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STRUCTURES AND CONFORMATIONS OF SOME D-*GLYCERO*-PENT-2-ENOPYRANOSYL DERIVATIVES AND DETERMINATION OF THE RELATIVE SIGNS OF SOME ASSOCIATED LONG-RANGE PROTON COUPLING CONSTANTS

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Abstract—Methyl 3,4-dichloro-4-deoxy-α-D-*glycero*-pent-2-enopyranoside and 3,4-dichloro-4-deoxy-β-D-*glycero*-pent-2-enopyranose have been synthesized from L-arabinose. The ring conformations of these unsaturated derivatives and those of the previously reported methyl β-D-glycoside and dimeric analogue have been determined by PMR spectroscopy, the conformational assignments being based upon both vicinal and long range coupling constants. Frequency swept spin decoupling experiments at 100 Mc/s showed that the bi-allylic and $J_{1,3}$ vicinal coupling constants in the methyl α-D-anomer are of the same sign, whereas its allylic and $J_{1,2}$ vicinal couplings have opposite signs. The α and β derivatives exist predominantly in different half-chair conformations, controlled in each case by the presence of the anomeric effect. The free energy difference of the anomeric methyl glycosides has been obtained by GLC analysis of equilibrated mixtures. The greater stability of the β-anomer is interpreted in terms of Van der Waals energies and dipole interactions.

THE synthesis and properties of 2,3-unsaturated derivatives of carbohydrates have attracted continuing attention.[1-7] Many examples of hex-2-enopyransoyl derivatives are now known,[1,4,5,7] but the corresponding structures derived from pentoses appear to be less common.[3] Two further examples of the latter class of substances have recently been described.[6] Thus pyridine catalysed elimination of chlorosulphuric

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[1] F. H. Newth, *J. Chem. Soc.* 471 (1956); R. J. Ferrier, W. G. Overend and A. E. Ryan, *ibid*, 3667 (1962).
[2] R. K. Ness and H. G. Fletcher, Jr., *J. Org. Chem.* **28**, 435 (1963).
[3] N. F. Taylor and G. M. Riggs, *Chem. & Ind.* 209 (1963); *J. Chem. Soc.* 5600 (1963).
[4] [a] R. J. Ferrier, *J. Chem. Soc.* 5443 (1964); *Advances in Carbohydrate Chem.* **20**, 67 (1965); [b] R. J. Ferrier, W. G. Overend and G. H. Sankey, *J. Chem. Soc.* 2830 (1965); [c] D. M. Ciment and R. J. Ferrier, *ibid.* (C) 441 (1966); D. M. Ciment, R. J. Ferrier and W. G. Overend, *Ibid.* (C) 446 (1966).
[5] E. F. L. J. Anet, *Aust. J. Chem.* **18**, 837 (1965); and previous papers in a series.
[6] H. J. Jennings and J. K. N. Jones, *Canad. J. Chem.* **43**, 3018 (1965).
[7] E. F. L. J. Anet, *Carbohydrate Research* **1**, 348 (1966).

acid from methyl 3,4-dichloro-3,4-dideoxy-β-D-ribopyranoside 2-chlorosulphate yielded methyl 3,4-dichloro-4-deoxy-β-D-*glycero*-pent-2-enopyranoside (I).[6] Structural proof for I was based in part on its PMR spectrum which at 60 Mc/s was only partially resolved. A 1,1′ linked dimeric analogue of I was reported, which on methanolysis also gave I.[6]

The pyranose rings of these unsaturated derivatives are expected to exist in either the half-chair, or less likely, in the half-boat conformations. Progress has been made recently towards the elucidation of the ring conformations of hex-2-enopyranosyl derivatives using PMR spectroscopy.[4b,5,7] It is now apparent[8,9] that conformational preference in *saturated* pentopyranose rings may be dominated completely by the operation of the anomeric effect[10] of the substituent at C_1. It was found for example, that tri-O-benzoyl-α- and β-D-ribopyranosyl 1-halides exist predominantly in different chair conformations, always containing the 1-halogen atom in axial orientation.[8] Similar derivatives containing a 1-substituent for which a positive anomeric effect was not expected, tended to adopt mainly the chair conformation in which this substituent was equatorial.[8] The question arose, therefore, as to whether similar effects govern the half chair conformations of *unsaturated* pentopyranosyl derivatives. The synthesis of the α-anomer IV of I reported herein, and the fact that at a spectrometer frequency of 100 Mc/s both I and IV yielded well resolved PMR spectra (Figs. 1 and 2), provided the opportunity for an investigation of the factors which influence conformational preference and stability in these unusual sugar derivatives.

Further evidence for the structure of the β-D-glycoside (I) was obtained as follows. Acidic hydrolysis of I gave a crystalline product which displayed reducing properties, mutarotation, OH absorption in the IR, and which retained ethylenic absorption characteristics in the IR and UV identical with those of I. The PMR spectrum of the product showed a broad singlet at low field which was assigned to a OH proton. The close relationship of the structure and anomeric configuration of the product to those of I was further indicated by the marked similarity of the spectra of the ring protons in the two compounds. In agreement with its elemental analysis, the product of hydrolysis was therefore assigned the structure 3,4-dichloro-4-deoxy-β-D-*glycero*-pent-2-enopyranose (II). Its downward mutarotation in methanolic solution appears to be anomalous (see below). Under the conditions of acidic hydrolysis, the alternatively possible structure VIII of I would have been expected to give a 2-deoxy-aldonolactone derivative by preliminary protonation at C_2.[4a] No analytical or spectroscopic evidence was found to support such a possibility, and the structure of I is therefore confirmed by its hydrolysis to the 1-hydroxy derivative II.

Previously, the dimeric analogue of I had been tentatively assigned the structure of a symmetrical αα′-linked disaccharide.[6] In order to confirm or refute this structure, the preparation of an authentic example of an α-glycoside was necessary. Attempts to prepare the methyl α-D-glycoside IV by methods similar to those used to synthesize its β-anomer I had failed, since the precursor methyl 3,4-dichloro-3,4-dideoxy-α-D-ribopyranoside 2-chlorosulphate (VI) could not be prepared from methyl-β-L-arabinopyranoside because of the unfavourable steric effect of the axial anomeric methoxyl

[6] B. Coxon, *Tetrahedron* **22**, 2281 (1966).
[9] cf. D. Horton and W. N. Turner, *Chem. Comm.* 113 (1965); *J. Org. Chem.* **30**, 3387 (1965).
[10] J. T. Edward, *Chem. & Ind.* 1102 (1955); R. U. Lemieux, *Molecular Rearrangements* (Edited by P. de Mayo) part 2; p. 735. Interscience, New York (1963).

