

## CONFORMATIONS AND PROTON COUPLING CONSTANTS IN SOME METHYL 4,6-O- BENZYLIDENE- $\alpha$ -D-HEXOPYRANOSIDES

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**Abstract**—The PMR spectra of thirty-six methyl 4,6-O-benzylidene-aldohexopyranosides with the  $\alpha$ -D-*altro*,  $\alpha$ -D-*manno*,  $\alpha$ -D-*allo*,  $\alpha$ -D-*gluco*, and 2-deoxy- $\alpha$ -D-*arabino* configurations have been measured at 60 Mc/s and partially analysed. Several further examples of both stereospecific long range coupling over four saturated bonds, and of virtual long-range coupling, have been observed. The values of the coupling constants  $J_{1,2}$ ,  $J_{1,3}$ ,  $J_{2,3}$ , and  $J_{3,4}$  obtained by 1st order analysis support the assignment of the chair conformation to the pyranoid ring for all five configurations. It has been found that a small splitting (0.6–1.7 c/s) is characteristic of equatorial H<sub>1</sub>–equatorial H<sub>2</sub> proton arrangements in these compounds, whereas a larger splitting (3.3–3.8 c/s) is characteristic of the equatorial H<sub>1</sub>–axial H<sub>2</sub> arrangement. The possible reasons for these, and similar differences, are discussed.

SOME recent investigations of the conformations of pyranose rings in solution by PMR spectroscopy have shown that whereas some pyranose chair conformations are only slightly deformed by the fusion to them of a *cis*-vicinal 5-membered cyclic acetal ring, others in which the cyclic acetal is fused to C<sub>1</sub> and C<sub>2</sub> of the pyranose ring undergo a rather unexpected conformational modification. Thus Hall *et al.*<sup>1</sup> showed that the pyranose ring conformation of 4-O-acetyl-2,3-O-isopropylidene diethylsulphonyl-( $\alpha$ -D-lyxopyranosyl) methane is close to a chair, whereas Coxon and Hall<sup>2</sup> found that the conformation of the six-membered ring in various 1,2-O-alkylidene derivatives of  $\alpha$ -D-glucopyranose is best represented as a skew boat. A similar skew conformation has been observed by Cone and Hough<sup>3</sup> in 1,2:3,4-di-O-isopropylidene derivatives of  $\beta$ -L-arabinopyranose and  $\alpha$ -D-galactopyranose. The existence of a skew conformation in the case of the 1,2 cyclic acetals of  $\alpha$ -D-glucopyranose is especially surprising, since a C1 chair conformation with this configuration might normally be expected to be highly stable. It is interesting to contrast these results with those from the IR studies of Angyal and Hoskinson<sup>4</sup> who determined that the chair conformation of an inositol is distorted only slightly by the *cis*-vicinal fusion of an isopropylidene ring, but that the presence of two such *cis*-ketal rings modifies the cyclohexane ring to a skew boat. Lemieux and Lown,<sup>5</sup> on the other hand, have suggested that the proton coupling constants found in the isopropylidene derivative of 1,4,4-trideuterio *cis*-cyclohexane-1,2-diol require considerable distortion of the cyclo-hexane ring.

The reasons for these differences are not well understood, and as part of a general investigation of the factors governing conformational preference in polysubstituted pyranose rings, the PMR spectra of several series of methyl 4,6-O-benzylidene- $\alpha$ -D-hexopyranosides have been measured and partially analysed. The study has been

<sup>1</sup> L. D. Hall, L. Hough, K. A. McLauchlan and K. G. R. Pachler, *Chem & Ind.* 1465 (1962).

<sup>2</sup> B. Coxon and L. D. Hall, *Tetrahedron* **20**, 1685 (1964).

<sup>3</sup> C. Cone and L. Hough, *Carbohydrate Research* **1**, 1 (1965).

<sup>4</sup> S. J. Angyal and R. M. Hoskinson, *J. Chem. Soc.* 2991 (1962).

<sup>5</sup> R. U. Lemieux and J. W. Lown, *Canad. J. Chem.* **42**, 893 (1964).

restricted initially to those derivatives with the  $\alpha$ -D-*altro*,  $\alpha$ -D-*manno*,  $\alpha$ -D-*allo*, and  $\alpha$ -D-*gluco* configurations since in these compounds the number of possible conformations is necessarily limited by the *trans*-fusion of the benzylidene ring to the pyranoid ring. Additionally, these derivatives appeared to be suitable for a fundamental study of proton coupling constants in pyranose rings since any equilibria involving the alternative IC chair conformation are effectively prevented.

It has often been suggested that chair conformations, e.g. (A) will tend to change to boats or skew boats if all of the substituents can thereby become equatorial or pseudo-equatorial<sup>6,7</sup> (e.g. in boat (B) and skew boat (D)), or if a suitable choice of large substituents is made.<sup>8-13</sup>

It was of particular interest, therefore, to examine a series of compounds with the  $\alpha$ -D-*altro* configuration in order to determine if the presence of a 1,2,3 triaxial system of substituents, and a possible 1:3 diaxial repulsion in the chair conformation (A) results in any conformational modification.

The conformations of some of these benzylidene derivatives have been studied previously by IR spectroscopy of carbon tetrachloride solutions,<sup>14</sup> but the method is naturally restricted to very dilute solutions, and to those compounds which contain at least one substituent capable of intramolecular hydrogen bonding. The presence of such bonding may, in some cases, stabilize particular conformations.<sup>15,16</sup> Methods such as cuprammonium<sup>17</sup> or borate<sup>18</sup> complex formation, and periodate<sup>19a</sup> and lead tetra-acetate<sup>19b</sup> oxidation, are also restricted in application (to polyols), and would appear to be slightly less valid as indicators of ground-state conformation, since in some circumstances the molecule may change conformation to form a cyclic complex. Some of these examples have therefore been re-examined, and compared with derivatives in which hydrogen bonding or complex formation is not possible, i.e. those in which vicinal gauche and 1:3-diaxial interactions might be expected to be maximal. It is of interest to note that hydrogen bonding in methyl 4,6-O-benzylidene  $\alpha$ -D-*altro*-pyranoside, and in its 2-O-methyl and 3-O-methyl derivatives was found to be anomalously incomplete.<sup>14</sup> The PMR spectra of some related compounds, the 2,3-epoxides, -episulphides, and -epimine derivatives of methyl 4,6-O-benzylidene- $\alpha$ -D-*manno* and - $\alpha$ -D-*allo*pyranosides have recently been studied by Buss *et al.*<sup>20a</sup> who obtained evidence for the stereospecificity of the vicinal proton coupling constants near the

<sup>6</sup> J. A. Mills, *Advances in Carbohydrate Chem.* **10**, 44 (1955).

<sup>7</sup> R. E. Reeves and F. A. Blouin, *J. Amer. Chem. Soc.* **79**, 2261 (1957).

<sup>8</sup> N. L. Allinger and L. A. Freiberg, *J. Amer. Chem. Soc.* **82**, 2393 (1960).

<sup>9</sup> E. L. Eliel, *Stereochemistry of Carbon Compounds* p. 207. McGraw-Hill, New York (1962).

<sup>10</sup> E. W. Garbisch, Jr. and D. B. Patterson, *J. Amer. Chem. Soc.* **85**, 3228 (1963).

