Tetrahedron, 1964, Vol. 20, pp. 1685 to 1694. Pergamon Press Ltd. Printed in Northern Ireland

THE CONFORMATIONS OF CYCLIC COMPOUNDS IN SOLUTION—II

SOME 1,2-O-ALKYLIDENE-PYRANOSE DERIVATIVES[1]

B. COXON and L. D. HALL
Department of Chemistry, The University, Bristol 8, England, and
Department of Chemistry, University of British Columbia,
Vancouver 8, B.C., Canada

(*Received* 18 *February* 1964)

Abstract—The 60 Mc/sec proton resonance spectra of a series of 1,2-O-alkylidene α-D-glucopyranoses have been measured. From the derived vicinal coupling constants it is suggested that the pyranose ring in these derivatives adopts essentially a skewed boat conformation.

UNTIL quite recently it was not generally realised that five-membered cyclic acetal rings adopt a non-planar conformation in solution. Proton Magnetic Resonance (PMR) studies have now established unequivocally that such acetal rings *cis*-fused to furanose rings,[2] *cis*-fused to pyranose rings[3] and unbridged[4,5] are in every case non-planar and that the angle between the bridgehead hydrogens is approximately 40°. In particular Hall *et al.*[3] showed for the first time that bridging of the *cis*-hydroxyls on the pyranose ring of certain pyranose carbohydrate derivatives by a five-membered acetal ring caused only a slight flattening of the normal pyranose chair conformation, and did not force it to adopt the half-chair modification. Similar conclusions reached by Angyal and Hoskinson[6] were based on IR studies of hydrogen bonding in cyclic acetal derivatives of inositols. These workers suggested that the conformation of a six-membered ring was only slightly deformed by the fusion to it of *one cis*-oriented cyclic acetal substituent whereas the addition of a second such group caused the pyranose ring to adopt the so-called "skew" conformation. The conformations which are possible for cyclic acetals of sugars have been discussed by Tipson *et al.*[7]

During the course of an investigation[8b] of the reactions of acetobromoglucose with silver and mercuric cyanides, some substituted 1,2-O-alkylidene derivatives of D-glucopyranose were prepared which yielded some interesting PMR spectra. It seemed appropriate, therefore, to investigate the conformations of these derivatives by the PMR method and to compare the results with those obtained previously. It should perhaps be pointed out that in none of those derivatives (I–VI) which possess an asymmetric dioxolane 2-carbon atom (using the nomenclature described in Ref. 8b) is the absolute configuration of this carbon atom known.

---

[1] Part I: *J. Org. Chem.* **21**, 297 (1964).

[2] R. J. Abraham, L. D. Hall, L. Hough and K. A. McLauchlan. *Chem. & Ind.* 213 (1962); *J. Chem. Soc.* 3699 (1962).

[3] L. D. Hall, L. Hough, K. A. McLauchlan and K. J. Pachler, *Chem. & Ind.* 1465 (1962).

[4] F. A. L. Anet, *J. Amer. Chem. Soc.* **84**, 747 (1962).

[5] R. U. Lemieux, J. D. Stevens and R. R. Fraser, *Canad. J. Chem.* **40**, 1955 (1962).

[6] S. J. Angyal and R. M. Hoskinson, *J. Chem. Soc.* 2991 (1962).

[7] R. S. Tipson, H. S. Isbell and J. E. Stewart, *J. Res. Nat. Bur. Stand.*, **62**, No. 6, 257 (1959).

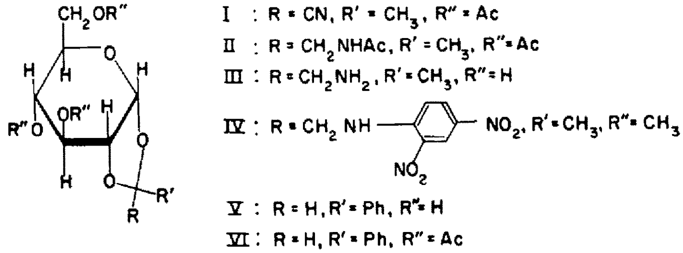
[8a] H. B. Wood, H. W. Diehl and H. G. Fletcher, Jr., *J. Amer. Chem. Soc.* **79**, 1986 (1957); [b] B. Coxon and H. G. Fletcher, Jr., *Ibid.* **85**, 2637 (1963).

