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A REVISION OF THE VALUE FOR THE ANOMERIC EFFECT

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Abstract—An analysis of literature data has resulted in the establishment of an equation for the correlation of the apparent size of a substituent in a tetrahydropyran with its size in cyclohexane. This correlation permits the re-evaluation of the anomeric effect for ether oxygen and the assignment of anomeric effects to carbomethoxy, methylamino and dimethylamino.

The term "anomeric effect" refers to the observed stability of an axial electronegative substituent at C-1 of a tetrahydropyran ring as opposed to the expected stability of equatorial substitution predicted on steric grounds.[1] Its origin and nature are fairly well understood. However, the numerical value of the anomeric effect has always been in doubt because of one unknown in all methods of its calculation. Thus the observed $-\Delta G$ favoring isomer **2** where the substituent is axial is added to the predicted $-\Delta G$ which should favor isomer **1** if there were only steric effects controlling isomer population. The described sum is taken to be the anomeric effect of the axial substituent. The predicted $-\Delta G$ favoring the equatorial substituent has always been taken as the value for the group determined for the substituted cyclohexane. It has been recognized for many years that the use of cyclohexane substituent values was probably not correct. For example, Eliel and Giza,[2] in 1968 said, "Although the effect is defined as the difference in ΔG_x^0 between the heterocycle and cyclohexane, it must not be concluded that this difference as such represents the added stabilization of the axial substituent in the heterocycle. Such a conclusion would presume that the steric interaction in a heterocycle is the same as that in the analogously substituted cyclohexane. In general, however, this is not true—a steric compression would be expected to exist—and the fact that the alkoxy group prefers the axial configuration must indicate the operation of a factor whose magnitude is in excess of the calculated anomeric effect..." More recently Deslongchamps *et al.*[3] pointed out that their use of spiro compounds to determine the value of the anomeric effect as 1.4 kcal/mole and that similar conclusions made by Descotes[4] with data from bicyclic compounds must be taken as a minimum value because axial steric interactions in tetrahydropyrans may be amplified over those in cyclohexanes. The purpose of this note is to suggest that the amplification factor for the steric effect of an axial substituent in a tetrahydropyran can now be approximated. Thus, from work by Kleinpeter,[5] and the very recent results of Eliel,[6] a series of ΔG values for C substituents at C-1 of tetrahydropyrans have been determined (in CD_2Cl_2 solvent). Two assumptions are made for our analysis: (i) that the steric size of H is the same in both tetrahydropyran and cyclohexane, (ii) that, if the groups used for the correlation have anomalous electronic effects equivalent to the anomeric effect, they are so small that they can be neglected.[7,8] Then a plot of the cyclohexane value (determined in halomethane solvent) for the C substituent vs the tetrahydropyran value yields a fairly good correlation (Fig. 1). The line fits the equation $\Delta G\ (\mathrm{THP}) = 1.53 \times \Delta G\ (\mathrm{Cyclohex.}) + 0.02$ with a correlation coefficient of 0.988. Thus, taking the accepted $-\Delta G$ as 0.75 kcal/mole for a $-OCH_3$ on cyclohexane,[9] one can interpolate from the graph a value of 1.2 kcal/mole for the substituent at C-1 of tetrahydropyran. Now, adding the observed axial preference for methoxytetrahydropyran of 0.9 kcal/mole,[10] one can derive a minimum O-alkyl anomeric effect of 2.1 kcal/mole, nearly 50% larger than currently accepted values. The most recent *ab initio* calculation for the stabilization of methanediol predicts a value of 2.8 kcal/mole for the anomeric effect, in reasonable agreement with our new value.[1b]