<sup>11</sup> R. D. Stolow and M. M. Bonaventura, *J. Amer. Chem. Soc.* **85**, 3636 (1963).

<sup>12</sup> N. O. Brace, *J. Amer. Chem. Soc.* **86**, 665 (1964).

<sup>13</sup> H. Booth and G. C. Gidley, *Tetrahedron Letters* 1449 (1964).

<sup>14</sup> H. Spedding, *J. Chem. Soc.* 3617 (1961); *Advances in Carbohydrate Chem.* **19**, 23 (1964).

<sup>15</sup> K. W. Buck, A. B. Foster, N. K. Richtmyer and E. Zissis, *J. Chem. Soc.* 3633 (1961); A. B. Foster, A. H. Haines, J. Homer, J. Lehmann and L. F. Thomas, *J. Chem. Soc.* 5005 (1961).

<sup>16</sup> R. U. Lemieux and S. Levine, *Canad. J. Chem.* **42**, 1473 (1964).

<sup>17</sup> R. E. Reeves, *J. Amer. Chem. Soc.* **72**, 1499 (1950).

<sup>18</sup> S. J. Angyal and D. J. McHugh, *Chem. & Ind.* 1147 (1956).

<sup>19a</sup> J. Honeyman and C. J. G. Shaw, *J. Chem. Soc.* 2454 (1959); <sup>19b</sup> H. R. Goldschmid and A. S. Perlin, *Canad. J. Chem.* **38**, 2280 (1960).

<sup>20a</sup> D. H. Buss, L. Hough, L. D. Hall and J. F. Manville, *Tetrahedron* **21**, 69 (1965);

*epi*-ring. These examples are not directly comparable with those of the present study since fusion of the 3-membered ring to the pyranose ring was expected to cause the latter to adopt the half-chair conformation. All of the 4,6-O-benzylidene derivatives in the present study were prepared under equilibration conditions, and hence the preferred conformation of the benzylidene ring is assumed to be the chair in which the phenyl substituent is equatorial.<sup>20b</sup>

## EXPERIMENTAL

M.p.s were determined on a Kofler micro heating stage. Optical rotations were measured on  $\text{CHCl}_3$ -solutions unless stated otherwise. Thin layer chromatography (TLC) was conducted on microscope slides coated with Kieselgel G (E. Merck A. G., Darmstadt), and after spraying with 5% v/v  $\text{H}_2\text{SO}_4$  in EtOH, the developed chromatograms were heated on an electric hot plate. Solutions were evaporated under red. press. IR spectra were obtained from a Unicam S.P. 100 spectrometer, and absorption maxima are described as either strong (s) or medium (m) intensity, and are followed by probable assignments.

Solutions for PMR spectroscopy contained 100–250 mg of compound in 0.35–0.8 ml solvent, except in cases of limited solubility when saturated solutions were used; before being used the solutions were filtered near the poles of a small magnet to remove any contaminating magnetic particles.

The spectra were measured at 60 Mc/s on a Varian A-60 spectrometer with tetramethylsilane as internal reference. The calibration of the spectrometer was checked periodically using a 2% v/v solution of benzene in  $\text{CCl}_4$  with added tetramethylsilane, the spacing between the proton resonances of this sample being assumed to be 436 c/s.<sup>21</sup> Multiplet splittings were measured at a sweep width of 250 c/s. The assignments of resonances due to OH and NH protons were confirmed in most cases by deuterium exchange. Examination of  $\text{CDCl}_3$  solutions of the compounds listed below showed that exchange of hydroxyl and amino protons was essentially complete after the solution had been shaken with  $\text{D}_2\text{O}$  for several min. Exchange of acetamido NH was usually not complete after this time however, but was obtained under uncatalysed conditions by shaking of the  $\text{CDCl}_3$  solution with  $\text{D}_2\text{O}$  overnight. Simplifications of the resonance signals of some of the pyranose ring protons were obtained in this way, and useful solvent shifts of the signals were frequently obtained by evaporation of the exchanged  $\text{CDCl}_3$  solutions to dryness, followed by re-examination of the spectrum of a solution in pyridine. The D-substituted materials referred to below are deuterated only on either O, or N, or on both. Satisfactory spectrum integrals were obtained for all of the compounds investigated. In the Tables of chemical shifts and coupling constants, the multiplicities of proton signals are indicated by a symbol following the chemical shift. If there is no symbol listed then it is implied that the signal in question was observed as a singlet; otherwise the multiplicities are described as doublet (d), triplet (t), quartet (q), quintet (qi), sextet (sx), octet (o), or as a complex multiplet (m). Where a range of chemical shift for a group of protons is given in the Tables, this means merely that the signals of the individual protons occurred somewhere within the range. For the sake of simplicity, coupling constants in aromatic rings are omitted from the Tables.

The compounds which were examined included: *Methyl 4,6-O-benzylidene- $\alpha$ -D-altropyranoside* (I)<sup>22</sup>; *Methyl 4,6-O-benzylidene- $\alpha$ -D-altropyranoside-d<sub>3</sub>* (II); *Methyl 2,3-di-O-acetyl-4,6-O-benzylidene- $\alpha$ -D-altropyranoside* (III). The diol (I) was acetylated with pyridine-acetic anhydride in the usual manner yielding a brown syrup which was purified by passage of a solution in  $\text{CH}_2\text{Cl}_2$  through a small column of silica gel (Davison grade 950, 60–200 mesh). Crystallization from EtOH, and then from isopropanol afforded the diacetyl derivative as colourless flat slivers (46%), m.p. 103–104°. A further recrystallization from isopropanol gave material with m.p. 104–105°,  $[\alpha]_D^{25} + 55.7^\circ$  (c, 1.06). (Found: C, 58.8; H, 5.7; OMe, 8.6.  $\text{C}_{18}\text{H}_{22}\text{O}_8$  requires: C, 59.0; H, 6.0; OMe, 8.5%.)

*Methyl 2,3-di-O-benzoyl-4,6-O-benzylidene- $\alpha$ -D-altropyranoside* (IV). Conventional benzoylation of the diol (I) using benzoyl chloride and pyridine gave the dibenzoate as a syrup  $[\alpha]_D^{25} + 7^\circ$  (c, 1.57) which was almost homogeneous according to TLC in 20:1 benzene-ether. (Found: C, 68.5; H, 5.5; OMe, 6.5.  $\text{C}_{28}\text{H}_{30}\text{O}_8$  requires: C, 68.6; H, 5.4; OMe, 6.3%.)

<sup>20a</sup> Cf. N. Baggett, J. M. Duxbury, A. B. Foster and J. M. Webber, *Chem. & Ind.* 1832 (1964).

<sup>21</sup> Technical bulletin from Varian A. G., Zürich, Switzerland.

<sup>22</sup> G. J. Robertson and W. Whitehead, *J. Chem. Soc.* 319 (1940).