EXPERIMENTAL

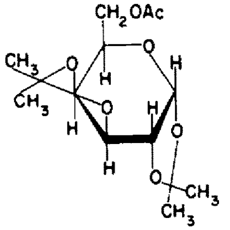
The preparation of some of the derivatives has been described elsewhere.[8] Those substances which had been prepared a number of years ago were recrystallized if their m.ps indicated that this was necessary. The PMR spectra were measured on either A.60 or H.R.60 spectrometers the double resonance experiments being performed on the latter with a Varian V-3521 A Integrator-Decoupler unit utilizing the method proposed by Johnson.[9] Unless otherwise stated chloroform solutions were used with tetramethylsilane as internal reference.

Spectral assignments

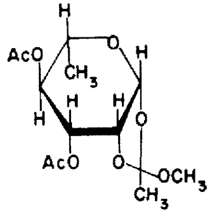
3,4,6-*Tri-O-acetyl*-1,2-O-(1-*cyanoethylidene*)-α-D-*glucopyranose* (I). The assignments were straight forward since the ring hydrogens gave well resolved multiplets (Fig. 1). Because of the unexpected magnitudes of some of the coupling constants, additional support for the assignments was obtained from the double-resonance experiments, spectra from which are shown in Fig. 2. These are discussed later together with the long range coupling between H_2 and H_4.



I : $R = CN, R' = CH_3, R'' = Ac$
II : $R = CH_2NHAc, R' = CH_3, R'' = Ac$
III : $R = CH_2NH_2, R' = CH_3, R'' = H$
IV : $R = CH_2NH$ — $NO_2, R' = CH_3, R'' = CH_3$ (NO_2)
V : $R = H, R' = Ph, R'' = H$
VI : $R = H, R' = Ph, R'' = Ac$



VII



VIII

1,2-O-*Acetamidoisopropylidene*-3,4,6-*tri-O-acetyl*-α-D-*glucopyranose* (II). Although the signal due to H_2 was partially obscured by the H_5 and H_6 multiplets, an unequivocal assignment was possible.

1,2-O-*Aminoisopropylidene*-α-D-*glucopyranose* (III). The spectrum was measured in deuterium oxide solution with cyclohexane as an external reference. The hydroxyl and amino resonances were not observed because of deuterium exchange. The assignments for H_2 and H_3 are tentative and based on the relative chemical shifts found for 1,2-O-isopropylidene α-D-glucofuranose derivatives.[2]

1,2-O-(2,4-*Dinitrophenylaminoisopropylidene*)-3,4,6-*tri*-O-*methyl*-α-D-*glucopyranose* (IV). This compound gave only two resolved multiplets; by comparison with compound (I) the doublet at τ 4·45 was assigned to H_1 which gave $J_{1,2}$. The triplet at τ 5·84 could be assigned to either H_2 or H_3 since it could accommodate the known $J_{1,2}$. In either assignment $J_{2,3}$ must be approximately equal to $J_{1,2}$; if the triplet were assigned to H_3 then $J_{3,4}$ would also be ca. 4 c/s.

1,2-O-*Benzylidene*-α-D-*glucopyranose* (V). This spectrum was measured using pyridine as solvent, which obscured the aromatic hydrogen resonances.

3,4,6-*Tri-O-acetyl*-1,2-O-*benzylidene*-α-D-*glucopyranose* (VI). Although only H_1, H_3 and H_4 displayed well resolved multiplets, these yielded all of the ring coupling constants. The assignments of H_3 and H_4 were made consistent with those of compound (I).

6-O-*Acetyl*-1,2:3,4-*di*-O-*isopropylidene*-α-D-*galactopyranose* (VII). $J_{1,2}$ was obtained from the H_1 doublet and since this splitting was not observed in the quartet centered at τ 5·38, the latter could be assigned to H_3.

---

[9] L. F. Johnson, *Varian Tech. Inf. Bulletin* 3, No. 3 (1962).