group on chloro-substitution at C_3.[6] Additionally, methanolysis of the dimer had been shown to yield predominantly I. Therefore, another approach was made. It had been postulated[6] that 3,4-dichloro-3,4-dideoxy-D-ribopyranosyl chloride 2-chlorosulphate was one of the unisolated products of the reaction of L-arabinose with sulphuryl chloride, and it was anticipated that the isolation of this product, and its subsequent methanolysis might yield the appropriate precursor VI of IV. The syrupy reaction mixture from the chlorosulphation containing at least two components (TLC) was chromatographed on silica gel, and two crystalline products were obtained. A minor product was the previously isolated[6] 4-chloro-4-deoxy-D-xylopyranosyl chloride-2,3-dichlorosulphate. Its PMR spectrum in $CDCl_3$ at 60 Mc/s displayed a doublet at τ 3·51, a very complex multiplet at τ 4·61, a sharp quartet at τ 5·05, and a complex multiplet (intensity 3 protons) at τ 5·8. These multiplets were assigned to H_1, H_3, H_2, and to the group H_4, H_{5e} and H_{5a}, respectively. The H_1 and H_2 multiplets yielded spacings $J_{1,2} = 3·8$ and $J_{2,3} = 9·6$ c/s. The complexity of the H_3 signal was evidently due to virtual coupling[11] with the strongly coupled ABC sub-system comprised by H_4, H_{5e} and H_{5a} (cf. virtual coupling of H_3 in α-D-glucopyranoside derivatives[12a]). However, if H_3 is treated as the X part of an ABCX system and it is assumed furthermore that it couples to H_2 and H_4 only, then the separation of the outermost lines represents the sum of $J_{2,3}$ and $J_{3,4}$.[12b] This implies that $J_{3,4} \approx 8·8$ c/s. The large values of $J_{2,3}$ and $J_{3,4}$ show that this chloride exists mainly in the Cl conformation IX in which the proton pairs H_2–H_3, and H_3–H_4 are diaxial. The comparatively small value of $J_{1,2}$ indicates that its anomeric configuration (previously undefined) is α-D (cf. $J_{1,2} = 3·3$, and $J_{2,3} = J_{3,4} = 9·5$ c/s in α-D-xylopyranose tetra-acetate[13]). Elemental analysis of the major product V showed that it contained three chlorine atoms attached to the carbon chain and one chloro-sulphate group. Its reaction with sodium iodide in aqueous acetone yielded the known crystalline 3,4-dichloro-3,4-dideoxy-β-D-ribopyranose,[6] revealing thereby the location and configuration of two of the chlorine atoms. That the third chlorine atom was situated at C_1 of V was ascertained by treatment with methanol in the presence of silver carbonate which gave a methyl glycoside still containing the chlorosulphate group, which must, therefore, have been at C_2. Since the formation of furanosides is not possible without expulsion of chlorine from C_4, and because the glycoside was isomeric with, but had different physical properties to, the known methyl 3,4-dichloro-3,4-dideoxy-β-D-ribopyranoside 2-chlorosulphate ($[\alpha]_D$ −102°)[6] it was assigned therefore as the α-anomer VI, in agreement with an optical rotation $[\alpha]_D$ +65°. At 60 Mc/s in $CDCl_3$, the PMR spectrum of VI was complex and uninformative. The specific rotation −174° of the 1-chloro precursor indicated that its anomeric configuration was β-D (cf. $[\alpha]_D$ −147° in tri-O-benzoyl-β-D-ribopyranosyl chloride[14]), and hence the major isolated product of the chlorosulphation of L-arabinose is 3,4-dichloro-3,4-dideoxy-β-D-ribopyranosyl chloride 2-chlorosulphate (V). By analogy with other β-D-ribopyranosyl halides,[8,9] V is expected to be the thermodynamically stable anomer existing preferentially in the 1C chair conformation (V as shown). PMR evidence in support of this configuration

[11] J. I. Musher and E. J. Corey, *Tetrahedron* **18**, 791 (1962).

[12] [a] B. Coxon, *Tetrahedron* **21**, 3481 (1965); [b] C. N. Banwell and N. Sheppard, *Proc. Roy. Soc.* A, **263**, 136 (1961).

[13] R. U. Lemieux and J. D. Stevens, *Canad. J. Chem.* **43**, 2059 (1965).

[14] R. K. Ness, H. G. Fletcher, Jr., & C. S. Hudson, *J. Am. Chem. Soc.* **73**, 959 (1951).

and conformation was not immediately available, since the spectrum of V in $CDCl_3$ at 60 Mc/s was complex. A group of lines at τ 3·72 consisting of a triplet of lines of almost equal intensity flanked by weak wings was assigned to H_1 (cf. H_1 at τ 3·66 in tri-O-benzoyl-β-D-ribopyranosyl chloride[8]), and a narrow complex multiplet (intensity two protons) at τ 5·05 to H_2 and H_3. A wide complex multiplet (intensity three protons) at τ 5·7 was assigned to H_4 and $2H_5$. The complexity of the H_1 signal was undoubtedly caused by virtual coupling[11] due to the tightly coupled H_2 and H_3. The α-D-xylopyranosyl chloride derivative IX would also be expected to be the thermodynamically more stable anomer, and hence it seems likely that the conditions of the chlorosulphation reaction favour anomerization of the 1-chlorides which are produced.

Since a *trans*-β-glycoside was not obtained in the methanolysis of V it appears that there was no participation in the displacement of the chlorine from C_1 by the neighbouring chlorosulphate group, a process which if it occurred, would be at a maximum in the 1C conformation V. Predominant inversion of configuration at C_1 is a common consequence of alcoholysis reactions of hexopyranosyl 1-halides containing a non-participating substituent in *trans* relationship at C_2.[15,16] In the D-arabino-furanose series, methanolyses of anomeric 1-chlorides containing a nitrate group at C_2 (in the absence of an acid acceptor) have recently given major yields of the 1,2 *cis*-glycoside, regardless of the anomeric configuration of the chloride.[17] This has been rationalized in terms of anomerization to a more stable *trans* ion-pair intermediate.[1]

As a non-participating substituent, the chlorosulphate group is advantageous since it is easily synthesized, and since subsequent regeneration of the OH group may be achieved rapidly.[18]

Treatment of the α-glycoside-2-chlorosulphate (VI) with pyridine gave only a single unsaturated syrupy product IV (TLC and GLC), the structure of which was proved as follows. It had been demonstrated previously[19] that the preferred mode of elimination of the elements of chlorosulphuric acid under these conditions involves the expulsion of *trans*-diaxial substituents, suggesting that the reaction in this case would proceed *via* the 1C conformation VI to give either the 2-ene IV, or the 1-ene VIII. Structure VIII could not be immediately discarded by inspection of the PMR spectrum (Fig. 2) of the elimination product; however acid hydrolysis of the latter gave only the crystalline 1-hydroxy derivative II which, as noted above, is not expected to be the hydrolysis product of VIII. This structure may therefore be ruled out. It was observed that the hydrolyses of the glycosides I and IV were quite rapid, as might be expected from the likely formation under acidic conditions of the stable allylic oxocarbonium ion VII. The structural relationships of the glycosides I and IV and the dimeric analogue III were further confirmed by their acid-catalysed methanolysis reactions, from which the products were either isolated, or estimated by GLC. On a preparative scale, methanolyses of III and IV both gave the crystalline β-glycoside I in good yield, suggesting that I is the thermodynamically favoured product of an equilibration process. GLC analysis showed that methanolyses of I, III, and IV at 20°, in

[15] M. L. Wolfrom and I. C. Gillam, *Science, Lond.* **130**, 1424 (1959); M. L. Wolfrom, A. O. Pittet, and I. C. Gillam, *Proc. Nat. Acad. Sci.* **47**, 700 (1961); M. L. Wolfrom, A. Thompson and D. R. Lineback, *J. Org. Chem.* **28**, 860 (1963); M. L. Wolfrom and K. Koizumi, *Chem. Comm.* 2 (1966).

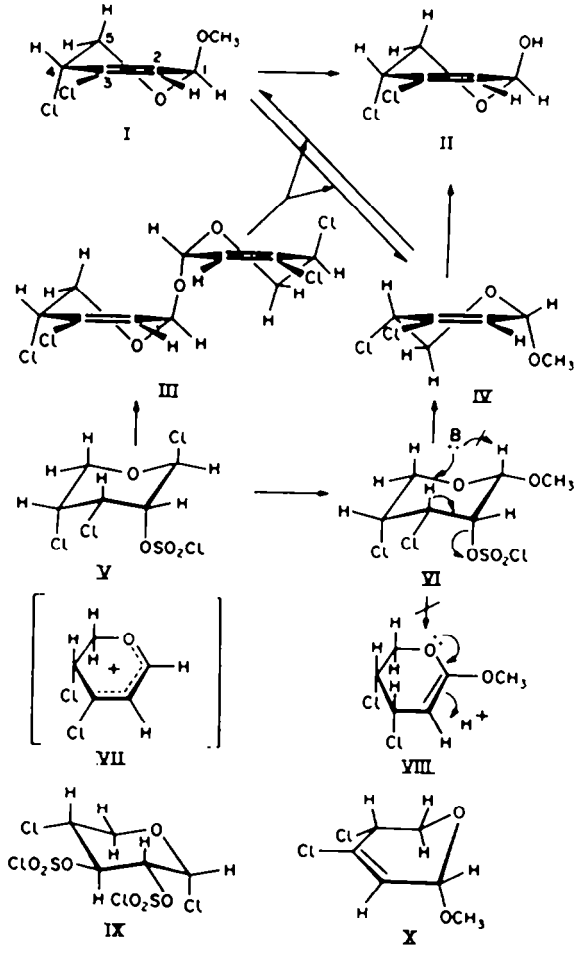
[16] P. A. J. Gorin and A. S. Perlin, *Canad. J. Chem.* **39**, 2474 (1961).

[17] C. P. J. Glaudemanns and H. G. Fletcher, Jr., *J. Am. Chem. Soc.* **87**, 2456 (1965).

[18] H. J. Jennings and J. K. N. Jones, *Canad. J. Chem.* **43**, 2372 (1965).

