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NON-BONDED INTERACTIONS, AND THE ALLYLIC AND ANOMERIC EFFECTS*

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ABSTRACT

The steric dependence of anomeric and allylic effects has been subjected to classical conformational analysis. The allylic effect of a methyl group is determined by steric interactions that also play an important role in the anomeric effect. Contradictory experimental results on cyclohexen-3-ol concerning the allylic effect are critically discussed.

INTRODUCTION

5,6-Dihydro-2*H*-pyrans substituted at C-2 by an electronegative group (**1**; X = $\dot{O}$; Y = OH, OMe, or OCOMe) are appropriate models for analysing the conformational equilibrium of 2,3-unsaturated carbohydrates. They exhibit inversion of a six-membered ring, and the equilibrium between conformers having pseudoequatorial (p*eq*) and pseudoaxial (p*ax*) orientations of the electronegative substituent Y is different from that found for the axial (*ax*) and equatorial (*eq*) orientations of the substituent in cyclohexane derivatives[1] (**2**, X = CH_2). Two effects were invoked to describe the observed orientational preference of the electronegative substituent in the vicinity of a double bond and/or ring oxygen, namely, allylic and anomeric effects. The latter effect was introduced for tetrahydropyran derivatives (**2**, X = O) which, contrary to those of cyclohexane (**2**, X = CH_2), favour[2–5] the axial orientation for an electronegative substituent Y at C-2. On the basis of its sensitivity to polar interactions, the effect was ascribed to electronic interactions[2,3,5], although its steric dependence was also observed[3]. The allylic effect, first observed by Ferrier *et al.*[6,7], involves a drastic decrease in the proportion of the isomer **1a** having the pseudoequatorial orientation of the substituent Y, in comparison with the well-known, strongly pronounced, equatorial preference in cyclohexane derivatives. The magnitude of the allylic effect, as measured by various research groups, differs considerably. On the basis of equilibration measurements in acetone–water solutions, Ferrier and Prasad[7] claimed that the allylic hydroxyl-group favours the pseudoequatorial orientation by 0.4 kcal/mol, whereas Senda *et al.*[8,9], using ^{13}C-n.m.r.

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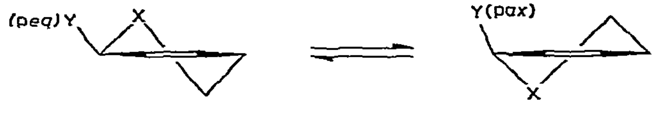
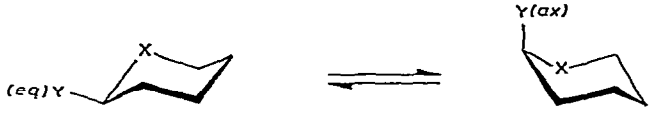
*Part I.



1a 1b



2a 2b

$X = CH_2$ or O ; Y = Me or OH

spectroscopy for solutions in $CDCl_3$ found an ~1 kcal/mol preference for the pseudo-axial isomer. A considerable steric dependence of the allylic effect was also found[8] on analysis of the spectra of appropriate methyl derivatives. The significant difference between the data reported by the Senda and Ferrier groups requires explanation, and makes plausible a further study of the allylic effect.

Several theoretical analyses of the anomeric effect have been published[10–18], but none concerning the allylic effect. *Ab initio* quantum-mechanical calculations (using a minimal basis set) performed by Jeffrey *et al.*[10] on the model compound methanediol revealed preferences corresponding to the anomeric effect. For dimethoxymethane, Tvaroška and Bleha[11,12] showed that, of the semiempirical quantum methods, EHT and MINDO failed to reproduce experimental trends, while CNDO and INDO properly yielded the larger stability of the gauche–gauche rotamer corresponding to the carbohydrate conformation stabilized by the anomeric effect.

Another approach to the description of the anomeric effect in saturated carbohydrates was carried out by Rao and his co-workers[13–17]. In order to determine the conformational equilibrium in aldopentopyranoses and aldohexopyranoses and their tetra-acetates, Rao *et al.* minimized steric energy as a function of the deformations of the ring-substituent C–O bond-length and bond-angles, and that of non-bonded and electrostatic interactions. Additionally, increments for the anomeric effect and entropy factors were included. This means that the authors took into account some of the terms on the left-hand side of equation *1* plus increments allowing for electrostatic interactions, anomeric effect, and entropy factors. The physical foundations of the model used by the Rao group are unclear, as steric and electrostatic interactions should be sufficient to describe the anomeric effect without further involvement of the anomeric increment. The calculations yielded semi-quantitative agreement with experimental data for hexoses, while serious disagreement occurred for the pentoses.

Rees and Smith[18] performed a similar analysis for a series of pentopyranoses, making somewhat different, simplifying assumptions than that used by the Rao group. Taking into account polar, van der Waals, and torsional terms, they obtained a comparable degree of accuracy for the calculated values as the latter group.