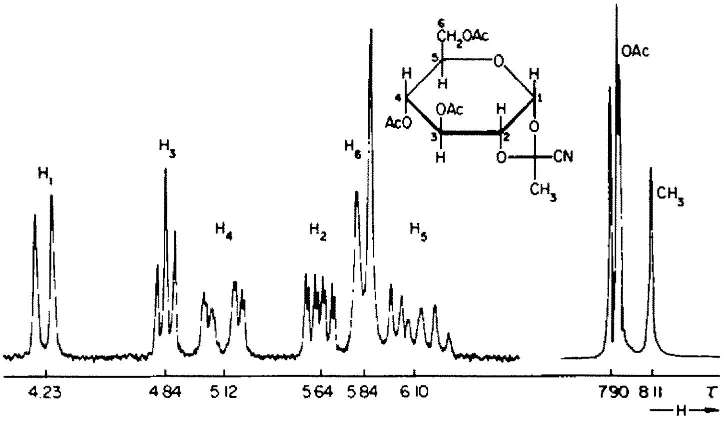


FIG. 1. PMR spectrum of 3,4,6-tri-O-acetyl-1,2-O-(1-cyanoethylidene)-α-D-glucopyranose (I) in $CDCl_3$. The methyl resonances are recorded at reduced gain.

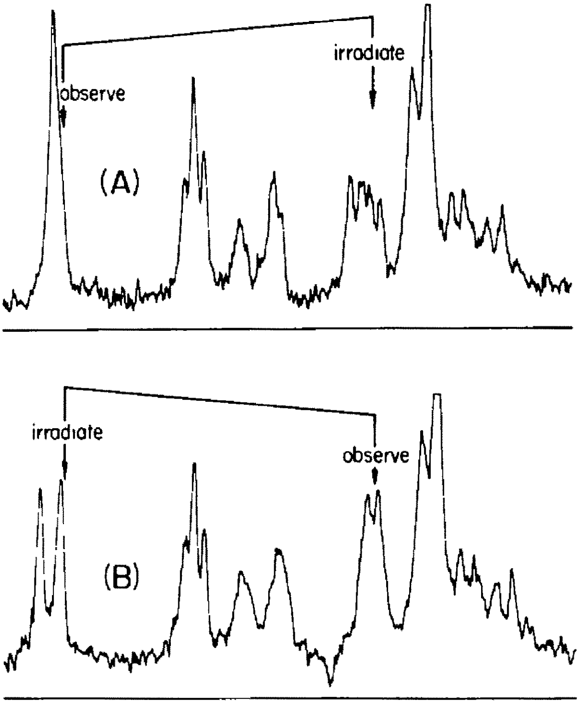


FIG. 2. Spin decoupling experiments with 3,4,6-tri-O-acetyl-1,2-O-(1-cyanoethylidene)-α-D-glucopyranose (I). (A) Irradiation of H_2 whilst observing H_1 and (B) irradiation of H_1 whilst observing H_2.

*3,4-Di-O-acetyl-6-deoxy-*1,2-O-(1-*methoxyethylidene*)-β-L-*mannopyranose* (VIII). Assignment of the substituent resonances was straightforward. H_1 occurred as a sharp doublet at τ 4·60 whilst H_5 showed as a broad highly split multiplet centred at τ 6·42. Both H_3 and H_4 are attached to carbon atoms bearing an acetoxy substituent and should hence resonate at lower field than H_2. On this basis the multiplet at τ 5·42 was assigned to H_2 and the multiplets centred at τ 4·9 to H_3 and H_4. From this spectrum only $J_{1,2}$ and $J_{2,3}$ were obtained.