[19] H. J. Jennings and J. K. N. Jones, *Canad. J. Chem.* **41**, 1151 (1963).

each case yielded the same equilibrated mixture of anomers, as indicated by the observation of peaks with retention times identical with those of pure I and IV. *After* neutralization of the hydrogen chloride catalyst, the $\beta:\alpha$ ratio was in each case 9:1. However, *before* neutralization, the apparent $\beta:\alpha$ ratio was 6·4:1 in each case. This difference may be ascribed to a rapid acid-catalysed redistribution of the equilibrium in the unneutralized samples towards the less stable α-anomer, due to the high



temperature (150°) in the inlet port of the GLC column. Although the formation of IV from I in methanolic hydrogen chloride could be detected readily by GLC, syrupy IV was difficult to isolate because of the preponderance of its β-anomer I in the equilibrium mixture. Additionally, detection of the signals of IV in the PMR spectrum of the methanolysis product ($\beta:\alpha$, 9:1) of I was also difficult. However, measurement of a spectrum of the mother liquors ($\beta:\alpha$, 3:1 by GLC) obtained by removal of the bulk of the β-anomer I by crystallization enabled several of the characteristic signals of the α-anomer IV to be observed, thus confirming the presence of IV in the mixture.

The conclusion that compounds I–IV are all 3,4-dichloro-4-deoxy-D-*glycero*-pent-2-enopyranosyl derivatives is supported by their similar IR and UV spectroscopic

properties, ν_{max} 1650 cm^{-1} and λ_{max} 212 mμ. The PMR spectra of the β-glycoside I (Fig. 1), its parent sugar II, and the dimer III were all markedly similar, but quite dissimilar to that (Fig. 2) of the α-glycoside IV. It now seems more likely therefore, that the dimer has the $\beta\beta'$ anomeric configuration III rather than the $\alpha\alpha'$ previously assigned tentatively[6] on the basis of the chemical shift of its anomeric protons, and its large positive rotation. In fact, the chemical shifts of H_1 in the anomeric glycosides I and IV are very similar (Table 1), as are also their specific rotations at the sodium D-line, which are both positive and differ by only two degrees. It has been observed recently[4] that the optical rotatory properties of many hex-2-enopyranosyl derivatives contravene Hudson's rules of isorotation.[20] (cf. the downward mutarotation of the β-D-reducing sugar II.) The usual application of optical rotatory data is therefore an unreliable means of determining anomeric configuration in both pent- and hex-2-enopyranosyl derivatives.

It is perhaps surprising that none of the 1-ene VIII was isolated from the pyridine catalysed elimination reaction of the chlorosulphate VI, since on steric grounds alone its formation appears to be as probable as that of the 2-ene. Some evidence is available to suggest that removal of a proton from a carbon atom bearing oxygen substituents is less facile than from one having chlorine substituents, due probably to stabilization of the chloro-carbanion by d-orbital resonance.[21] Such stabilization would be relevant to the transition state of the elimination reaction of VI if this possessed at least some carbanion character.[22] Alternatively, the resemblance of the stability of the transition state to that of the product may favour the formation of the more stable vinyl chloride IV. Although vinyl chlorides are generally thought to be stabilized by resonance involving a positively charged chlorine atom,[23] the vinyl di-ether VIII may not be stabilized to the same extent because of the presence in its most likely mesomeric form of two oxygen atoms carrying partial positive charges in close proximity. More complex mechanisms for the formation of IV are possible, for example, those involving hydrogen migrations in the 1-ene VIII or in its C_2-protonated form. (Cf. the greater stability of hex-2-enopyranose derivatives compared with 2-hydroxyl-1-enopyranose compounds.[4a]) To our knowledge, no example of an elimination reaction incorporating the removal of a proton from C_1 has been observed in carbohydrate chemistry.

It had been postulated previously[6] that the mixture resulting from the reaction of L-arabinose with sulphuryl chloride contained the D-ribopyranosyl chloride (V) and that this was a precursor of the dimer III. This has been confirmed by the isolation of V, and by the observation that treatment of it with pyridine in chloroform followed by partitioning of the product between chloroform and dilute aqueous acid led to the separation from the latter solution of crystalline III. A 60 Mc/s PMR spectrum obtained from a solution of V in 1:3 v/v pyridine-d_5:chloroform-d displayed doublets of equal intensity and spacing 3·4 c/s at τ 3·31 and 2·53 which resembled the signals

[20] C. S. Hudson, *J. Am. Chem. Soc.* **31**, 66 (1909); cf. D. Horton, *J. Org. Chem.* **29**, 1776 (1964) and Ref. therein.

[21] L. H. Slaugh and E. Bergmann, *J. Org. Chem.* **26**, 3158 (1961).

[22] E. S. Gould, *Mechanism and Structure in Organic Chemistry* p. 497. Holt, Rinehart and Winston, New York (1959).

[23] L. Pauling, *The Nature of the Chemical Bond* (3rd Edition) p. 288. Cornell University Press, Ithaca, New York (1960).

due to H_1 and H_2 in the spectra of the 3,4-dichloro-4-deoxy-β-D-*glycero*-pent-2-enopyranosyl derivatives I–III. Because of their appearance at low field, it seems likely that these doublets represent the signals of H_1 and H_2 in a 1-pyridinium analogue of compounds I–IV.[24] The spectrum also contained a doublet at τ 3·45, with spacing

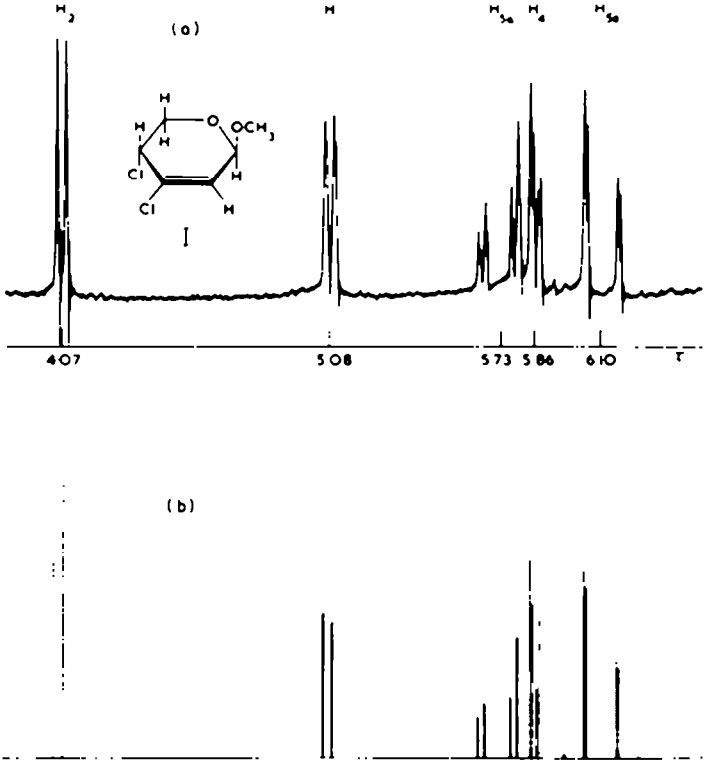


FIG. 1. PMR spectra of methyl 3,4-dichloro-4-deoxy-β-D-*glycero*-pent-2-enopyranoside (I), (a) in $CDCl_3$ at 100 Mc/s, (b) computed. The methoxyl resonance is not shown.

2·1 c/s, and intensity about half that of the doublets described above, due possibly to an anomeric N-glycoside. It was not possible to interpret the remainder of the spectrum.

Neutralization of the aqueous acid-wash of the chloroform-soluble product from the L-arabinose-sulphuryl chloride reaction yielded the crystalline 1-hydroxy derivative II thus suggesting the presence of a water soluble intermediate of similar structure to compounds I–IV.

The foregoing observations support a previous suggestion[6] that the dimer III is formed *via* an intermediary pyridinium glycoside. One possibility is that the latter N-glycoside is hydrolysed to the OH derivative II which then dimerizes by an acid catalysed reversion process in which the equilibrium is displaced towards the dimer III by its insolubility in aqueous acid.

