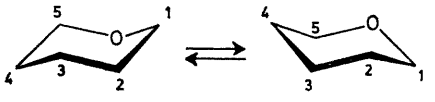
The Conformational Equilibria of Peracylated D-Aldopentopyranosyl Derivatives. Relative Anomeric Effect of Various Groups and the Influence of Configuration and Solvent

By PHILIPPE L. DURETTE and DEREK HORTON*
(*Department of Chemistry, The Ohio State University, Columbus, Ohio* 43210)

Summary The conformational equilibria of a wide range of peracylated D-aldopentopyranosyl derivatives in solution have been measured by n.m.r. spectroscopy, and the results obtained are discussed in terms of steric and electronic effects.

As part of a study[1] of the steric and electronic effects of multiple substituents on the conformational and configurational stability of tetrahydropyran ring-systems, we have measured by high-resolution n.m.r. spectroscopy the conformational equilibria in solution of fifty different peracylated D-aldopentopyranosyl derivatives. The results are presented in the Table; complete configurational series representing all possible stereochemical arrangements for a 2,3,4,5-tetrasubstituted tetrahydropyran are given for the tetra-acetates[2] (**1**), tetrabenzoates[3] (**2**), and methyl pyranoside triacetates (**5**).



1C *C1*

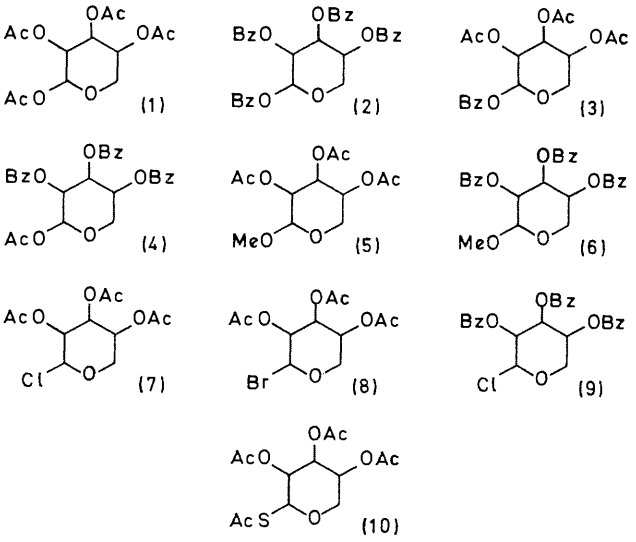
For each compound the n.m.r. spectral method of averaging of spin coupling[4] was used, as previously detailed,[1,2] to determine the proportions of the 1*C* (D) and *C*1 (D) conformers present at equilibrium. Spin couplings were obtained from spectra measured at 100 MHz (sweep width 100 Hz) with 20% (w/v) solutions. From the conformational populations determined[1] from the spin-coupling data, the equilibrium constants (K) and free-energy differences (ΔG^0) for the 1*C* (D) $\rightleftharpoons$ *C*1 (D) equilibria (Table), were calculated. The estimated uncertainty of $\pm 0{\cdot}5$ Hz in the magnitude of the model coupling constants and $\pm 0{\cdot}1$ Hz in the time-averaged couplings measured directly were used to assess the limits of accuracy in the measurements.

For several of the examples (Table) it was possible at low temperature to observe directly the spectra of the separate chair-like conformers, as already described[5] for β-D-*ribo*-(**1**); spectral integration allowed determination of equilibrium constants at low temperature for these examples.

The data obtained permit the following conclusions:

(a) For aldopentopyranoid sugar derivatives in solution, a conformational equilibrium between the two chair forms, with an appreciable (10% or more) proportion of the less favoured chair form, is the rule rather than the exception. Of the examples in the Table, only in the α-*xylo*-series is the *C*1 (D) conformer favoured overwhelmingly for a range of substituents at C-1, and only in the β-*arabino*-series is the 1*C* (D) conformer favoured very strongly for a range of substituents at C-1.

(b) The polar effect that favours the axial disposition of an electronegative C-1 substituent (anomeric effect)[6,7] can outweigh the combined steric effects of the sterically most unfavourable arrangement, a tetra-axially-disposed conformation having two *syn*-diaxial interactions. This is exemplified by β-D-*xylo*-(**9**) (>95% all axial) and β-D-*xylo*-(**7**) (79% all axial).