The values of the chemical shifts and coupling constants obtained by *first-order* measurement of the spectra are shown in Tables 1 and 2 respectively. For the purposes of an explicit analysis

TABLE 1. CHEMICAL SHIFTS (τ-VALUES)

Compound	H_1	H_2	H_3	H_4	H_5	H_6	R_3''	R_4''	R_6''	O Me O	O OMe O	O Ph O	O H O	—NH—	—NHAc—	—CH_2N	Ph.
I	4·23	5·64	4·84	5·12	6·10	5·84	7·90;	7·96(2x)		8·11	—	—	—	—	—	—	—
II	4·35	[1]	4·82	5·10	5·96	[1]	7·90;	7·91(2x)		8·44	—	—	—	3·91	7·98	6·66	—
III[a]	4·21	5·62	5·98	< 6·10–6·44 >			—	—	—	8·40	—	—	—	—	—	7·25	—
IV	4·45	5·84	[2]	[2]	[2]	[2]	6·46(3x)			8·30	—	—	—	1·42	—	6·52	1·04 1·85 3·03
V[b]	3·81	< 5·13–5·85 >					—	—	—	—	—	[c]	3·44	—	—	—	—
VI	4·29	[3]	4·67	5·03	[3]	[3]	7·93(3x)			—	—	2·64	3·59	—	—	—	—
VII	4·49	[4]	5·38	[4]	[4]	[4]	—	—	7·94	8·51 8·57 8·69	—	—	—	—	—	—	—
VIII	4·60	5·42	< 4·94 >		6·42	8·78	7·90;	7·95	—	8·29	6·74	—	—	—	—	—	—

[1] Incompletely resolved multiplet, 5·65–6·00
[2] Incompletely resolved multiplet, 6·10–6·95
[3] Incompletely resolved multiplet, 5·78
[4] Incompletely resolved multiplet, 5·64–5·98

[a] In D_2O
[b] In pyridine
[c] Obscured by solvent peak.

TABLE 2. FIRST-ORDER COUPLING CONSTANTS (c/s)

Compound	J_{12}	J_{23}	J_{34}	J_{45}	J_{56}	$J_{H,NH}$
I	5·0	2·7	2·5	9·0	4·2	—
II	5·0	2·7	2·8	8·5	[1]	6·1
III	4·8	4·8	4·8	[1]	[1]	[1]
IV	5·0	*ca.* 4·1	*ca.* 4·1[2]	[1]	[1]	5·3
V	3·9	[1]	[1]	[1]	[1]	—
VI	4·0	4·0	4·0	8·5	[1]	—
VII	5·0	7·5	2·2	[1]	[1]	—
VIII	2·1	3·6	[1]	[1]	[1]	—

[1] Unresolved

[2] Tentative

the protons associated with the pyranose ring of compound (I) would have to be considered as making up an "$A(H_1)$, $B(H_3)$, $C(H_4)$, $X(H_2)$, $Y_2(H_6)$, $Z(H_5)$" system. Fortunately the major coupling only occurs between vicinal protons so that this apparently complex system may be subdivided into several component sub-systems, each of which can be considered separately. Moreover, the relative chemical shifts are such that the errors due to second order effects in the multiplets due to H_1, H_2, H_3 and H_4 are relatively small; in view of the approximate nature of the subsequent calculations an explicit analysis was not attempted.

DISCUSSION

Applications of PMR spectroscopy to the determination of carbohydrate conformations have been made by many workers.[2,3,5,10,11,12] Each of these investigations has utilized the Karplus equation[13] which relates the coupling constant (J) of two protons attached to adjacent carbon atoms, to the dihedral angle (ϕ) between them. This equation has the form

$$J = J_0 \cos^2 \phi - K.$$

It has been shown[14] that the precise value of this relationship depends on the electronegativity of substituents attached to the carbon-hydrogen system under consideration, but there is some controversy[2,5,10] as to how the parameters "J_0" and "K" should be modified to allow for this dependence. In view of the success[15,16] of the method involving modification of J_0 in conformational investigations of compounds other than carbohydrates as well as in carbohydrates,[2,3,10] this modification has been adopted in the present study. The coupling constants obtained from the PMR spectra were converted to the corresponding angles shown in Table 3 using the J_0-parameters obtained by Abraham *et al.*[2]

$$J_0 = 9{\cdot}3 \text{ c/s for } 0^\circ < \phi < 90^\circ \ (8{\cdot}5 \text{ c/s})$$
$$J_0 = 10{\cdot}4 \text{ c/s for } 90^\circ < \phi < 180^\circ \ (9{\cdot}5 \text{ c/s})$$

For comparison the angles were also calculated using the original parameters of

---

[10] R. W. Lenz and J. P. Heeschen, *J. Polymer. Sci.* **51**, 247 (1961).