In the 100 Mc/s spectrum (Fig. 1) of the β-glycoside I in $CDCl_3$ under optimized resolution, the anomeric proton appeared as a quartet at τ 5·08 with one very small

[24] Cf. R. U. Lemieux and A. R. Morgan, *Canad. J. Chem.* **43**, 2205, 2214 (1965).

spacing of 0·4 c/s, and the vinylic H_2 as a very sharp doublet at τ 4·07.[6] The octet at τ 5·73, also with one small spacing, and the quartet at τ 6·10 both contained a large splitting (12·5 c/s), and hence were assigned to the geminal protons H_6 and $H_{6'}$ respectively. Two of the other splittings in these multiplets were present in the remaining quartet at τ 5·86, which was therefore assigned to H_4. Irradiation of H_1 with a strong radiofrequency field under frequency swept conditions caused the H_2 doublet to collapse to a singlet thereby confirming its assignment, and also removed the smallest splitting from the H_6 octet, thus demonstrating that there is a small long range coupling (0·4 c/s) between H_1 and H_6. Analysis of the H_4, H_6 and $H_{6'}$ group was performed initially as an ABX system. In order to refine the parameters further, theoretical spectra were computed for the five-spin system comprised by the ring protons, using the Frequint IV program. Mean chemical shifts weighted according to peak heights in the multiplets were used for H_1, H_2 and $H_{5'}$, and ν_A and ν_B derived from the ABX analysis, for H_6 and H_4 respectively. Values of $J_{1,2}$ and $J_{1,5}$ derived by first-order analysis were inserted in the program, and the remaining coupling constants were taken from the ABX analysis. For the purposes of computation, the geminal coupling constant $J_{5,5'}$, and the four (or six) bond long range coupling $J_{1,5}$ were taken as being negative.[25] Comparison of the computed and experimental spectra indicated that only small adjustments (1 c/s or less) of the chemical shifts were necessary to obtain a good fit. Recomputation then gave the theoretical spectrum in Fig. 1, in which the maximum deviation between observed and calculated line positions was 0·22 c/s. The spin system was insufficiently strongly coupled to be variant on the sign of $J_{1,5}$ which could not therefore be determined. The parameters obtained are listed in Table 1.

The spectra of the reducing sugar II (in 2:1 $CDCl_3$:pyridine) and the dimer III (in pyridine) were assigned by analogy with the methyl β-D-glycoside I. The broadness of the H_1 and H_5 multiplets in these spectra again suggested the presence of a small long range coupling between H_1 and H_5. The chemical shifts of II and III calculated either as weighted means, or from the ABX analyses (ν_A and ν_B only) are shown in Table 1 together with coupling constants derived from first order or ABX analyses.

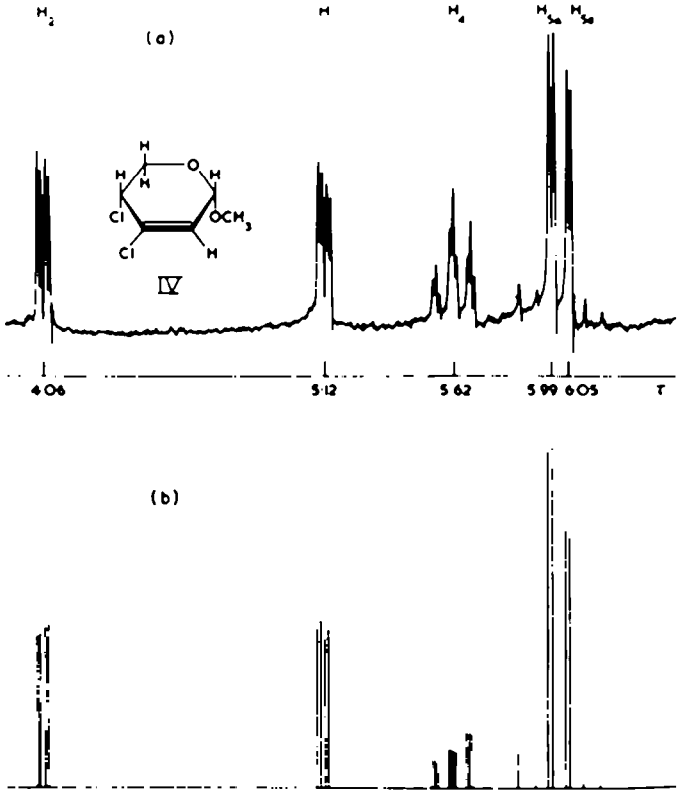
The small values of $J_{4,5}$ and $J_{4,5'}$ in these β-derivatives indicate that they exist predominantly in conformations, for example, the half-chairs I, II, and III, in which looking along the C_4—C_5 bond, H_4 lies inside the dihedral angle subtended by the H_5 protons. For example, if the values $J_{4,5} = 2{\cdot}7$ and $J_{4,5'} = 1{\cdot}04$ c/s in the β-glycoside I are used in the Karplus equation[26]

$$J_{vic} = 4{\cdot}22 - 0{\cdot}5 \cos \phi + 4{\cdot}5 \cos 2\phi \qquad (1)$$

to calculate *very approximate* values of the vicinal dihedral angles, one obtains $\phi_{4,5} \simeq 53°$ or 123°, and $\phi_{4,5'} \simeq 66°$ or 111°. Since these angles must add or subtract to give approximately 120°, therefore the only valid combination is 53° and 66°. Measurement of a Crystal Structures Ltd (CSL) scale molecular model of the half chair conformation I suggested dihedral angles $\phi_{4,5a} = 50°$, and $\phi_{4,5e} = 70°$. If the H_5 multiplets are assigned on this basis, then the octet at τ 5·73 must be assigned to the axial H_5, and the quartet at higher field to H_{5e}. The appearance of H_{5a} at lower field

[25] S. Sternhell, *Rev. Pure & Appl. Chem.* **14**, 15 (1964).
[26] M. Karplus, *J. Am. Chem. Soc.* **85**, 2870 (1963).

than H_{5e} may be explicable in terms of deshielding of H_{5a} by the almost *trans*-coplanar chlorine at C_4, and the *syn*-quasiaxial methoxyl group.[27] This assignment implies that it is H_{5a} which shows a coupling of 0·4 c/s to H_1, whereas H_{5e} and quasi-equatorial H_1 which in the half chair I possess the planar zig-zag arrangement of intervening σ bonds normally considered to be optimum for long range coupling over four bonds,[25,28] did not display an observable coupling. Such behaviour is unusual. On the basis of results from 4-substituted-1,3-dioxanes in chair conformations, it has recently been



IV

FIG. 2. PMR spectra of methyl 3,4-dichloro-4-deoxy-α-D-*glycero*-pent-2-enopyranoside (IV), (a) in $CDCl_3$ at 100 Mc/s, (b) computed. The methoxyl resonance is not shown.

pointed out that a planar zig-zag arrangement is not necessary for the observation of long range couplings of the order of 0·5 c/s.[29] However, in the cases reported, $J_{2e,4e}$ was always appreciably larger than the other types of long range coupling which were present. It is to be noted however, that a change in ϕ of 10° would suffice to reverse the assignment, and it may well be that the model and measurements taken from it are not accurate to this degree. The assignment is very largely independent of the parameters used in the Karplus equation. In any event, the assignments given above for H_{5e} and H_{5a} must be regarded as tentative.

[27] N. S. Bhacca and D. H. Williams, *Applications of NMR Spectroscopy in Organic Chemistry. Illustrations from the steroid field* p. 185. Holden-Day, San Francisco (1964).
[28] M. Barfield, *J. Chem. Phys.* **41**, 3825 (1964).
[29] K. C. Ramey & J. Messick, *Tetrahedron Letters* 4423 (1965).

In the spectrum (Fig. 2) of the methyl α-D-glycoside IV in $CDCl_3$, the sharp quartet at lowest field was assigned to the vinylic proton at C_2, and the less sharp quartet at τ 5·12 to H_1. Strong irradiation in the H_5 region of the spectrum caused the latter quartet to sharpen, thus suggesting the presence of a very small long range coupling between H_1 and one of the H_5 protons. The latter geminal protons were assigned as the AB system at high field with $J = 11{\cdot}6$ c/s. The smaller splittings in the H_1 and H_2 quartets also appeared in the nonet assigned to H_4 which is therefore coupled to all four other ring protons. First order analysis gave the values $J_{2,4} = 1{\cdot}2$