*Methyl 4,6-O-benzylidene-2-O-methyl- $\alpha$ -D-altropyranoside (V)<sup>23</sup>; Methyl 4,6-O-benzylidene-3-O-methyl- $\alpha$ -D-altropyranoside (VI)<sup>23</sup>; Methyl 4,6-O-benzylidene-2,3-di-O-methyl- $\alpha$ -D-altropyranoside (VII)<sup>23</sup>; Methyl 4,6-O-benzylidene-2-O-methyl-3-O-toluene-p-sulphonyl- $\alpha$ -D-altropyranoside (VIII)<sup>23</sup>; Methyl 2-amino-4,6-O-benzylidene-2-deoxy- $\alpha$ -D-altropyranoside (IX)<sup>24</sup>; Methyl 3-amino-4,6-O-benzylidene-3-deoxy- $\alpha$ -D-altropyranoside<sup>25a-d</sup>, d<sub>3</sub> (X); Methyl 3-acetamido-4,6-O-benzylidene-3-deoxy- $\alpha$ -D-altropyranoside (XI). A solution of the 3-acetamido-2-O-acetyl derivative (XII, 0.5 g) in ice-cold methanol (50 ml) was saturated with dry ammonia and kept at room temp overnight. Concentration of the solution followed by sublimation of acetamide at 100°/15 mm left a pale yellow syrup (0.44 g) which was deionized with Amberlite IR-4B (OH) resin in water. The syrup crystallized after 6 months yielding the N-acetate as colourless plates (0.17 g), m.p. 141–142° [ $\alpha$ ]<sub>D</sub><sup>25</sup> +53° (c, 0.98). (Found: C, 59.7; H, 6.8; N, 4.4. C<sub>18</sub>H<sub>21</sub>NO<sub>8</sub> requires: C, 59.4; H, 6.6; N, 4.4%.)*

*Methyl 3-acetamido-2-O-acetyl-4,6-O-benzylidene-3-deoxy- $\alpha$ -D-altropyranoside (XII)<sup>25b</sup>; Methyl 3-benzamido-4,6-O-benzylidene-3-deoxy- $\alpha$ -D-altropyranoside (XIII)<sup>25</sup>; Methyl 4,6-O-benzylidene-3-deoxy-3-(2,4-dinitrophenylamino)- $\alpha$ -D-altropyranoside (XIV). A solution of methyl 3-amino-4,6-O-benzylidene-3-deoxy- $\alpha$ -D-altropyranoside (2.05 g) in EtOH (75 ml) was added to a stirred mixture of 2,4-dinitrofluorobenzene (1.38 g, 1 mole equiv.), powdered CaCO<sub>3</sub> (20 g) and 50% EtOHaq (20 ml). The bright yellow suspension was stirred at room temp for 23 hr when a further small amount of CaCO<sub>3</sub> was added, and stirring was continued for a further 10 min. Solids were then filtered off on Filter-cel, and were washed with CHCl<sub>3</sub> until the washings were colourless. Concentration of the filtrate and crystallization of the product from EtOH-pet. ether (b.p. 60–80°) yielded the 2,4-dinitrophenyl derivative as bright yellow hexagonal prisms (3.17 g, 97%), m.p. 237–238° unchanged by further recrystallization; [ $\alpha$ ]<sub>D</sub><sup>25</sup> +37.2° (c, 2.59). (Found: C, 53.3; H, 4.7; N, 9.7. C<sub>22</sub>H<sub>21</sub>N<sub>3</sub>O<sub>8</sub> requires: C, 53.6; H, 4.7; N, 9.4%.)*

*Methyl 2-O-acetyl-4,6-O-benzylidene-3-deoxy-3-(2,4-dinitrophenylamino)- $\alpha$ -D-altropyranoside (XV). Acetylation of the 2,4-dinitrophenyl derivative (XIV) with acetic anhydride-pyridine afforded the O-acetyl derivative (from isopropanol) as a bright yellow amorphous solid (68%), m.p. 102–105°, raised to m.p. 104–106° by two recrystallizations from isopropanol, and homogeneous according to TLC in benzene and 1:1 benzene-ether; [ $\alpha$ ]<sub>D</sub><sup>25</sup> -2° (c, 0.97). (Found: C, 54.0; H, 4.9; N, 8.7; OMe, 6.4. C<sub>22</sub>H<sub>21</sub>N<sub>3</sub>O<sub>10</sub> requires: C, 54.1; H, 4.7; N, 8.6; OMe, 6.3%.)*

*Methyl 4,6-O-benzylidene-3-deoxy-3-(2,4-dinitrophenylamino)-2-O-methyl- $\alpha$ -D-altropyranoside (XVI). A mixture of the 2,4-dinitrophenyl derivative (1.0 g of XIV), MeI (15 ml), CHCl<sub>3</sub> (30 ml), powdered anhydrous CaSO<sub>4</sub> (5 g), and Ag<sub>2</sub>O (7 g) was boiled under reflux for 16 hr. The suspension was filtered through Filter-cel and the insoluble solids washed with hot CHCl<sub>3</sub>. Evaporation of the combined filtrate and washings then yielded a syrup which crystallized on addition of EtOH:—0.98 g (95%), m.p. 176–178°. Recrystallization from EtOH afforded the 2-O-methyl derivative as brilliant yellow hexagonal plates (0.8 g) which had m.p. 177–178°, [ $\alpha$ ]<sub>D</sub><sup>25</sup> +23.1° (c, 1.25),  $\nu_{max}$  (cm<sup>-1</sup> in nujol) 3300 m (NH), 1620 s, 1590 s, and 1510 s (shoulder) (Ar), 1520 s (NO<sub>2</sub>). (Found: C, 54.5; H, 5.1; N, 9.2; OMe, 14.1. C<sub>21</sub>H<sub>21</sub>N<sub>3</sub>O<sub>8</sub> requires: C, 54.7; H, 5.0; N, 9.1; OMe, 13.5%.)*

*Methyl 4,6-O-benzylidene- $\alpha$ -D-mannopyranoside (XVII)<sup>27</sup>; Methyl 2,3-di-O-acetyl 4,6-O-benzylidene- $\alpha$ -D-mannopyranoside (XVIII). Acetylation of the diol (XVII) in pyridine-acetic anhydride at room temp gave the di-O-acetate as a syrup which on TLC displayed a trace of a slow moving impurity. The syrup was therefore purified by passing a solution in CH<sub>2</sub>Cl<sub>2</sub> through a short column of silica gel (Davison, grade 950), whence concentration of the eluate yielded material with [ $\alpha$ ]<sub>D</sub><sup>25</sup> +23.1° (c, 1.06). (Found: C, 59.3; H, 6.2; OMe, 8.3. C<sub>18</sub>H<sub>21</sub>O<sub>8</sub> requires: C, 59.0; H, 6.1; OMe, 8.5%.)*

*Methyl 2,3-di-O-benzoyl-4,6-O-benzylidene- $\alpha$ -D-mannopyranoside (XIX). The diol (XVII) was benzoylated with 3 mole equivs of benzoyl chloride in pyridine yielding the di-O-benzoyl derivative as a pale yellow syrup (91%) which was homogeneous on TLC eluted with 1:1 benzene-ether. The syrup showed [ $\alpha$ ]<sub>D</sub><sup>25</sup> -141.0° (c, 1.62). (Found: C, 68.6; H, 5.3; OMe, 6.2. C<sub>28</sub>H<sub>24</sub>O<sub>8</sub> requires: C, 68.6; H, 5.4; OMe, 6.3%.)*

<sup>23</sup> Kindly donated by Dr. D. Lloyd from the collection of carbohydrate derivatives at the University of St. Andrews.