[11] C. D. Jardetzky, *J. Amer. Chem. Soc.* **82**, 229 (1960); **83**, 2919 (1961); **84**, 62 (1962).

[12] R. U. Lemieux, *Canad. J. Chem.* **39**, 116 (1961).

[13] M. Karplus, *J. Chem. Phys.* **30**, 11 (1959); *J. Amer. Chem. Soc.* **85**, 2870 (1963).

[14] K. L. Williamson, *J. Amer. Chem. Soc.* **85**, 516 (1963); P. Laszlo and P. von R. Schleyer, *Ibid.* **85**, 2709 (1963).

[15] R. J. Abraham and K. A. McLauchlan, *Mol. Phys.* **5**, 195, 513 (1962).

[16] K. L. Williamson and W. S. Johnson, *J. Amer. Chem. Soc.* **83**, 4623 (1961); R. J. Abraham and J. S. E. Holker, *J. Chem. Soc.* 806 (1963).

Karplus,[13] shown in parentheses above. In both cases the value of the "K" parameter was taken as 0·28 c/s. Owing to the "$\cos^2 \phi$" dependence of the Karplus equation, two angles may be calculated for each measured coupling constant. However, it appears to be a general finding[17] that in six-membered rings the dihedral angle is directly dependent with the coupling constant; thus large dihedral angles of *ca.* 180° have large coupling constants of *ca.* 10 c/s, and the angles in Table 3 are calculated on this basis. It should perhaps be stressed at this point that the same situation does not necessarily prevail in five-membered rings as has been demonstrated for the camphane-2,3-diols by Anet.[18]

TABLE 3. CALCULATED DIHEDRAL ANGLES (DEGREES)

Compound		H_1, H_2	H_2, H_3	H_3, H_4	H_4, H_5
I	[1]	38	54	55	171
	[2]	41	55	57	161
II	[1]	38	54	53	164
	[2]	41	55	55	157
III	[1]	39	39	39	—
	[2]	42	42	42	—
IV	[1]	38	44	44	—
	[2]	41	47	47	—
V	[1]	45	—	—	—
	[2]	48	—	—	—
VI	[1]	45	45	45	164
	[2]	47	47	47	157
VII	[1]	38	155	57	—
	[2]	41	150	59	—
VIII	[1]	58	47	—	—
	[2]	59	50	—	—

[1] Calculated with the Karplus parameters.[13]
[2] Calculated with the modified parameters.[2]

To provide a reference for discussion of the experimentally calculated dihedral angles, a list is given in Table 4 of dihedral angles corresponding to some of the conformations which are theoretically possible for the α-D-glucopyranose ring.

---

[17] R. U. Lemieux, R. K. Kullnig, W. G. Schneider and H. J. Bernstein, *J. Amer. Chem. Soc.* **80**, 6098 (1958).

[18] F. A. L. Anet, *Canad. J. Chem.* **39**, 789 (1961).

TABLE 4. THEORETICAL DIHEDRAL ANGLES FOR SOME OF THE POSSIBLE CONFORMATIONS OF THE α-D-GLUCOPYRANOSE RING

Conformation	H_1, H_2	H_2, H_3	H_3, H_4	H_4, H_5
Chair (A)[a]	60°	180°	180°	180°
Boat (B)[a]	60°	60°	60°	180°
Boat (C)[a]	0°	60°	60°	120°
Skew Boat (D)[b]	33°	49°	87°	155°

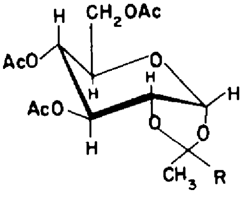
[a] Measured with Barton Models.[19]

[b] From Angyal and Hoskinson.[6]

These values were obtained by measurements of Barton Molecular Models[19] and do not, therefore, make any allowance for angular deformation. This is not a serious limitation since the Karplus calculation itself makes the assumption that the carbon atoms are truly tetrahedral.