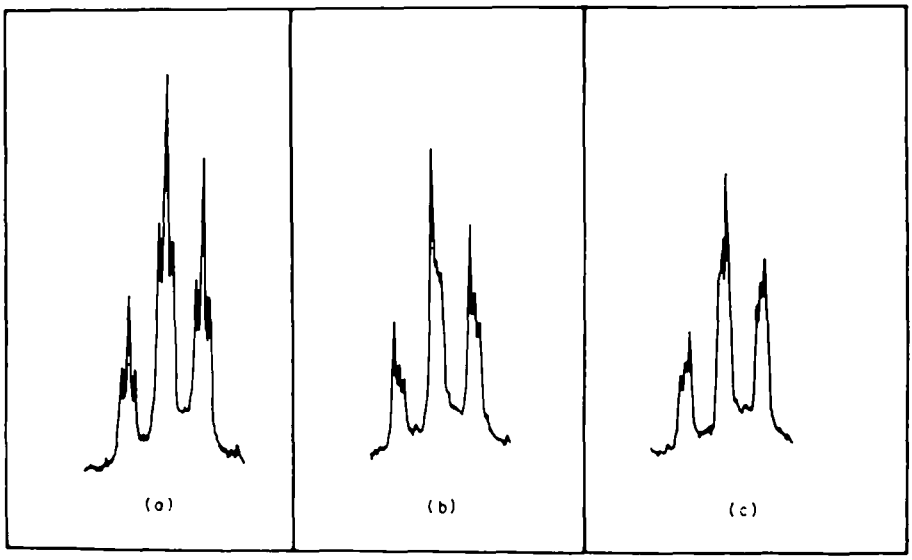


FIG. 3. Frequency swept spin decoupling experiments with methyl 3,4-dichloro-4-deoxy-α-D-*glycero* pent-2-enopyranoside (IV) in $CDCl_3$ at 100 Mc/s. Resonance due to H_4 (a) unperturbed, (b) with irradiation of the low field pair of lines of the H_5 quartet, and (c) with irradiation of the low field pair of lines of the H_1 quartet.

for the allylic, and $J_{1,4} = 1{\cdot}3$ c/s for the biallylic[30a] (homoallylic[25]) long range couplings. The relative signs of the allylic, biallylic and vicinal $J_{1,2}$ coupling constants were determined by the frequency-sweep spin decoupling technique, and some of the results are shown in Fig. 3. For the purpose of this experiment, the H_1, H_2 and H_4 spectrum can be considered as a 3-spin AMX system in which the X resonance, due to H_4 and showing two almost equal small splittings, is further coupled to the H_5 protons to give the major triplet. It is expected therefore, that the effect of any double resonance experiment will be seen on each component of this triplet. Fig. 3a shows the H_4 nonet whilst 3b shows the effect on it of irradiating the lowest field pair of lines in the H_2 quartet. It is seen that this has affected the lowest field pair due to the $J_{2,4}$ coupling in each line of the H_4 resonance, which implies that $J_{1,4}$ and $J_{1,2}$ are of like sign.[30b] Similarly, as seen in Fig. 3c irradiation of the low field pair of lines in the H_1 quartet, due to the $J_{1,4}$ coupling, affects the high field pair in each of the H_4 lines and demonstrates that $J_{2,4}$ is of opposite sign to $J_{1,2}$. These observations are in agreement with previous work showing that in the many cases where coupling is dominated by a

[30] [a] C. R. Narayanan and N. K. Venkatasubramanian, *Indian J. Chem.* **2**, 274 (1964). [b] R. Freeman and D. H. Whiffen, *Mol. Phys.* **4**, 321 (1961).

TABLE 1. CHEMICAL SHIFTS (τ) AND COUPLING CONSTANTS (c/s) OF 3,4-DICHLORO-4-DEOXY-D-*glycero*-PENT-2-ENOPYRANOSYL DERIVATIVES

Compound	R_1	Solvent	H_1	H_3	H_4	H_{5e}	H_{5a}	R_1
I[a]	β-OCH_3	$CDCl_3$	5·08q[c] $J_{1,2}$ = 3·3 $J_{1,5a}$ = −0·4[e]	4·07d	5·86q[d] $J_{4,5e}$ = 1·04 $J_{4,5a}$ = 2·70	6·10q[d] $J_{5e,5a}$ = −12·49[e]	5·73o[d]	6·62
II[b]	β-OH	$CDCl_3$:Pyridine (2:1 v/v)	4·36d[f] $J_{1,2}$ = 3·4	3·80d	5·68q[d] $J_{4,5e}$ = 1·45 $J_{4,5a}$ = 2·67	5·96q[d] $J_{5e,5a}$ = −12·70[e]	5·36q[f,g]	3·40[g]
III[e,h]	β-$C_8H_6Cl_3O_3$	Pyridine	4·42d[f] $J_{1,2}$ = 3·4	3·92d	5·43m[f,i] $J_{4,5e}$ = 0·91 $J_{4,5a}$ = 2·71	5·99q[f] $J_{5e,5a}$ = −12·79[e]	5·67q[f,i]	As for H_1, H_3, H_4, H_{5e}, and H_{5a}.
IV[a]	α-OCH_3	$CDCl_3$	5·12q $J_{1,2}$ = 3·1 $J_{1,4}$ = 1·3	4·06q $J_{3,4}$ = −1·2	5·62n[f] $J_{4,5e}$ = 6·36 (5·56)[k] $J_{4,5a}$ = 7·07 (7·87)[k]	6·05q[f] $J_{5e,5a}$ = −11·61[e]	5·99q[f]	6·62

[a] Measured at 100 Mc/s
[b] Measured at 60 Mc/s
[c] Signal multiplicities are indicated by d(doublet), q(quartet), o(octet), n(nonet), and m(complex multiplet)
[d] Analysed as an $A(H_{5a})B(H_4)X(H_{5e})$ sub-system
[e] Assumed negative
[f] Broadened multiplet
[g] Broad singlet. Assignment confirmed by deuterium exchange
[h] Measured at 60° because of low solubility
[i] Unresolved
[j] Analysed as an $A(H_{5a})B(H_{5e})X(H_4)$ sub-system
[k] Values in parentheses were determined by two iterations of a computer program for five spins.

σ–π contact mechanism,[25] allylic couplings are negative, and biallylic ones positive. Examples of *positive* allylic couplings in bicyclo-alkenes, -alkadienes, and -alkatrienes have been attributed to dominance of the σ-contribution to the coupling over the π-contribution for the particular proton geometries involved[28,31] (see below). Since the H_5 protons in IV were strongly coupled, they were analysed as the AB part of an ABX sub-system with H_4 as X. The derived chemical shifts ν_A and ν_B together with weighted mean chemical shifts for H_1, H_2 and H_4, first order values of $J_{1,2}$, $J_{1,4}$ and $J_{2,4}$, and values of $J_{4,5}$, $J_{4,5'}$ and $J_{5,5'}$ from the ABX analysis (Table 1) were then used to compute a theoretical spectrum for IV taking $J_{2,4}$ and $J_{5,5'}$ to have negative sign. Since a good fit of experimental and theoretical spectra was not obtained due evidently to the fact that the H_4, H_5, $H_{5'}$ sub-system was quite closely coupled, three iterations of the computer program were carried out. Two modifications of the $J_{4,5}$ and $J_{4,5'}$ couplings gave the values listed in parentheses in Table 1 which when combined with small changes in the chemical shifts then yielded a theoretical spectrum (Fig. 2) in which the line positions agreed with those in the experimental spectrum within 0·28 c/s.

If Eq. 1 is again used to calculate approximate dihedral angles from the vicinal couplings $J_{4,5} = 7{\cdot}87$ and $J_{4,5'} = 5{\cdot}56$ c/s (Table 1) determined for the α-glycoside IV by iteration, then we obtain $\phi_{4,5} = 12°$ or 158° and $\phi_{4,5'} = 34°$ or 141°. The pair of angles which add or subtract to give an angle closest to the methylene dihedral angle ($\approx 120°$) is 158° and 34°. These values are consistent with a conformation resembling the half chair IV in which looking along the C_4—C_5 bond, H_4 lies outside the methylene dihedral angle. The same result may be inferred from a previous generalization based on a Karplus equation that two large (>5 c/s) vicinal coupling constants in a CH—CH_2 group can arise only from dihedral angles of ϕ and $120° + \phi$.[32] Measurement of a CSL model of the half-chair IV indicated dihedral angles $\phi_{4,5a} = 170°$ and $\phi_{4,5e} = 50°$, and the larger coupling of 7·87 c/s was therefore assigned as $J_{4,5a}$, and the coupling of 5·56 c/s as $J_{4,5e}$. The fact that τ_{5e}–τ_{5a} is only 0·06 ppm and much less than that (0·37 ppm) in the β-anomer I may be ascribed to the absence in the half chair IV of a chlorine in approximately *trans*-coplanar orientation to H_{5a}, which however, still has the methoxyl group in *syn*-quasi-axial relationship.