<sup>24</sup> W. H. Myers and G. J. Robertson, *J. Amer. Chem. Soc.* **65**, 8 (1943).

<sup>25a</sup> G. J. Robertson, W. H. Myers and W. E. Tetlow, *Nature, Lond.* **142**, 1076 (1938); <sup>b</sup> G. J. Robertson and W. H. Myers, *Ibid. Lond.* **143**, 640 (1939).

<sup>26</sup> D. H. Buss, L. Hough and A. C. Richardson, *J. Chem. Soc.* 5295 (1963).

<sup>27</sup> J. G. Buchanan and J. C. P. Schwarz, *J. Chem. Soc.* 4770 (1962).

*Methyl 4,6-O-benzylidene-2,3-di-O-toluene-p-sulphonyl- $\alpha$ -D-mannopyranoside (XX)<sup>25</sup>; Methyl 4,6-O-benzylidene-2,3-di-O-nitrobenzene-p-sulphonyl- $\alpha$ -D-mannopyranoside (XXI).* The diol (XVII) was reacted with 2.5 mole equivs of nitrobenzene-*p*-sulphonyl chloride in pyridine. Isolation of the product in the usual way afforded a pale yellow syrup which crystallized from aqueous ethanolic acetone as fine, almost colourless needles (53%), m.p. 180–182° (dec). Recrystallized from aqueous acetone, and then from ethanolic acetone the di-*o*-nitrobenzene-*p*-sulphonate had m.p. 185–187° (dec),  $[\alpha]_D^{25} -4.4^\circ$  (*c*, 1.7). (Found: C, 48.0; H, 3.7; N, 4.2; S, 9.8; OMe, 4.9.  $C_{28}H_{34}N_2O_{14}S_2$  requires: C, 47.9; H, 3.7; N, 4.3; S, 9.8; OMe, 4.8%.)

*Methyl 3-acetamido-4,6-O-benzylidene-3-deoxy- $\alpha$ -D-allopyranoside (XXII)<sup>26</sup>; Methyl 3-acetamido-4,6-O-benzylidene-3-deoxy- $\alpha$ -D-allopyranoside-*d*<sub>3</sub> (XXIII); Methyl 3-acetamido-2-O-acetyl-4,6-O-benzylidene-3-deoxy- $\alpha$ -D-allopyranoside (XXIV)<sup>26</sup>; Methyl 3-acetamido-2-O-acetyl-4,6-O-benzylidene-3-deoxy- $\alpha$ -D-allopyranoside-*d* (XXV); Methyl 4,6-O-benzylidene- $\alpha$ -D-glucopyranoside (XXVI)<sup>26</sup>; Methyl 4,6-O-benzylidene- $\alpha$ -D-glucopyranoside-*d*<sub>3</sub> (XXVII); Methyl 2,3-di-O-acetyl-4,6-O-benzylidene- $\alpha$ -D-glucopyranoside (XXVIII)<sup>26</sup>; Methyl 2,3-di-O-benzoyl-4,6-O-benzylidene- $\alpha$ -D-glucopyranoside (XXIX)<sup>21</sup>; Methyl 3-O-benzoyl-4,6-O-benzylidene-2-O-toluene-*p*-sulphonyl- $\alpha$ -D-glucopyranoside (XXX)<sup>22</sup>; Methyl 4,6-O-benzylidene-2,3-di-O-toluene-*p*-sulphonyl- $\alpha$ -D-glucopyranoside (XXXI)<sup>22</sup>; Methyl 2-O-acetyl-4,6-O-nitrobenzylidene- $\alpha$ -D-glucopyranoside-3-nitrate (XXXII)<sup>22</sup>; Methyl 4,6-O-benzylidene-2,3-di-O-methyl- $\alpha$ -D-glucopyranoside (XXXIII)<sup>22</sup>; Methyl 2-acetamido-3-O-acetyl-4,6-O-benzylidene-2-deoxy- $\alpha$ -D-glucopyranoside (XXXIV)<sup>22</sup>; Methyl 4,6-O-benzylidene-2-deoxy- $\alpha$ -D-arabino hexopyranoside (XXXV).* To methyl 2-deoxy- $\alpha$ -D-arabino hexopyranoside (2.36 g) in benzaldehyde (12 ml) was added 98–100% formic acid (12 ml), and the mixture shaken until the crystals had dissolved. After 4–5 min at room temp the solution was poured gradually into an ice-cold mixture of  $K_2CO_3$  (27 g of anhydrous), water (95 ml) and pet. ether (95 ml, b.p. 60–80°). The suspension was cooled with stirring in an ice-salt bath for 1 hr; the filtered product was then washed with ice-water, and ice-cold pet. ether, and dried at 50°–2.05 g (58%), m.p. 149–150° unchanged by recrystallization from EtOH–pet. ether. The fine silky needles showed  $[\alpha]_D^{25} +83.8^\circ$  (*c*, 1.56 in EtOH)

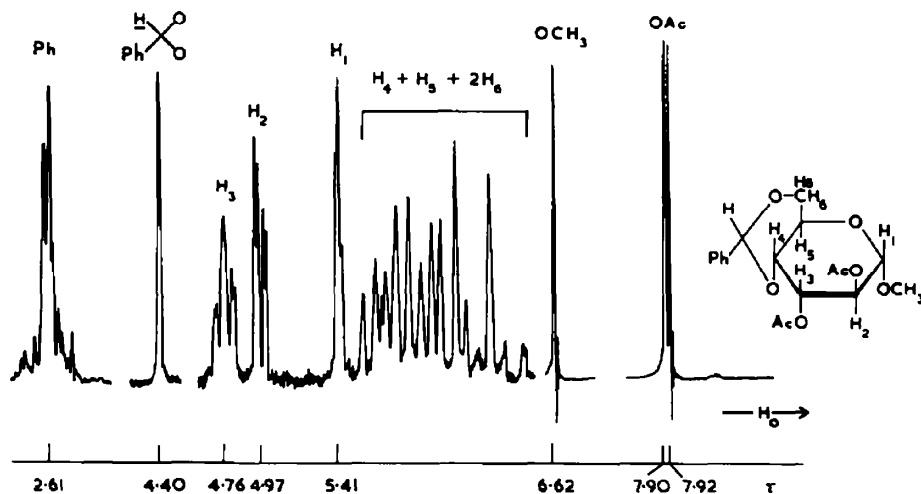


FIG. 1. PMR spectrum of methyl 2,3-di-O-acetyl-4,6-O-benzylidene- $\alpha$ -D-allopyranoside (III) in  $CDCl_3$  with some of the resonances displayed at reduced amplitude.

<sup>25</sup> B. R. Baker and R. E. Schaub, *J. Org. Chem.* **19**, 646 (1954).

<sup>26</sup> L. Light and Co. Ltd.

<sup>20</sup> D. S. Mathers and G. J. Robertson, *J. Chem. Soc.* 696 (1933).

<sup>21</sup> H. Ohle and K. Spencker, *Ber. Dtsch. Chem. Ges.* **61**, 2387 (1928).

<sup>22</sup> J. C. Irvine and J. P. Scott, *J. Chem. Soc.* 575 (1913).