(c) The net axial-directing influence of a substituent at C-1 (presumably the resultant of a positive polar contribution and a negative steric contribution) is not independent of total stereochemistry. This influence falls in the order Br ≈ Cl ≫ OMe ≈ OBz ≈ OAc > SAc for the β-*ribo*- and α-*lyxo*-series. For the β-*xylo*-series, on the other hand, the order is Cl > OBz > SAc ≈ OAc > OMe; a similar order (SAc ≈ OBz > OAc ≈ OMe) is observed in the α-*arabino*-series. The axial-directing influence of the halogeno-groups is consistently strong, presumably because the C–halogen bond moments are larger than the C–O bond moment, but the influence of other groups appears to depend on whether or not the axial C-1 substituent has a *syn*-axial group at C-3. If such a *syn*-diaxial arrangement is present, the directing influence of the SAc group is relatively strong and that of the OMe group weak; if it is not, the directing influence of the SAc group is relatively weak and that of the OMe group relatively strong.

(d) The axial-directing influence of a substituent at C-1 is not independent of the substituents on O-2, O-3, and O-4. In the β-*ribo*-series the axial-directing influence of the C-1 substituent (OAc, OMe, or OBz) in the 2,3,4-tribenzoates is *ca.* 0·6 kcal. mole^{-1} higher than for the 2,3,4-triacetates; similar behaviour is observed in the β-*xylo*-series (for OAc, OMe, OBz, and Cl). In contrast, changing the 2,3,4-substituents from acetates to benzoates causes scarcely any change in the axial-directing influence of the C-1 substituent in the α-*lyxo*- (for OAc and OBz), α-*arabino*- (for

Free-energy differences and equilibrium constants for the $1C(D) \rightleftarrows C1(D)$ *conformational equilibria of peracylated aldopentopyranosyl derivatives*[a]

ΔG^0, kcal mole^{-1} [equilibrium constants ($K = C1/1C$) given in parentheses] for configuration shown

Structure[b]	α-D-*ribo*	β-D-*ribo*	α-D-*arabino*[c]	β-D-*arabino*	α-D-*xylo*	β-D-*xylo*	α-D-*lyxo*	β-D-*lyxo*
(1)	−0·74±0·33 (3·4)	+0·18±0·26 (0·74)[d]	+0·81±0·34 (0·26)	+1·9±1·0 (0·04)	<−2·4 (>50)[e]	−0·58±0·30 (2·6)	−0·55±0·30 (2·5)	+0·28±0·27 (0·63)[f]
(2)	−0·60±0·29 (2·7)	+0·72±0·31 (0·30)	+0·51±0·28 (0·43)	+1·8±0·9 (0·05)	<−2·4 (>50)[e]	+0·01±0·21 (0·98)	−0·63±0·30 (2·8)	+0·76±0·32 (0·29)
(3)	—	+0·16±0·28 (0·77)[g]	+0·62±0·31 (0·36)	—	—	−0·28±0·27 (1·6)	−0·58±0·30 (2·6)	—
(4)	—	+0·76±0·32 (0·29)	+0·57±0·29 (0·39)	—	—	−0·08±0·26 (1·1)	−0·60±0·29 (2·7)	—
(5)	−0·36±0·29 (1·8)	+0·28±0·28 (0·63)[g]	+0·98±0·40 (0·20)	+2·1±1·1 (0·03)	<−2·4 (>50)[e]	−0·89±0·37 (4·3)	−0·95±0·39 (5·0)[h]	−0·20±0·28 (1·4)
(6)	—	+0·85±0·36 (0·25)	—	+1·8±0·9 (0·05)	<−2·4 (>50)[e]	−0·63±0·32 (2·8)	—	—
(7)[c]	—	+1·5±0·60 (0·08)	—	+2·4±1·2 (0·02)	<−2·4 (>50)[e]	+0·81±0·32 (0·26)	−1·4±0·52 (9·6)	—
(8)[c]	—	+1·8±0·9 (0·05)	—	+2·1±1·1 (0·03)	<−2·4 (>50)[e]	—	−1·9±1·0 (24)	—
(9)[c]	—	—	—	—	<−2·4 (>50)[e]	+2·4±1·2 (0·02)	—	—
(10)	—	−0·41±0·28 (2·0)[g]	+0·47±0·29 (0·46)	—	—	−0·58±0·30 (2·6)	—	—

[a] $(CD_3)_2CO$ at 31—32°, unless otherwise stated. [b] Details of preparation of new compounds will be given in forthcoming reports. [c] All in $CDCl_3$. [d] Conformational "freeze-out" observed at −84°; $K_{-84°} = 0·5$. [e] Almost exclusively *C*1 (D) at 31°. [f] Conformational "freeze-out" observed at −97°; $K_{-97°} = 1·5$. [g] Conformational "freeze-out" observed at low temperatures. [h] Determined at 220 MHz at 23°.