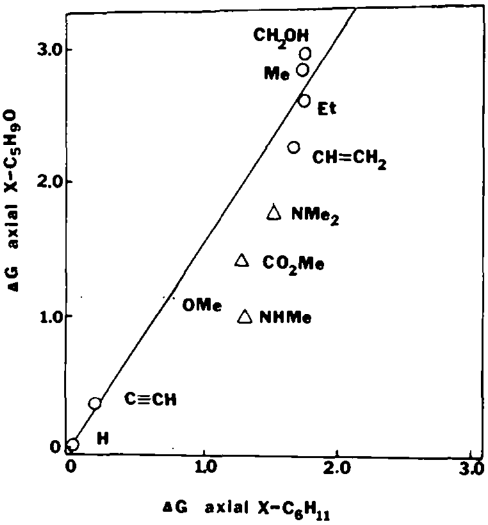

Fig. 1. Plot of ΔG values for substituents at C-1 of tetrahydropyran (THP) taken from Eliel, Ref. 6 or J. Tesse, C. Glacet and C. Couturier, *C. R. Acad. Sci. Ser. C* **280**, 1525 (1975), vs those for substituted cyclohexanes (Me, H. Booth and J. R. Everett, *Chem. Commun.* **278**, (1976), Et, H. Booth, Ref. 7, CH_2OH, W. Kitching, H. Olszowy and W. Adcock, *Org. Mag. Res.* **15**, 230 (1981); vinyl E. Eliel, Ref. 11; ethynyl, J. A. Hirsch, *Top. Stereochem.* **1**, 199 (1967); CO_2Me, J. A. Hirsch, as above; OMe, A. J. de Hoog, Ref. 8; $NHCH_3$, NMe_2, H. Booth and M. L. Josefowicz, *J. Chem. Soc.* Perkin II 895 (1976). The CO_2Me, $NHCH_3$, and Me_2N points were not included in the calculation of the slope in order to search for the existence of an anomeric effect. The line fits the equations $\Delta G\ (\mathrm{THP}) = 1.53 \times \Delta G\ (\mathrm{Cyclohex}) + 0.02$ with a correlation coefficient of 0.988.

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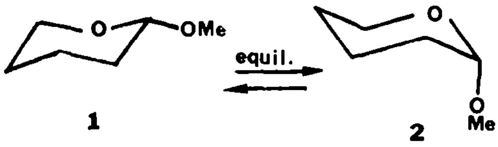

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One other datum from Eliel's work, that the -CO_2Me group in tetrahydropyrans has a ΔG of 1.38, may be compared to the predicted value of 1.98 kcal/mole. Thus one might conclude that, contrary to literature suggestions for the existence of a reverse anomeric effect,[11] there, in fact, exists a weak normal anomeric effect of 0.6 kcal/mole for the carbomethoxy group.

Our analysis can be used to clarify the question of an anomeric effect for the amino group. Theory predicts a "reverse anomeric effect" of 0.83 kcal/mole.[1b] It can be seen from the graph that for the methylamino and dimethylamino groups, the $-\Delta G$ favoring the equatorial isomers in the tetrahydropyran series are 1.0 and 0.56 kcal/mole *less* than predicted. Again, one must infer that there in fact exists moderate anomeric effects for ordinary amino substituents. One is forced to conclude that the amplification effect on C-1 axial substituents in tetrahydropyrans must be taken into account carefully in analyzing conformational equilibria in these systems.

Finally, it must be emphasized that as more data becomes available, the correlation line which reveals the amplification of "size" of axial substituents in tetrahydropyrans may be improved. Nevertheless, *the principle* will remain the same, namely that the difference between the observed ΔG values of an axial substituent of tetrahydropyran and the ΔG predicted by our correlation will measure the anomeric effect of the substituent. In addition, as data becomes available, the same principle can be extended to other important hetercycles.

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[7] The value for the ethynyl group in our data set may be uncertain. In 2 - ethynyl - 1,3 - dioxan, the conformer population is susceptible to solvent effects, thus suggesting the possible existence of anomeric-like effects, at least in dioxans; W. F. Bailey and E. L. Eliel, *J. Am. Chem. Soc.* **96**, 1798 (1974).

[8a] A third assumption is that the $\Delta G°$ values can be used in place of temperature-independent $\Delta H°$ values. For example, there are appreciable entropy effects (for OMe, D. Hofner, S. A. Lesko and G. Binsch, *Org. Mag. Res.* **11**, 179 (1978); for Et, H. Booth and J. R. Everett, *J. Chem. Soc.* Perkin III, 255 (1980), which would affect the "size" of the groups at different temp. When and if $\Delta H°$ values become available, it will be interesting to construct a revised correlation curve. [b]A very recent communication by Booth seems to show that the anomeric effect in methoxytetrahydropyran is entirely due to the greater entropy of the axial conformer. Certainly the underlying assumption of most previous authors is that an electronic component, hence a ΔH term is involved in the anomeric effect; H. Booth, T. B. Grindley and K. A. Khedhair *Chem. Commun.* 1047 (1982).

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