot be due entirely to the larger steric repulsions for axial NHMe as against axial OMe (*cf.* ~ 1 kcal mol$^{-1}$ difference for $\Delta H°$ in the cyclohexane case). It is noted that *endo*-anomeric (solid curved arrows) and exo-anomeric (broken curved arrows) effects are *in competition*[13] in the preferred rotamers (**8**),(**9**) of the axial conformations. At the same time the *exo*-anomeric effect in the most stable rotamers (**10**),(**11**) of the equatorial conformations do not suffer competition from an *endo*-anomeric effect. Since the C–N bond is a weaker acceptor than the C–O bond, the *endo*-anomeric effect in (**9**) is weaker than in (**8**). Also, as nitrogen is a stronger donor than oxygen, the *exo*-anomeric effect in (**11**) is stronger than in (**10**). The consequence is a very strong preference for equatorial NHMe in 2-methylaminotetrahydropyran. The assumption that (**12**) is the dominant rotamer for the *cis*-isomer (**6**; R = NHMe) is supported by the following n.m.r. coupling constants: (a) 12.3 Hz (±0.3 Hz), measured at 170—195 K for $^3J_{HH}$ ($H$-C$_2$-N-$H$), for which the expected values[16] are 3—4 (dihedral angle $\Phi$~60°) or 11—13 Hz ($\Phi$~180°); (b) 3.67 Hz (±0.15 Hz) for $^3J_{CC}$ ($C_3$-C$_2$-N-$C$H$_3$), for which the expected values[17,18] are 0—1 ($\Phi$~60°) or 3—5 Hz ($\Phi$~180°); (c) 3.30 Hz (±0.15 Hz) for $^3J_{HC}$ ($H$-C$_2$-N-$C$H$_3$), for which the expected values[17,19,20] are 1.5—4.5 ($\Phi$~60°) or 6—8.5 Hz ($\Phi$~180°).

*syn*-Axial steric interactions are weaker for axial chlorine than for methoxy or methylamino, owing largely to the relatively long C–Cl bond. In addition, the *exo*-anomeric effect for chlorine is expected to be weak. On the other hand the powerful acceptor properties of the C–Cl bond ensure that the *endo*-anomeric effect is strong. Consequently, the equilibrium in 2-chlorotetrahydropyran is heavily biased towards the conformation with axial chlorine.

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