The observation of allylic and bi-allylic couplings in the α-glycoside supports the assignment of the half chair conformation IV since these couplings are most frequently observed to have appreciable magnitude when the dihedral angle of an allylic proton with its vicinal vinyl substituent is near 90°.[25] In a CSL model of IV, measurement of H_4 gave a dihedral angle of 80°. The variations of the magnitudes and signs of *allylic* couplings with dihedral angle have been described[31c] by the empirically derived equation

$$J_{all} \cong 1{\cdot}3 \cos^2 \phi - 2{\cdot}6 \sin^2 \phi \text{ for } 0° < \phi < 90°. \quad (2)$$

Putting $\phi = 80°$ in this equation gives a theoretical value $J_{2,4} = -2{\cdot}48$ c/s which agrees with the experimentally determined sign of this coupling constant, if not its magnitude. This value may be contrasted with the theoretical value −2·67 c/s for

[31] [a] E. I. Snyder and B. Franzus, *J. Am. Chem. Soc.* **86**, 1166 (1964); [b] P. Laszlo and P. R. Schleyer, *Ibid.* **86**, 1171 (1964); [c] E. W. Garbisch, Jr., *Ibid.* **86**, 5561 (1964).

[32] R. J. Abraham and K. A. McLauchlan, *Mol. Phys.* **5**, 513 (1962).

the through-bond contribution to the coupling constant predicted by a semi-empirical valence bond theory of allylic coupling.[28]

Conversely, the non-observation of allylic and bi-allylic couplings in the β-compounds supports the assignment of the alternative half chair conformations I–III which in CSL models gave allylic dihedral angles of $\approx 40°$ for both H_1 and H_4. For $\phi = 40°$, Eq. 2 predicts $J_{2,4} = -0{\cdot}31$ c/s which is not expected to be readily observable.[33] The estimation of allylic dihedral angles from empirical equations[31e] describing the variation of the coupling constant of the allylic proton with its vicinal vinyl proton does not appear to be reliable for angles which are less than 90°.[7,31c]

The preference of the methyl α- and β-D-glycosides for different half chair conformations IV and I each containing the OMe group in quasi-axial orientation must be attributed to the dominating presence[8] of an anomeric effect.[10] Support for this conclusion is provided by the conformational behaviour of the 1-hydroxy derivative II and the dimer III. Although the importance of anomeric effects in half chair conformations of methyl pyranosides has not been clearly demonstrated previously, the existence of these effects in half chairs of 2-enopyranosides may be anticipated from the similarity of the steric relationship of the C_1—O_1 and C_5—O_5 dipoles and oxygen orbitals with that in chair conformations, despite the fact that in these half chairs the substituents at C_1 are only either quasi-axial or quasi-equatorial with respect to the ring as a whole. These results are in contrast to those reported recently[7] for methylated methyl hex-2-enopyranosides where the stronger conformation locking effect of a methoxymethyl substituent at C_5 evidently caused these derivatives to adopt mainly conformations in which this substituent was equatorial, irrespective of the configuration of the methoxyl group at C_1 (cf. Ref. 4*b*).

The half chair conformations I and IV are remarkably alike, since inversion of the configuration at C_4 in one would give the enantiomorph of the other. This relationship is supported by the similarity of the values of $J_{1,2}$ in the two anomers, and by the observation that the chemical shifts of H_1 differ by only 0·04 ppm, those of H_2 by only 0·01 ppm, and those of the OMe protons are identical (Table 1). It seems certain therefore, that the difference in stability of the anomeric glycosides revealed by their equilibration reactions in methanol is due to the differing orientations of the chlorine and hydrogen atoms at C_4 with respect to other atoms, in the two half chair conformations. At 20°, the $\beta:\alpha$ ratio of 9:1 in the equilibrated mixtures corresponds to a free energy difference of 1·28 kcal/mole. It is difficult to assess the enthalpy change since the change in entropy is unknown. However the entropies of stereoisomers are likely to be very similar since the vibrational and rotational modes of motion will be similar. Furthermore, one isomer is much more abundant at 20° than the other and so the entropy change may be negligible in which case the enthalpy itself is about 1·28 kcals/mole. Alternatively, if it is assumed that the ratio of isomers of 6·4:1 observed before neutralization of the hydrogen chloride catalyst represents the equilibrium ratio at the inlet temperature of the GLC column (150°), a value of the enthalpy can be obtained independent of assumptions on the size of the entropy term. This yields a value of 0·91 kcals/mole. In fact the mixture may not have equilibrated during its short residence time in the inlet port, and so this represents a lower limit to the enthalpy. It in turn implies a value of −1·26 cals/deg/mole for the entropy change, which must be numerically a maximum possible value. Whilst this is sufficient

[33] Cf. Ref. 7.

to make the enthalpy differ by 25% from the free energy value it is not large enough to affect its order of magnitude. In consequence the postulated neglect of the entropy above may be reasonably justified in cases in which equilibrium concentrations are known only at one temperature. Furthermore, since the entropy change is negative, 1·28 kcals/mole represents an upper limit to the enthalpy which must therefore have a value between 0·91 and 1·28 kcals/mole. This uncertainty is insufficiently large to preclude a discussion of the factors which make the β anomer the more stable. In order to estimate what proportion of the enthalpy difference was due to steric interactions, Van der Waals interaction energies of pairs of atoms having different orientations in each half chair conformation (i.e. those non-bonded, non-geminal pairs including either H_4 or Cl_4) were computed from Hill's equation[34]

$$E_v = \varepsilon\{-2{\cdot}25[r/(r_1 + r_2)]^{-6} + 8{\cdot}28 \times 10^5 \exp[-r/0{\cdot}0736(r_1 + r_2)]\}$$

where ε is a parameter which varies with the size of the atoms, and which may in some cases be calculated from critical temperature data,[34] or, as in this case, obtained from tables,[35] and where r is the interatomic distance and r_1 and r_2 the Van der Waals radii of the atoms.[36] Approximate values of r were obtained from measurements of CSL models. Interactions involving atoms in the Me group which is conformationally indeterminate but probably remote from H_4 and Cl_4, were neglected. The approximate interaction energies obtained for 18 pairs of atoms in each conformation are shown in Table 2. The majority of the interactions are attractive, and the total attractive interaction (−1·626 kcal/mole) in the β-anomer outweighs that (−1·065 kcal/mole) in the α-anomer thus suggesting that on *steric* grounds alone the half chair conformation I is more stable than the half chair IV by 0·56 kcal/mole. By far the most important difference in the two conformations is that in the interaction of the chlorine atoms (Cl_3 and Cl_4) with each other. In IV, these atoms suffer a small repulsion, but experience a large attraction in the β-anomer I giving an energy difference of 0·46 kcal/mole in favour of I. This difference arises from the fact that the Cl_3–Cl_4 distance measured from models of IV is appreciably less than twice the Van der Waals radius of chlorine, but approximately equal to it in models of I, corresponding to Cl_3–Cl_4 dihedral angles of $\approx 40°$ and $\approx 80°$ respectively. Thus in the half chair I the Cl_3:Cl_4 energy lies very close to the theoretical minimum of −0·38 kcal/mole.[34]

These calculations are based on the idealized, undistorted, conformations I and IV, whereas the actual conformations adopted will be dictated by minimization of the sum of the energies due to bond length distortion, bond angle strain, torsional strain, Van der Waals forces, dipole interaction, and other terms.[37,38] However, since even for simple systems the complete calculations are formidable,[38] and since molecular conformation may often be predicted by minimization of the Van der Waals forces alone,[39] only the latter interactions are considered here.