It is convenient to discuss compounds (I) and (II) initially since the conformations of these are identical. Without recourse to any calculations of the Karplus type it is immediately obvious from inspection of the coupling constants that these compounds are unlikely to have the expected chair conformation (A) since this would require H_2, H_3, H_4 and H_5 to have axial orientations and hence $J_{2,3} \simeq J_{3,4} \simeq J_{4,5} > 9$ c/s. The experimental H_4, H_5 coupling constant has a value consistent with (A) but the small values found for the H_2, H_3 and H_3, H_4 couplings are characteristic of ring-hydrogens having approximately "gauche" orientations rather than "diaxial" orientations. This indicates that some fundamental change of conformation must have accompanied the attachment of the 1,2-acetal ring. The value of $J_{1,2}$ on the other hand is close to the values found elsewhere[3,20] for similarly positioned "bridgehead" protons and shows that some flattening of this end of the ring must have occurred, whilst the large value of $J_{4,5}$ shows that the other end of the pyranose ring must have remained virtually unaltered. Comparison of the experimental and theoretical angles shows that the dihedral angles of compound (I) lie within the range corresponding to conformations (B), (C) and (D) where the "Skew boat" conformation (D) may be regarded as being intermediate between the two boat forms (B) and (C). It can be seen that the experimental angles support a conformation intermediate between (B) and (D) but most closely related to (D). It is tempting to suggest that the value of $J_{3,4}$ corresponds to a dihedral angle greater than 90° since this would give a slightly closer correlation between experimental and theoretical dihedral angles. Such an assumption would, however, be entirely without precedent, and is hence rejected.

(A)



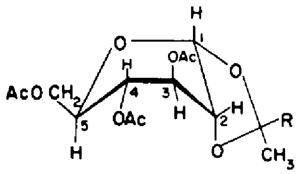
I : R = CN

II : R = CH_2NHAc

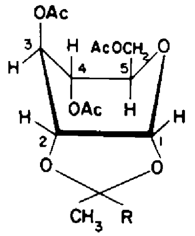
---

[19] D. H. R. Barton, *Chem. & Ind.* 1136 (1956).

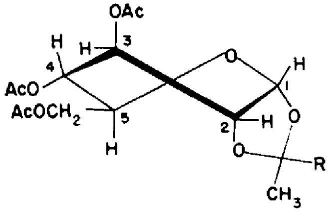
[20] A. S. Perlin, *Canad. J. Chem.* **41**, 399 (1963).



(B)



(C)



(D)

Before discussing the significance of this result it is worthwhile to consider the other compounds in the series. In those cases where the ring has the α-D-glucopyranose configuration (compounds III, IV, V and VI) the coupling constants between the ring protons are also consistent with a conformation differing from the expected one (A) in that a conformational inversion has occurred about the C_2—C_3 bond. The variations in the coupling constants are probably due in part to the second order effects not considered in the original analyses, but could result also from slight changes in conformation caused either by variations in size of the 2-substituents on the dioxolane ring, or by differing degrees of solvation of polar groups. We are forced to conclude that the *cis*-fusion of a 1,2-cyclic acetal ring forces the D-glucopyranose ring to depart from the expected chair conformation, a somewhat surprising finding in view of the fact that in the usual chair conformation these compounds would have the bulky substituents in predominantly equatorial orientations. The only possible alternative is that in these compounds the Karplus equation does not apply but this possibility is obviously less acceptable than the conformational inversion postulated above. A further experimental point which tends to support the finding of a rather "strained" pyranose conformation is the observation of a long range coupling, ca. 0·8 c/s for example in compound (I), between H_2 and H_4. It is evident from many investigations[21] that such couplings in cyclic compounds are highly stereoselective, occurring only between hydrogens possessing a critical steric relationship. Furthermore, it is also apparent that such couplings occur only in "strained" cyclic systems, or at least in systems having some rigid skeletal structure. For example, the only long range coupling thus far described[22] for a saturated carbohydrate is that between H_1 and H_3 of the 1,6-anhydro hexopyranoses. In these derivatives the pyranose ring must be held rigidly and perhaps somewhat strained by the five-membered 1,6-anhydro ring, and the coupling only occurs when the two hydrogens

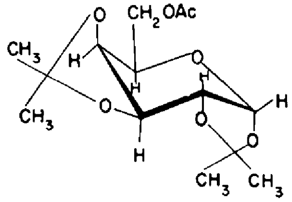
---

[21] D. R. Davis, R. P. Lutz and J. D. Roberts, *J. Amer. Chem. Soc.* **83**, 246 (1961); J. Meinwald and A. Lewis, *Ibid.* **83**, 2769 (1961); D. R. Davis and J. D. Roberts, *Ibid.* **84**, 2252 (1962).