The foregoing discussion shows that the factors determining the allylic and anomeric effects are still not well understood, and further work is required. Therefore, a classical conformational analysis of cyclohexane (**2**, X = CH_2), tetrahydropyran (**2**, X = O), and 5,6-dihydro-2*H*-pyran (**1**, X = O) substituted at position 2 by a methyl or hydroxyl group has been carried out. The results obtained were compared with those reported by Allinger *et al.*[19–21] for methylcyclohexane, cyclohexanol, and 3-methylcyclohexene (**1**; X = CH_2, Y = Me), and with the corresponding experimental data, in order to analyse to what extent the anomeric and allylic effects are determined by steric interactions.

METHOD

As described in detail elsewhere[22–24], the steric energy of a molecule as a function of its internal geometry is given by Equation *1*:

$$E_s = \sum_{\text{bonds}} \tfrac{1}{2}k_b(r - r_o)^2 + \sum_{\substack{\text{bond}\\ \text{angles}}} \tfrac{1}{2}k_v(v - v_o)^2 + \sum_{\substack{\text{torsional}\\ \text{angles}}} \tfrac{1}{2}V_o[1 - \cos m(\varphi - \varphi_o)] + \sum_{\substack{\text{nonbonded}\\ \text{pairs}}} V_{nb}, \qquad (1)$$

where the first term on the right-hand side represents the sum of the energies associated with a deformation of a bond from the ideal length (r_o) to the actual length (r), the second term represents the sum of the energies of deformations of a bond angle from the ideal value (v_o) to the actual value (v), the third term represents the sum of the Pitzer energies of torsional-angle distortions ($\varphi - \varphi_o$), and the last term describes the sum of the energies of non-bonded interactions. The parameters k_b and k_v are stretching and bending force-constants, respectively; V_o and m describe the height and multiplicity of the torsional barrier, respectively; and V_{nb} is the so-called Buckingham potential[25]. It is believed that no accurate description of electrostatic interactions within a molecule can be given at present. Therefore, no term describing the interactions of charges and dipoles has been included in Equation *1*. A comparison of calculated and experimental data indicated which of the effects observed could be explained in terms of non-bonded interactions. On the other hand, the inability of the model to reproduce an experimental finding would indicate that electronic interactions play a decisive role in the molecule. Therefore, the method applied allows some qualitative conclusions to be drawn concerning the steric and electronic involvement in the conformational equilibrium of a molecule under investigation. Although the accuracy of the model used is known to be low and the possibility of finding local minima cannot be fully excluded, it is recognized that errors cancel to a considerable extent when steric energy differences rather than absolute energy values are considered[22-24].

The calculations were carried out by means of an adaptation of the Wiberg programme[23], using parameters proposed by the Allinger group[26-28]. The steric energy was calculated twice for each molecule for (pseudo)equatorial and (pseudo)-axial orientations of the substituent Y. As already mentioned, no sharp, well-defined minima were found, because of the low barrier to internal rotation of the OH group and ring flexibility. Therefore, three orientations, corresponding approximately to the minimum-energy, staggered positions, were used in the calculations of the steric energy of the mixtures. The entropy factor due to the symmetry was added for cyclohexanol (**2**; X = CH_2, Y = OH) by the Allinger group[20]. No other entropy factors were taken into account, in view of the complexity of the problem studied. Such a procedure corresponds to the assumption of the equality of entropy factors for (pseudo)axial and (pseudo)equatorial conformations of a molecule.

RESULTS AND DISCUSSION

The results obtained in this work are given in Table I, together with the corresponding experimental data, and the calculated results for methylcyclohexane[19] (**2**; X = CH_2, Y = Me), cyclohexanol[20] (**2**; X = CH_2, Y = OH), and 3-methylcyclohexene[21] (**1**, X = CH_2, Y = Me). Inspection of the data in Table I reveals that, for the saturated compounds, the calculations based on a purely steric model reproduce very well the experimental results for methylcyclohexane, 2-methyltetrahydropyran (**2**; X = O, Y = Me), and cyclohexanol. This means that the steric requirements of the axial and equatorial substituent are similar for methylcyclohexane and 2-methyltetrahydropyran, and that the shift of the *ax–eq* equilibrium may be interpreted as a purely steric effect. In spite of the crudeness of the model used and parameter uncertainties for molecules involving two interacting heteroatoms, a more revealing result was obtained for tetrahydropyran-2-ol. The calculated preference for the conformer having the axial orientation of the substituent equals 0.44 kcal/mol, compared to the experimental value[29] of 0.75 kcal/mol. At first sight, it is striking that a purely steric model can qualitatively describe the mutual stability of the isomers having axial and equatorial orientations of the OH group. This result seemingly disagrees with the weak steric dependence of the anomeric effect found by de Hoog *et al.*[3,4] for the series 2-methoxy-, 2-ethoxy-, 2-isopropoxy-, and 2-(*tert*-butoxy)-tetrahydropyran. However, this disagreement is insubstantial, as, in these compounds, no steric changes were introduced into the tetrahydropyran ring itself. It should be stressed that it is usually very difficult to obtain direct experimental data on the magnitude of steric effects in both conformations of a 2-substituted tetrahydropyran. A full discussion of the relations in tetrahydropyran-2-ol will be given elsewhere[30], but the strong steric dependence of the anomeric effect should be emphasized.