<sup>23</sup> L. F. Wiggins, *J. Chem. Soc.* 18 (1947).

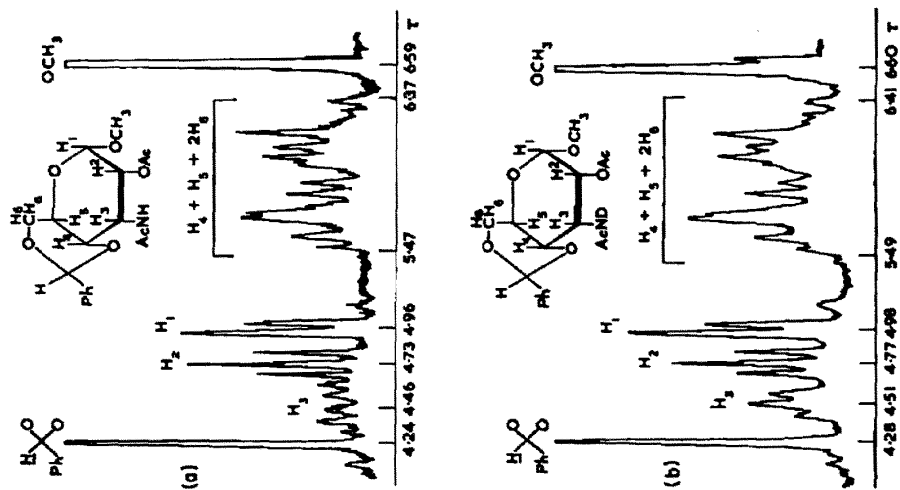


Fig. 3 Partial PMR spectra in pyridine of (a) methyl 3-acetamido-2-O-acetyl-4,6-O-benzylidene-3-deoxy- $\alpha$ -D-allopyranoside (XXIV), and (b) its N-deutero derivative (XXV).

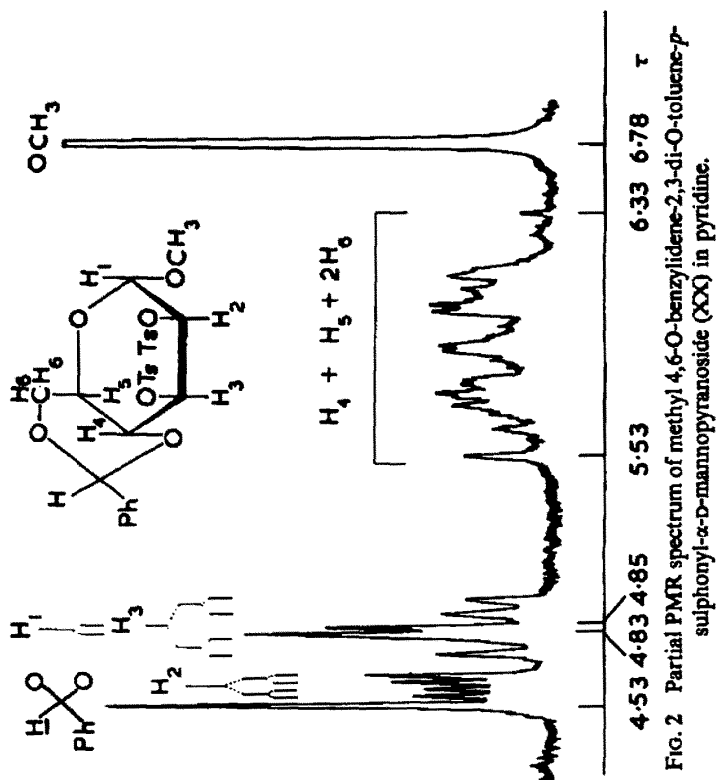


Fig. 2 Partial PMR spectrum of methyl 4,6-O-benzylidene-2,3-di-O-toluene-*p*-sulphonyl- $\alpha$ -D-mannopyranoside (XX) in pyridine.

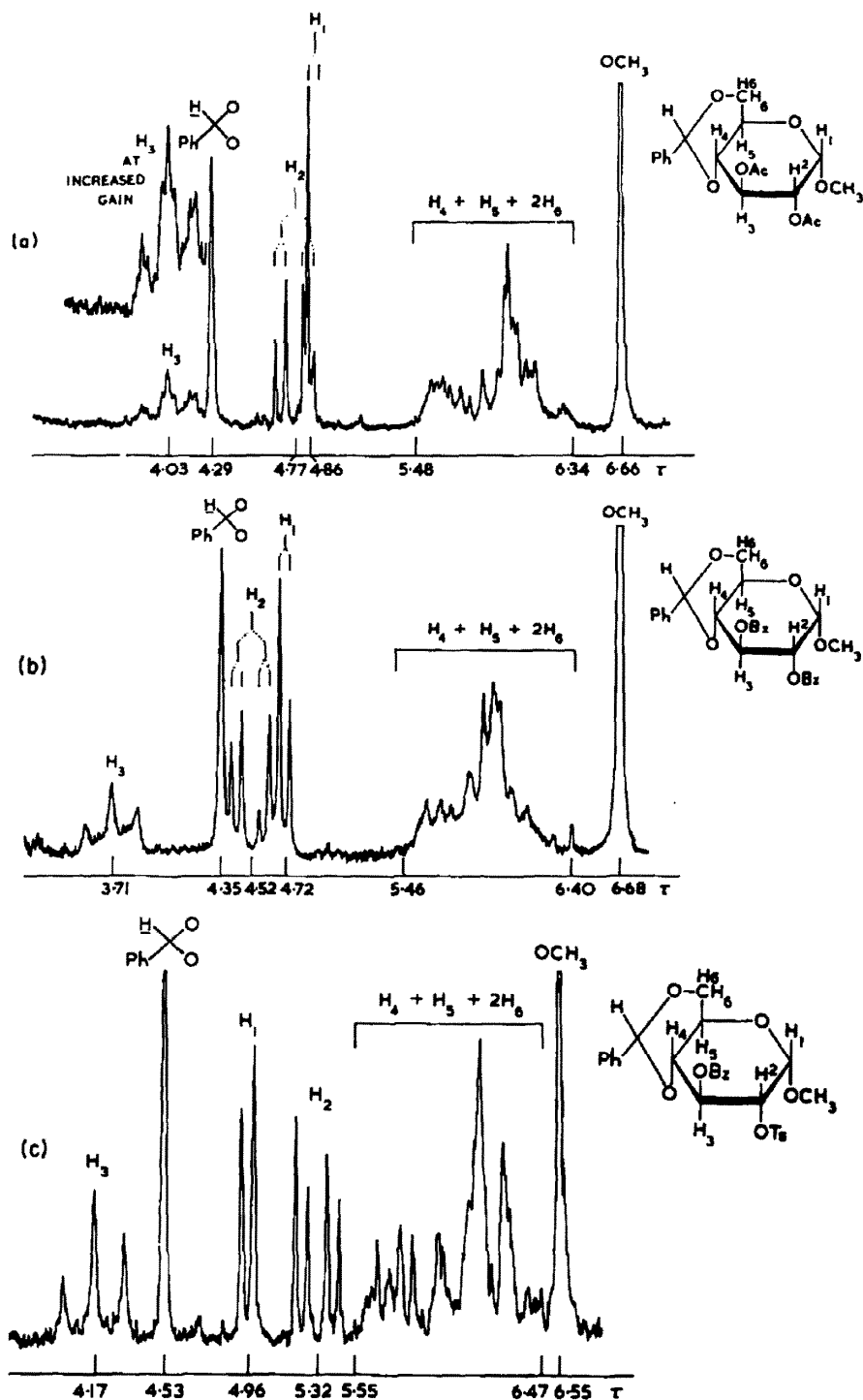


FIG. 4. Partial PMR spectra of (a) methyl 2,3-di-O-acetyl-4,6-O-benzylidene- $\alpha$ -D-glucopyranoside (XXVIII) in pyridine, (b) methyl 2,3-di-O-benzoyl-4,6-O-benzylidene- $\alpha$ -D-glucopyranoside (XXIX) in 1:1  $CDCl_3$ :pyridine, (c) methyl 3-O-benzoyl-4,6-O-benzylidene-2-O-toluene-*p*-sulphonyl- $\alpha$ -D-glucopyranoside (XXX) in  $CDCl_3$ .