OAc and OBz), or β-*arabino*- (for OMe) series. The strong influence observed in the β-*ribo*- and β-*xylo*-series may be correlated with *syn*-diaxial disposition of O-2 and O-4 in the conformation having the 1-substituent axial; an attractive interaction between *syn*-diaxial benzoyloxy-groups at C-2 and C-4 might be involved.

(e) The nature of the solvent and its polarity does not affect in any regular way the position of the conformational equilibria. Thus β-D-*xylo*-(**2**), which exists in $(CD_3)_2CO$ (dielectric constant $\epsilon = 20·7$) almost equally in the *C*1 (D) and 1*C* (D) conformations, shows approximately the same conformational populations, with no regular trend, through the solvent series C_6D_6 (ϵ 2·3), $C_6D_5{\cdot}CD_3$ (ϵ 2·4), $CDCl_3$ (ϵ 4·8), C_5D_5N (ϵ 12·3), hexachloroacetone, and $(CD_3)_2SO$ (ϵ 48·9). Similar results, showing negligible dependence of conformational populations on solvent polarity, are observed for β-D-*ribo*-(**1**) (*cf.* ref. 2), β-D-*xylo*-(**6**), and β-D-*xylo*-(**7**). That solvent effects on the position of conformational equilibria are not always explicable merely on the basis of solvent polarity is also evident from work in related systems.[8]

Various empirical treatments have been advanced for predicting the conformational preferences of polysubstituted tetrahydropyran ring-systems, based on additive contributions of steric interactions[9,10] and with the polar contribution of the anomeric effect.[6,7,11,12] The data presented in the present work cannot be accommodated within the framework of these existing interpretations except on a very broad, qualitative basis, even with adjustment of the magnitudes estimated for the various steric and polar elements. These results point out the need for reconsideration of other possible factors, such as polar contributions from other than the C-1 substituent, attractive interactions between *syn*-diaxial substituents, nonbonded interactions between atoms that have unshared pairs of electrons,[13] repulsive interactions between gauche-vicinal groups, the effect of solvent pressure and differences in molar volume between conformers,[14] and other contributing terms, in attempting to interpret quantitatively the conformational energies of polysubstituted, six-membered-ring systems, especially when a ring hetero-atom is involved.

This work was supported, in part, by a grant from the National Science Foundation.

(*Received, September 28th*, 1970; *Com.* **1649**.)

[1] Previous paper in this series: P. L. Durette, D. Horton, and N. S. Bhacca, *Carbohydrate Res.*, 1969, **10**, 565.
[2] P. L. Durette and D. Horton, *Chem. Comm.*, 1969, 516.
[3] P. L. Durette and D. Horton, Abstracts Papers Amer. Chem. Soc. Meeting, 1969, **158**, C25.
[4] F. A. L. Anet, *J. Amer. Chem. Soc.*, 1962, **84**, 1053; H. Feltkamp and N. C. Franklin, *ibid.*, 1965, **87**, 1616.
[5] N. S. Bhacca and D. Horton, *J. Amer. Chem. Soc.*, 1967, **89**, 5993.
[6] J. T. Edward, *Chem. and Ind.*, 1955, 1102.
[7] R. U. Lemieux in "Molecular Rearrangements," part 2, ed. P. de Mayo, Interscience, New York, 1964, pp. 735—743.
[8] R. U. Lemieux, A. A. Pavia, J. C. Martin, and K. A. Watanabe, *Canad. J. Chem.*, 1969, **47**, 4427; E. L. Eliel and M. K. Kaloustian, *Chem. Comm.*, 1970, 290.
[9] R. E. Reeves, *J. Amer. Chem. Soc.*, 1950, **72**, 1499; R. E. Reeves, *Adv. Carbohydrate Chem.*, 1951, **6**, 107.
[10] R. B. Kelly, *Canad. J. Chem.*, 1957, **35**, 149.
[11] E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis," Interscience, New York, 1965, ch. **6**, pp. 375—377.
[12] S. J. Angyal, *Angew. Chem. Internat. Edn.*, 1969, **8**, 157.
[13] R. U. Lemieux and A. A. Pavia, *Canad. J. Chem.*, 1969, **47**, 4441.
[14] R. J. Ouellette and S. H. Williams, *J. Amer. Chem. Soc.*, in the press.