[22] L. D. Hall and L. Hough, *Proc. Chem. Soc.* 382 (1962).

have approximately equatorial orientations. Inspection of the skew conformation (D) shows that H_2 and H_4 appear to be suitably disposed for long range coupling and moreover the molecule is likely to be "strained" in the sense that it has a somewhat deformed conformation.

As an example of a derivative containing a pyranose ring *cis*-fused to *two* acetal rings, 6-O-acetyl-1,2 : 3,4-di-O-isopropylidene-α-D-galactopyranose (VII) was studied. Inspection of the experimentally calculated dihedral angles of this compound shows that it has the expected chair conformation (E), although some slight flattening of the pyranoid ring may be present. The 6-deoxy-β-L-mannopyranose derivative (VIII) was studied as an example of a 1,2-cyclic acetal ring *cis*-fused to a pyranose ring other than that of D-glucose. Unfortunately only $J_{1,2}$ and $J_{2,3}$ could be measured for this compound and these do not contribute sufficient evidence for a conformational discussion. However, the small value for $J_{1,2}$ is close to that expected for an undeformed chair conformation and appears to be characteristic for this particular system, since the C_6-acetoxy derivative of VIII (actually in the D-series) also showed a small $J_{1,2}$.



(E)

Although the assignments made by inspection of the spectra of compounds (I–VI) were considered accurate, the somewhat unexpected coupling constants which were obtained prompted a more unequivocal assignment by proton-proton spin decoupling. Whilst this technique has been widely used in many branches of PMR spectroscopy, it has been embodied in comparatively few investigations of carbohydrates;[23–26] the latter investigation[26] discusses the technique in some detail. The instrumentation used in this investigation enables the observation of a particular multiplet in the spectrum whilst simultaneously irradiating another multiplet. Should the two multiplets in question be spin coupled, then the mutual coupling is removed leaving only the residual coupling with any other suitably positioned protons. Fig. 2 illustrates two decoupling experiments carried out on compound (I). Simultaneous irradiation of H_2 whilst observing H_1 eliminated the H_1, H_2 coupling, giving a singlet for H_1. Irradiation of H_1 whilst observing H_2 again removed the H_1, H_2 coupling and in this case left the residual coupling between H_2 and H_3 so that H_2 appeared as a "doublet" (neglecting the difficultly resolvable long range coupling between H_2 and H_4). There are many methods available for confirming the assignment of multiplets to hydroxyl and amino hydrogens, including deuterium exchange, and acid or base catalysed chemical exchange. In the case of the N-acetyl derivative (II) the PMR

[23] D. W. Turner, *J. Chem. Soc.* 847 (1962); R. D. Guthrie and L. F. Johnson, *Ibid.* 4166 (1961).

[24] R. J. Abraham, R. Freeman, L. D. Hall and K. A. McLauchlan, *J. Chem. Soc.* 2080 (1962).

[25] B. Coxon and H. G. Fletcher, Jr., *Chem. & Ind.* 662 (1964).

[26] L. D. Hall and L. F. Johnson, *Tetrahedron*, **20**, 883 (1964).

spectrum was merely measured at a variety of temps. The NH multiplet moved progressively to higher field as the temp was increased, until at 120° it was close to the H_1 doublet.

It should be noted that no attempt has been made to consider the proposed conformations quantitatively. In view of the controversies regarding the suitability of various empirical parameters when applying the Karplus equation to different systems, it is felt that such a quantitative discussion would be misleading.

Acknowledgements—We are indebted to the National Research Council of Canada (L.D.H.) and to the National Institutes of Health, Bethesda, Maryland (B.C.), for financial support and facilities provided. It is also a pleasure to thank Dr. R. B. Bradley who determined some of the PMR spectra initially, Dr. H. S. Isbell for gifts of compounds, and Dr. H. G. Fletcher, Jr., for his interest and further provision of derivatives.