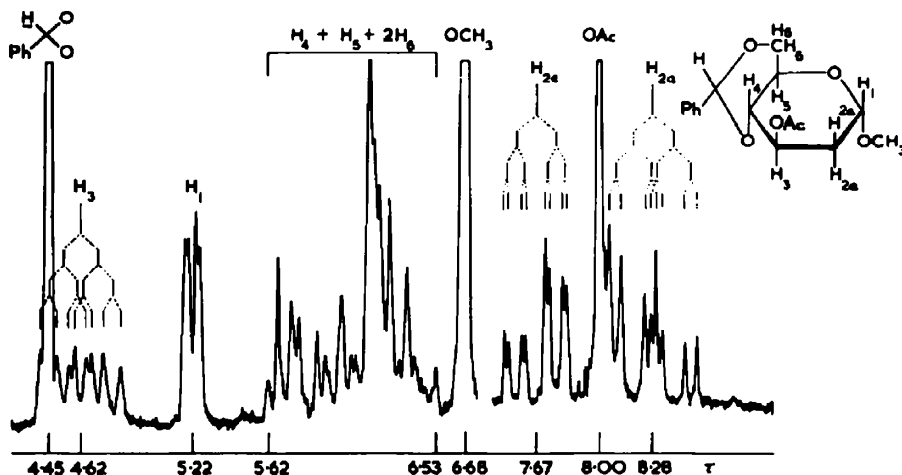


FIG. 5. Partial PMR spectrum of methyl 3-O-acetyl-4,6-O-benzylidene-2-deoxy- $\alpha$ -D-arabinohexopyranoside (XXXVI) in  $\text{CDCl}_3$ .

Hughes *et al.*<sup>34a</sup> reported m.p. 137–139° and  $[\alpha]_D^{19} + 77^\circ$  (in EtOH) for the product of a  $\text{ZnCl}_2$  catalysed acetalation. Inglis *et al.*<sup>34b</sup> quoted m.p. 149–150°.

*Methyl 3-O-acetyl-4,6-O-benzylidene-2-deoxy- $\alpha$ -D-arabinohexopyranoside* (XXXVI). The alcohol (XXXV) was acetylated at room temp in acetic anhydride–pyridine in the customary manner. Crystallization from aqueous pyridine then yielded the acetate as colourless needles m.p. 126–129° (99%). After recrystallization from aqueous EtOH they had m.p. 130–131° (with sublimation), unchanged by a further recrystallization from aqueous acetone, and showed  $[\alpha]_D^{25} - 79.1^\circ$  (c, 1.28). (Found: C, 62.2; H, 6.6; OMe, 10.3; OAc, 13.5.  $\text{C}_{18}\text{H}_{20}\text{O}_8$  requires: C, 62.4; H, 6.5; OMe, 10.1; OAc, 13.9%.)

## RESULTS AND DISCUSSION

In the determination of ring conformations in solution, extensive use has been made in recent years of the equation of Karplus<sup>35</sup> which describes the coupling constants of protons bonded to vicinal carbon atoms, in terms of the proton dihedral angle ( $\phi$ ). This relationship was derived theoretically<sup>35</sup> for only a simple "ethanic" type molecule, and whilst it was claimed<sup>36</sup> initially that the application of a slightly modified form of the equation to experimentally determined coupling constants allowed the calculation of dihedral angles in carbohydrates to an accuracy of  $\pm 1^\circ$  or  $2^\circ$ , it now appears that the use of the equation in this way has been considerably over extended.<sup>37</sup> It has been found that vicinal proton coupling constants depend on several factors other than dihedral angle. Thus the inverse variation of coupling constants with the electronegativity of the attached substituent(s) is now experimentally well established for several types of molecules,<sup>38,39</sup> although Huitric *et al.*<sup>40</sup> were unable to find a simple correlation

<sup>34a</sup> I. W. Hughes, W. G. Overend and M. Stacey, *J. Chem. Soc.* 2846 (1949); <sup>b</sup> G. R. Inglis, J. C. P. Schwarz and (in part) L. McLaren, *Ibid.* 1014 (1962).

<sup>35</sup> M. Karplus, *J. Chem. Phys.* 30, 11 (1959).

<sup>36</sup> R. W. Lenz and J. P. Heeschen, *J. Polymer Sci.* 51, 247 (1961).

<sup>37</sup> M. Karplus, *J. Amer. Chem. Soc.* 85, 2870 (1963).

<sup>38</sup> K. L. Williamson, *J. Amer. Chem. Soc.* 85, 516 (1963); P. Laszlo and P. von R. Schleyer, *Ibid.* 85, 2709 (1963); K. L. Williamson, C. A. Lanford and C. R. Nicholson, *Ibid.* 86, 762 (1964).

<sup>39</sup> R. J. Abraham and K. G. R. Pachler, *Mol. Phys.* 7, 165 (1963).

<sup>40</sup> A. C. Huitric, J. B. Carr, W. F. Trager and B. J. Nist, *Tetrahedron* 19, 2145 (1963).



between these quantities in a number of *cis* and *trans*-1-(substituted)-2-arylcyclohexanes-3,3,6,6-d<sub>4</sub>. Controversy exists as to the most useful definition of "electronegativity".<sup>38-40</sup> The definition in terms of chemical shift employed by Williamson<sup>38</sup> has the disadvantage that no allowance is made for substituent magnetic anisotropy, whereas the use of the Huggins electronegativity of the *first* substituent atom<sup>39</sup> neglects the remainder of the substituent, the effect of which however, is usually quite small. Williams and Bhacca have proposed<sup>41</sup> that vicinal proton coupling constants are also dependent upon the *orientation* of electronegative substituents, and have concluded from a study of a series of steroid derivatives that for a 1-hydroxy or 1-acetoxy substituent in a cyclohexane ring,  $J_{1e,2a}$  and  $J_{1e,2e}$  are approximately the same in the case where the substituent is axial, and are both appreciably smaller than  $J_{1a,2e}$  in the case where the substituent is equatorial. These observations have been extended by Booth<sup>42</sup> who has pointed out that the coupling constant is diminished to the greatest extent when the electronegative substituent is *trans*-coplanar (*trans*-anti-parallel) to one proton of the coupling pair.