Inspection of models suggested that the chlorine-chlorine repulsion in the half

[34] T. L. Hill, *J. Chem. Phys.* **16**, 399 (1948).
[35] E. L. Eliel, N. L. Allinger, S. J. Angyal and G. A. Morrison, *Conformational Analysis* p. 452. Interscience, New York (1965).
[36] Ref. 23, p. 260.
[37] Ref. 35 p. 446.
[38] J. B. Hendrickson, *J. Am. Chem. Soc.* **83**, 4537 (1961); *Ibid.* **84**, 3355 (1962); *Ibid.* **86**, 4854 (1964); K. B. Wiberg, *Ibid.* **87**, 1070 (1965).
[39] Ref. 35, p. 449.

chair IV could be relieved by flattening of the ring towards the sofa conformation X in which the ring oxygen is out of the plane containing the ring carbon atoms, and in which the chlorine atoms are more distant (dihedral angle ≈60°), and $\phi_{4,5e} \approx 30°$ and $\phi_{4,5a} \approx 150°$ (CSL models). Depending on the weight given to calculations of proton dihedral angles from the Karplus equation, some support for such a conformational distortion may be seen in the values of $\phi_{4,5e}$ and $\phi_{4,5a}$ derived from $J_{4,5e}$ and $J_{4,5a}$ above, and also in the closer agreement of $J_{2,4}$ with the semi-empirical value −1·6 c/s obtained by substitution of the allylic dihedral angle of H_4 in the sofa X (≈60° in CSL models) in Garbisch's Eq. 2. Van der Waals Energies were also computed for 18 atom pairs involving H_4 and Cl_4 in the sofa X (Table 2). It is seen that the only significant change in these interactions is in that of Cl_3:Cl_4 which becomes an attraction −0·26 kcal/mole. It is not possible to compare the sum of the 18 energy terms in the sofa X directly with those for the half chairs I and IV since the orientations of the remaining atom pairs are no longer the same. Indeed, computation of non-bonded interaction energies for the 34 other pairs of non-geminal atoms in IV and X suggested that the increase in Cl_3:Cl_4 attraction and decrease in C_2:C_5 repulsion in passing from IV to X are largely balanced by increased O_1:H_{5a} and O_1:C_5 repulsions.

The dipole–dipole interaction of the C_3—Cl_3 and C_4—Cl_4 bonds should also be of some importance in these conformations and is expected to be at a minimum in the β-anomer I, in which the Cl_3,Cl_4 dihedral angle is at a maximum. The magnitude of the interaction may be reduced somewhat in all of these conformations by the resonance contribution[23] of the polarized form of the vinyl chloride. By the same token, the effective Van der Waals radius of the vinylic chlorine atom may be slightly less than the standard value 1·8 Å used in the computations for both Cl_3 and Cl_4.[36]

TABLE 2. THEORETICAL VAN DER WAALS INTERACTION ENERGIES (KCAL/MOLE) IN METHYL 3,4-DICHLORO-4-DEOXY-D-*glycero*-PENT-2-ENOPYRANOSIDES

Atom pair	α-Anomer (IV)	β-Anomer (I)	α-Anomer in Sofa (X)
H_1:H_4	−0·0035[a]	0·0017	−0·0024
H_1:Cl_4	−0·0080	−0·0291	−0·0096
O_1:H_4	0·0071	0·0073	−0·0080
O_1:Cl_4	−0·0461	−0·0307	−0·0974
C_1:H_4	0·0521	−0·0296	0·0397
C_1:Cl_4	−0·1047	−0·1869	0·1392
H_5:H_4	−0·0043	0·0035	−0·0039
H_5:Cl_4	0·0188	−0·0251	0·0214
C_2:H_4	0·0744	0·0618	−0·0694
C_2:Cl_4	0·1920	0·2210	−0·2074
Cl_3:H_4	−0·1227	−0·1361	0·1389
Cl_3:Cl_4	0·0761	−0·3797	−0·2604
H_4:H_{5e}	0·0501	0·0501	−0·0370
H_4:H_{5a}	−0·0246	−0·0509	0·0268
Cl_4:H_{5e}	−0·1361	−0·1002	−0·1377
Cl_4:H_{5a}	−0·0954	−0·0755	0·1033
H_4:O_5	−0·0829	−0·0359	0·0674
Cl_4:O_5	0·1188	−0·2009	−0·1203
TOTALS	−1·0655	−1·6260	−1·2836

[a] Negative and positive energies signify attractive and repulsive interactions respectively.

In summary, it may be stated that consideration of the chlorine–chlorine Van der Waals and dipole–dipole interactions in two different conformations has given a reasonable interpretation of the observed difference in stability of the anomeric methyl 3,4-dichloro-4-deoxy-D-*glycero*-pent-2-enopyranosides.

EXPERIMENTAL

M.ps were determined on a Kofler hot stage, and optical rotations were measured at 21 ± 3°. Solns were concentrated below 50° under red press, and the pet. ether (petrol) used was the fraction of b.p. 60–80°. Chf solns were dried over Na_2SO_4. TLC was performed on silica gel G (Merck) coated plates with the solvent mixtures; (a) petrol–$CHCl_3$ (3:1 v/v), (b) ether–petrol (1:1), (c) petrol–$CHCl_3$ (5:1), and (d) petrol–ether (4:1). GLC was carried out at 90° using an F and M Biomedical Gas Chromatograph Model 400 equipped with a 6 ft column of 3·1% w/w S.E. 30 silicone rubber on Diatoport S (60–80 mesh), a flame-ionization detector, and a disc integrator. IR spectra (of nujol dispersions unless stated otherwise) and UV spectra (of 96% EtOH solns) were determined on Unicam S.P. 200 and S.P. 800 instruments respectively. The PMR spectra were obtained from Varian A-60 and HA-100 spectrometers with TMS as internal reference, the 100 Mc/s spectrometer being operated in the frequency-sweep mode whilst locked internally on TMS. Sweep widths were checked with a Venner 333-6 electronic counter. Soln concentrations were for I and IV, 70 mg in 0·4 ml of solvent, for II 50 mg in 1·5 ml, and for the remaining compounds 50–100 mg in 0·4 ml, except that a sat soln of III was used. Frequency-swept spin decoupling experiments were performed at 100 Mc/s using a Muirhead-Wigan Decade oscillator. Van der Waals interaction energies for conformations I, IV and X, and theoretical PMR spectra for the five spin systems of nuclei comprised by the ring protons of compounds I and IV were calculated on the Elliott 503 computer. The NMR program used was a modified version of Frequint IV.

The Isolation of 3,4,-*dichloro*-3,4-*dideoxy*-β-D-*ribopyranosyl chloride* 2-*chlorosulphate* (V)

L-Arabinose (15 g) was treated with sulphuryl chloride (32 ml) and pyridine (60 ml) in $CHCl_3$ soln.[6] The mixture was kept at room temp for 24 hr, and was then filtered and the filtrate washed with 10% H_2SO_4. The acid layer was divided into two equal fractions which were retained for further use. The $CHCl_3$ layer was further washed with sat $NaHCO_3$ aq and water, and concentrated to a syrup (10 g) which on TLC in solvent (a) displayed two components with slightly differing mobilities. The syrup (5 g) was chromatographed on silica gel (Davison grade 950, 60–200 mesh) whence elution of the faster moving component with 6% ether in petrol and concentration of the eluate yielded a crystalline solid (2·5 g). Recrystallization from $CHCl_3$–petrol gave V as large colourless crystals (1·5 g), m.p. 123–125° and $[\alpha]_D$ −174° (*c*, 1·0 in $CHCl_3$). (Found: C, 20·1; H, 2·1; Cl, 47·2; S, 10·7. $C_5H_6Cl_4O_6S$ requires: C, 19·8; H, 2·0; Cl, 46·8; S, 10·5%.)

The slower moving component was eluted with 20% ether in petrol and recrystallization from $CHCl_3$–petrol yielded large colourless crystals (0·6 g) of IX,[6] m.p. 84–85° and $[\alpha]_D$ +78° (*c*, 1·4 in $CHCl_3$). (Found: C, 15·9; H, 1·8. Calc. for $C_5H_6Cl_4O_7S_2$: C, 15·7; H, 1·6%.)

3,4-*Dichloro*-4-*deoxy*-β-D-glycero-*pent*-2-*enopyranosyl*-3′,4′-*dichloro*-4-*deoxy*-β-D-glycero-*pent*-2′-*enopyranoside* (III)[6]

(a) *From* L-*arabinose*. One fraction of the acid wash liquid from above was left in an open beaker for 7 d. Crystals (0·7 g) separated and after drying, had m.p. 223–226° undepressed on admixture with authentic III.[6]

(b) *From* 3,4-*dichloro*-3,4-*dideoxy*-β-D-*ribopyranosyl chloride* 2-*chlorosulphate* (V). Pyridine (0·11 g) was added to a soln of V (0·14 g) in $CHCl_3$ (2 ml). After 24 hr at room temp the soln was allowed to partition between $CHCl_3$ (3 ml) and 10% H_2SO_4 (4 ml). The acid layer was stored as in (a) and during 7 d crystals (0·04 g, 56%) separated, two recrystallizations of which from aqueous acetone yielded colourless needles (0·015 g, 21%), m.p. and mixed m.p. 223–225°, and IR spectrum identical with that of authentic III.[6]

3,4-*Dichloro*-4-*deoxy*-β-D-glycero-*pent*-2-*enopyranose* (II)