TABLE I

EXPERIMENTAL AND CALCULATED STERIC-ENERGY DIFFERENCES FOR (PSEUDO)AXIAL AND (PSEUDO)-EQUATORIAL CONFORMERS

Compound	ΔE_{exp}[a] *(kcal/mol)*	ΔE_{calc}[a] *(kcal/mol)*
2; X = CH_2, Y = Me	1.87–1.96[31]	ΔH = 1.81[19] ΔG = 1.77[32]
2; X = O, Y = Me	1.74[5]	1.84
2; X = CH_2, Y = OH	0.5–0.9[33]	ΔH = 0.58 ΔG = 0.41[20]
2; X = O, Y = OH	−0.75[29]	−0.44
1; X = CH_2, Y = Me	—	0.76[21]
1; X = O, Y = Me	—	0.66
1; X = CH_2, Y = OH	0.4[7]; −1.0[8,9]	0.98
1; X = O, Y = OH	—	0.04

[a] The minus sign corresponds to preponderance of the axial isomer.

The results obtained for the unsaturated compounds are more difficult to interpret, because (*a*) there is a lack of reliable and complete experimental data for comparison, and (*b*) the presence of a C=C double-bond in the molecule makes the parameters less reliable, and causes a loss of accuracy in the results. Therefore, trends rather than the calculated numerical values will be discussed. The data for the unsaturated compounds collected in Table I can be summarized and interpreted as follows.

(*1*) As with the saturated analogues, the pseudoequatorial preference of the allylic substituent in 3-methylcyclohexene (**1**, X = CH_2, Y = Me) and 2-methyl-5,6-dihydro-2*H*-pyran (**1**, X = O, Y = Me) is approximately the same at 0.7 kcal/mol.

(*2*) A similar orientational preference (1.0 kcal/mol) was found for the allylic OH group in cyclohexen-3-ol (**1**, X = CH_2, Y = OH). The value of the energy difference obtained is difficult to compare quantitatively with experimental findings, since it refers to the isolated molecule, whereas the corresponding experimental data were obtained for polar solution spectra. The results of Ferrier's group[6,7] are certainly influenced by water solvation, and intermolecular solute–solute associations should play an important role in the measurements[8,9] (10–30% w/v concentrations) of Senda's group. The data for the corresponding acetates, given by both groups, could, in principle, rule out the second type of association. Unfortunately, the difference between the data reported is much smaller for the acetates (0 and −0.45 kcal/mol, respectively) than for the corresponding alcohols (0.4 and −1.0 kcal/mol, respectively). Moreover, the amount of the pseudoaxial isomer increased when OH was replaced by OAc, according to Ferrier's group, while the reverse behaviour was found by Senda's group. Thus, the magnitude of the allylic effect is still unclear and requires further experimental study. The calculations performed in the present work seem to indicate a preference for the pseudoequatorial isomer in the case of the isolated cyclohexen-3-ol molecule.

(*3*) It is of interest to note that no orientational preference was found for 5,6-dihydro-2*H*-pyran-2-ol in the calculations neglecting electrostatic interactions. The molecule is an interesting example of the compensating action of the anomeric and allylic effects. Both effects are strongly orientationally dependent and, as far as steric effects are concerned, act competitively. The anomeric effect in 5,6-dihydro-2*H*-pyran-2-ol (**1**, X = O, Y = OH) is much less-pronounced, resulting in comparable stability of the pseudoequatorial and pseudoaxial isomers. Inclusion of electrostatic interactions in the calculations, which seem unreliable at present, would change this result.

(*4*) As discussed earlier, 5,6-dihydro-2*H*-pyran-2-ol exhibits pronounced, sterically determined, conformational lability. This effect should also be partly removed by the electronic interactions.

CONCLUSIONS

The influence of steric effects on the conformational equilibrium of six-membered ring compounds substituted by Me or OH groups has been studied by classical conformational analysis. The allylic effect of a methyl group is due to steric interactions that also play an important role in the anomeric effect. In view of the lack of reliable experimental data, the need for further experimental studies is stressed. For an isolated cyclohexen-3-ol molecule, the calculations performed seem to indicate a preference for the isomer having the pseudoequatorial orientation of the hydroxyl group.

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