Karplus has re-emphasized<sup>37</sup> that dependency of coupling constants on C—C bond length and on H—C—C bond angle may be expected, and has also advised that it is preferable if the solution to practical problems depends only on whether proton couplings are "large" or "small".

For the foregoing reasons, the calculation of dihedral angles from coupling constants has not been attempted in the present investigation.

In general, the signals due to H<sub>4</sub>, H<sub>5</sub>, and 2H<sub>6</sub> in the benzylidene derivatives (I-XXXVI) were not resolved at 60 Mc/s, and appeared as a complex band in the region of  $\tau$ 5.1-6.9. Because of this, no values of  $J_{4,5}$  were obtained from any of the compounds studied, but it is fortunately not necessary to do so in order to comment on their conformations, since the *trans*-fusion of the benzylidene ring to the pyranose ring effectively locks H<sub>4</sub> and H<sub>5</sub> in a near *trans*-diaxial arrangement. With the exception of the 2-deoxy- $\alpha$ -D-hexopyranosides (XXXV and XXXVI) the first bound atoms of the pyranose ring substituents R<sub>2</sub>, and R<sub>3</sub> were all either oxygen, or nitrogen, or both, and hence because of the limited range of substituent electronegativities involved, the major differences which were observed in the coupling constants were due to the differing stereochemical orientations of the protons. The results, therefore, are discussed in terms of these orientations and hence of the configurations of the substituents.

*Methyl 4,6-O-benzylidene- $\alpha$ -D-altropyranosides* (I-XVI). 1st order analysis of the spectra of this series of compounds yielded the chemical shifts and coupling constants shown in Table 1. The spectrum (Fig. 1) of the diacetyl derivative (III) was one of the better examples. In this series the signal due to H<sub>1</sub> was usually either a triplet of small splitting (as in Fig. 1), or a singlet which was invariably broader than that due to the benzylic methine proton. The coupling constant  $J_{1,2}$  was most frequently obtained by measurement of the quartet due to H<sub>2</sub>, but if this was not resolved then approximate values were obtained by measurement of the H<sub>1</sub> triplet. In those compounds (III, VII and VIII) in which the signal due to H<sub>2</sub> was resolved, extra splitting could be seen in this signal which therefore appeared as a sextet (e.g. Fig. 1). Since extra splittings were not observed in the spectra of the 3-epimeric  $\alpha$ -D-*manno* compounds (see below), those in the  $\alpha$ -D-altropyranosides may be described as further examples of

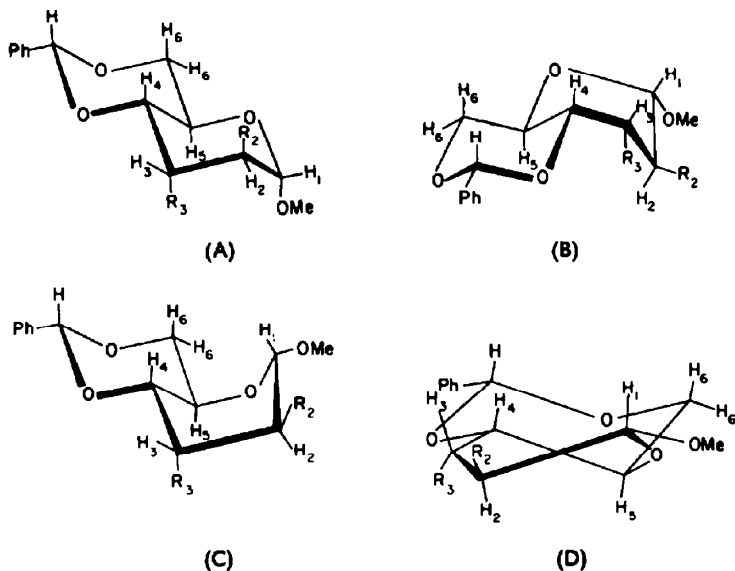
<sup>41</sup> D. H. Williams and N. S. Bhacca, *J. Amer. Chem. Soc.* **86**, 2742 (1964).

<sup>42</sup> H. Booth, *Tetrahedron Letters* 411 (1965).

stereospecific long-range coupling between  $H_1$  and  $H_3$ , over four saturated bonds. That these extra couplings are *not* due to *virtual* long range coupling<sup>43,20a</sup> of  $H_1$  to  $H_3$ , is shown by application of the theory of Musher and Corey,<sup>43</sup> which states that for a linear 3-spin system (for instance,  $H_1$ ,  $H_2$  and  $H_3$ ) the  $H_1$  quartet (with wings) is reduced to a doublet (splitting of the outside peaks  $< 0.1 J_{1,2}$ ) if (a)  $|\nu_2 - \nu_3| \geq 2 J_{1,2}$ , and  $|\nu_2 - \nu_3| \geq J_{2,3}$ , or if (b)  $|\nu_2 - \nu_3| \approx J_{1,2}$ , and  $|\nu_2 - \nu_3| \geq \frac{1}{2} J_{2,3}$ . These conditions are well satisfied for example by the parameters of the diacetate (III), which in deuteriochloroform had  $|\nu_2 - \nu_3| = 12.6$  c/s,  $J_{1,2} = 0.9$  c/s, and  $J_{2,3} = 2.9$  c/s; that is  $H_2$  and  $H_3$  are not sufficiently strongly coupled for virtual coupling to be observed in  $H_1$ .

Many examples of stereospecific long-range coupling are now known, both in carbohydrates,<sup>44,2</sup> and elsewhere.<sup>45</sup>

The signals of  $H_1$  therefore appeared as either triplets, or as singlets (unresolved triplets or quartets), because  $J_{1,2}$  and  $J_{1,3}$  were both small, and of comparable magnitude [e.g. for (III),  $J_{1,2} = J_{1,3} = 0.9$  c/s.] The ranges of coupling constants obtained from the pyranose rings of the derivatives (I–XVI) were  $J_{1,2} < 0.8$ – $1.1$ ,  $J_{1,3} < 0.5$ – $0.9$ ,  $J_{2,3} = 2.5$ – $3.1$  and  $J_{3,4} = 2.7$ – $2.9$  c/s.



The most likely possible conformations of the methyl 4,6-O-benzylidene- $\alpha$ -D-altrropyranosides are the chair (A), the classical boats (B) and (C), and the skew boat (D). Two further skew boat conformations may be obtained by twisting each of the classical boats (B) and (C) in senses opposite to those required to give skew boat (D) [(D) is intermediate between (B) and (C)], however inspection of Dreiding molecular models indicates that these skew-boats are even more strained than are (B) and (C), because of the restrictive influence of the benzylidene ring.

The proton dihedral angles ( $\phi$ ) in the pyranose rings of the conformations (A), (B), (C) and (D) are listed in Table 2 with the assumption of idealized cyclohexane

<sup>43</sup> J. I. Musher and E. J. Corey, *Tetrahedron* **18**, 791 (1962).

<sup>44</sup> L. D. Hall and L. Hough, *Proc. Chem. Soc.* 382 (1962); R. U. Lemieux and R. Nagarajan, *Canad. J. Chem.* **42**, 1270 (1964).