(a) *From methyl* 3,4-*dichloro*-4-*deoxy*-β-D-glycero-*pent*-2-*enopyranoside* (I). N H_2SO_4 was added to a soln of I (0·7 g) in acetone (25 ml) until it became slightly opalescent. On warming the mixture, the opalescence disappeared, and further heating for 15 min gave essentially complete hydrolysis

yielding only one component (TLC, solvent b). The soln was then partitioned between $CHCl_3$ and water. The $CHCl_3$ layer was washed with $NaHCO_3$ aq, water, dried, filtered and concentrated to a crystalline mass which when recrystallized from $CHCl_3$–petrol afforded colourless needles (0·4 g, 62%) of II, which melted initially at 130–132°, resolidified, and then melted finally at 205–210°, and showed $[\alpha]_D$ +127° (5 min) → +108° (24 hr final, *c*, 0·7 in MeOH). On TLC in solvent b, the product gave a brilliant yellow spot (*R*, 0·5) when sprayed with *p*-anisidine HCl; it also showed $\nu_{max}^{cm^{-1}}$ 3225 and 3310 (OH), 1650 (ethylenic bond), and λ_{max} 212 mμ. (Found: C, 35·5; H, 3·5; Cl, 42·5. $C_5H_6Cl_2O_3$ requires: C, 35·5; H, 3·6; Cl, 42·0%.)

(b) *From Methyl* 3,4-*dichloro*-4-*deoxy*-α-D-glycero-*pent*-2-*enopyranoside* (IV). Hydrolysis of IV (0·3 g) (whose preparation is described below) under the same conditions as in (a) above, also yielded crystalline II (0·2 g, 73%). Its identity with the product of hydrolysis of I was confirmed by mixed m.p., specific rotation, and comparison of IR and UV spectra. TLC suggested that only II was formed in the hydrolysis.

(c) *From* L-*arabinose*. The remaining fraction of the acid wash of the chlorosulphation reaction of L-arabinose was extracted with $CHCl_3$ until the extracts gave an insignificant residue on concentration, and was then made alkaline with solid Na_2CO_3, and extracted thrice further with $CHCl_3$. The latter extracts were combined, washed with water, dried, and concentrated to a syrup which crystallized spontaneously. Recrystallization of the product from $CHCl_3$–petrol gave colourless needles (0·4 g) with m.p. 130–132° (initial) and 205–211° (final), not depressed by admixture with II described in (a) above. The IR and UV spectra of the products were also identical.

3,4-*Dichloro*-3,4-*dideoxy*-β-D-*ribopyranose*[6]

A soln of V (0·24 g) in 95% v/v acetone aq was treated with NaI and $BaCO_3$.[10] The suspension was then filtered, concentrated to small volume, and after addition of water was treated with $Na_2S_2O_3$ to remove free iodine. Continuous extraction of the soln with $CHCl_3$ followed by concentration of the extract then gave a syrup which crystallized. Recrystallization from $CHCl_3$–petrol yielded needles (0·09 g, 61%) of m.p. 107–108° undepressed when mixed with authentic 3,4-dichloro-3,4-dideoxy-β-D-ribopyranose,[6] and showing $[\alpha]_D$ −8·5° (20 min) → −3·0° (equilibrium at 24 hr, *c*, 1·34 in MeOH).

Methyl 3,4-*dichloro*-3,4-*dideoxy*-α-D-*ribopyranoside* 2-*chlorosulphate* (VI)

A soln of V (0·5 g) in anhydrous MeOH (10 ml) was stirred with Ag_2CO_3 (2 g) for 16 hr. The mixture was then filtered, and the filtrate concentrated to a residue which was treated with $CHCl_3$ and the mixture again filtered to remove Ag-salts. Recrystallization of the solid obtained by evaporation of the filtrate yielded colourless crystals (0·35 g, 71%), m.p. 111–112° and $[\alpha]_D$ +65° (*c*, 0·8 in $CHCl_3$). (Found: C, 24·0; H, 3·2; Cl, 36·0; S, 10·8. $C_5H_6Cl_2O_5S$ requires: C, 24·0; H, 3·0; Cl, 35·6; S, 10·7%) PMR in $CDCl_3$: singlet at τ 6·51 (intensity 3 protons), OCH_3.

Methyl 3,4-*dichloro*-4-*deoxy*-α-D-glycero-*pent*-2-*enopyranoside* (IV)

The compound VI (0·75 g) was dissolved in $CHCl_3$ (2 ml), and pyridine (2 ml) was added. The solution was stored at room temp for 16 hr (TLC in solvents c and d suggested that only one product was formed), was then partitioned between $CHCl_3$ and water, and the $CHCl_3$ layer was washed with ice-cold dil H_2SO_4, $NaHCO_3$ aq, water, and dried. Concentration of the $CHCl_3$ soln gave a mobile brown syrup (0·35 g, 78%) whose homogeneity was indicated by TLC in solvents c and d, by GLC (one peak of retention time 8·8 min), and by PMR. Other spectroscopic data: IR (thin film), $\nu_{max}^{cm^{-1}}$ 1650 (double bond), and UV λ_{max} 212 mμ (cf. I, II, and III). The syrup was decolourized by charcoal with some loss (final yield 50%), and then rotated $[\alpha]_D$ +55° (*c*, 0·8 in MeOH). (Found: C, 39·0; H, 4·4; Cl, 38·4. $C_6H_8Cl_2O_3$ requires: C, 39·4; H, 4·4; Cl, 38·8%.)

Reactions of I, III *and* IV *with methanolic* HCl

(a) *Quantitative estimations*. Compounds I, III, and IV (10 mg of each) were dissolved in separate portions (1 ml) of N HCl in MeOH and the solns kept at 20° for 24 hr.* When small aliquots of the

* Trial estimations by GLC established that equilibrium was reached in times less than 24 hr.

equilibrated solutions were examined *directly* by GLC, each gave an identical chromatogram consisting of two peaks with retention times of 8·8 min (corresponding to pure IV), and 9·6 min (identical with that of the pure I) in a $\beta:\alpha$ ratio of 6·4:1.* When on the other hand, the acidic solns were first neutralized, either by the addition of Ag_2CO_3, or by adding $CHCl_3$ and shaking the resultant mixture with $NaHCO_3$ aq, the $\beta:\alpha$ ratio (GLC) became 9:1 in each case.

(b) *Further identification of the products-methanolysis of* I. A soln of crystalline I (1 g) in N HCl in MeOH was allowed to stand at room temp for 24 hr and was then diluted with excess of $CHCl_3$; the soln was then washed with $NaHCO_3$ aq and water, and concentrated to a crystalline mixture ($\beta:\alpha$ ratio, 9:1 by GLC) in whose PMR spectrum the signals of IV were not readily discernible. The mixture was therefore dissolved in MeOH and by the addition of water, some pure (by GLC and mixed m.p.) crystalline I (0·55 g) was removed. The mother liquors were partitioned between $CHCl_3$ and water, and the $CHCl_3$ soln was dried and concentrated to a syrupy mixture ($\beta:\alpha$ ratio 3:1 by GLC). In its 60 Mc/s PMR spectrum ($CDCl_3$) could be distinguished 3 lines of the H_1 quartet, 2 lines of the H_3 quartet, 8 lines of the H_4 nonet, and the four strongest lines of the $2H_6$ octet of the α-glycoside (IV), superimposed on the spectrum of its β-anomer I. Due to the overlap of the multiplets, determination of the anomeric ratio by integration of the spectrum of the mixture was not convenient. However, this spectrum was identical with that of a mixture prepared by the addition of 3 parts of pure β-anomer I to 1 part of pure α-anomer IV. The OMe signals of the anomers were not resolved at 60 Mc/s.

Methanolysis of III. The dimer III (1 g) was dissolved in warm N HCl in MeOH. The soln was kept at room temp for 2·5 hr, then concentrated to dryness. A $CHCl_3$ soln of the residue was washed with $NaHCO_3$ aq, water, dried and evaporated to a mass of crystals which when recrystallized from MeOH aq afforded silky plates (0·9 g, 76%), m.p. 74°, mixed m.p. with I undepressed.

Methanolysis of IV. A soln of IV (0·17 g) in N HCl in MeOH (20 ml) was left at room temp for 24 hr, then evaporated to a small volume. The addition of water yielded colourless silky plates (0·07 g, 41%) of m.p. 74° not depressed on admixture with authentic I.*

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* Although the peaks were not completely separated at the base-line, a fairly accurate estimation of their respective areas could be made by using the disc-integrator.