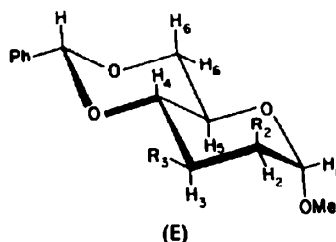
<sup>45</sup> S. Sternhell, *Rev. Pure and Appl. Chem.* **14**, 15 (1964).

geometry for the rings (i.e. equal bond lengths and classical tetrahedral angles in the rings).<sup>46</sup> The ranges of values of  $J_{1,2}$ ,  $J_{2,3}$  and  $J_{3,4}$  described above are all characteristic of vicinal protons in approximately *gauche* ( $\phi = 60^\circ$ ) orientation,<sup>47</sup> and it may be seen by reference to Table 2 that the only conformation possible for the  $\alpha$ -D-altropyranosides is indeed the chair (A).

The fact that  $J_{1,2}$  is unusually small in these compounds indicates that the contributions of the boats (B) and (C), and of the skew boat (D) to any conformational equilibria are insignificant, since in these conformations  $\phi_{1,2}$  has values of  $180^\circ$ ,  $180^\circ$  and  $169^\circ$  respectively, for which large values of  $J_{1,2}$  of the order of 8–10 c/s would be expected.<sup>47</sup> This conformational assignment is confirmed by the observation of the long-range coupling of  $H_1$  and  $H_3$ , since it has been found that this type of coupling usually occurs most strongly through saturated bonds when the 1,3 protons, and the intervening carbon atoms are in a "planar zig-zag" orientation.<sup>44,45</sup> Such an arrangement occurs for 1,3 di-equatorial protons in chair conformations and is apparently the most favourable for the transmission of spin-state information via overlap of either the intervening  $\sigma$ -bond orbitals,<sup>46</sup> or the "tail-ends" of the  $C_1-H_1$  and  $C_3-H_3$  bond orbitals.<sup>49</sup>

*Methyl 4,6-O-benzylidene- $\alpha$ -D-mannopyranosides* (XVII–XXI). The chemical shifts and 1st order coupling constants which were obtained from these derivatives are listed in Table 3. The signal of  $H_1$  was usually a sharp doublet of small splitting, except that the parent diol (XVII) in pyridine displayed a singlet which was only slightly broader than the resonance of the benzylic proton. Where the multiplets due to  $H_2$  and  $H_3$  were resolved, they appeared as quartets. The spectrum of the di-O-toluene-*p*-sulphonyl derivative (XX) in pyridine was typical of this series, and is shown in Fig. 2. In this case, the  $H_1$  doublet at  $\tau$ 4.83 was superimposed on the quartet due to  $H_3$  at  $\tau$  4.85, and  $H_2$  occurred as a well defined quartet at lower field.

For this series were obtained the ranges of values  $J_{1,2} = 0.6$ – $1.7$ ,  $J_{2,3} = 3.3$ – $3.6$  and  $J_{3,4} = 9.3$ – $9.4$  c/s. The values of  $J_{1,2}$  and  $J_{2,3}$ , although markedly different, are again characteristic of protons in approximately *gauche* orientation, and the large values of  $J_{3,4}$  represent protons in *trans* diaxial arrangement.<sup>47</sup> By arguments similar to those above it can be seen that the only conformation possible for the  $\alpha$ -D-mannopyranosides is one approximating to the chair (E).



Supporting evidence for differing orientations of the acetoxy groups in the 2,3

<sup>46</sup> Ref 9, p. 246. This point is considered in more detail later in the paper.

<sup>47</sup> R. U. Lemieux, R. K. Kullnig, H. J. Bernstein and W. G. Schneider, *J. Amer. Chem. Soc.* **80**, 6098 (1958); B. Coxon and H. G. Fletcher, *Chem. & Ind.* 662 (1964).

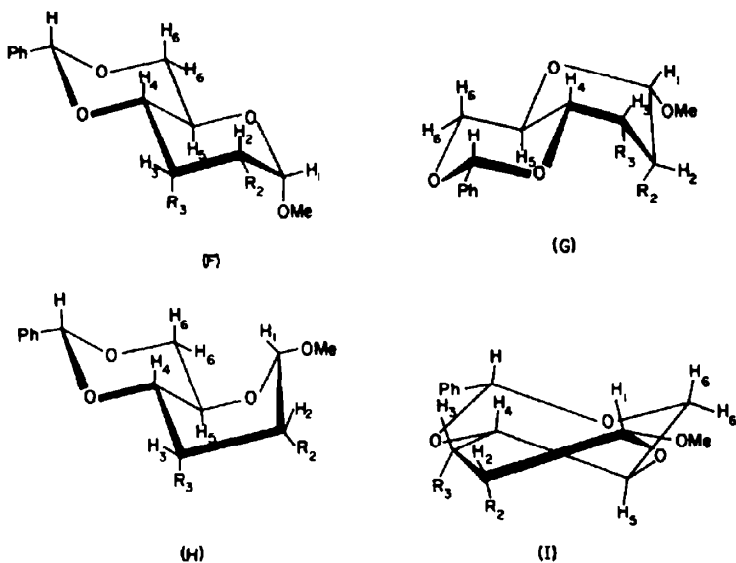
<sup>48</sup> J. A. Elvidge and R. G. Foster, *J. Chem. Soc.* 981 (1964).

<sup>49</sup> J. Meinwald and A. Lewis, *J. Amer. Chem. Soc.* **83**, 2769 (1961).

di-O-acetyl derivative (XVIII) was obtained from their chemical shifts  $\tau$  7.87 and 8.03, which indicated axial and equatorial substituents respectively.<sup>47</sup>

*Methyl 4,6-O-benzylidene- $\alpha$ -D-allopyranosides* (XXII–XXV). The parameters for this small series are shown in Table 4. The spectra of the N, O-di-acetyl derivatives (XXIV and XXV) in pyridine (Fig. 3) provided useful examples of the simplification of the spectrum resulting from N-deuteration, which caused the broad sextet at  $\tau$  4.46 due to H<sub>3</sub> in (XXIV) to collapse to a broad triplet in the N-deuterated analogue (XXV). The signal of H<sub>2</sub> in (XXIV) appeared as a quartet (almost a triplet) at  $\tau$  4.73, and that of H<sub>1</sub> as a quartet at  $\tau$  4.96 (Fig. 3a). The extra splitting (0.5 c/s) in the latter multiplet was on the threshold of resolution, and was not definitely observed in the spectra of the other compounds (XXII, XXIII and XXV) with the  $\alpha$ -D-*allo* configuration, although broadening of the H<sub>1</sub> doublet is present in XXV (Fig. 3b). Application of the conditions of Musher and Corey<sup>43</sup> again showed that this extra splitting could not be due to virtual coupling of H<sub>1</sub> with H<sub>3</sub>, since in the case of (XXIV),  $|\nu_2 - \nu_3| = 16.2$ ,  $J_{1,2} = 3.5$ , and  $J_{2,3} = 4.4$  c/s. By analogy with the  $\alpha$ -D-altropyranosides, and because it was not observed in the spectra of any of the 3-epimeric  $\alpha$ -D-glucopyranosides (below), the extra splitting was again assigned to stereospecific long range coupling of H<sub>1</sub> with H<sub>3</sub>. Unfortunately this small splitting could not be discerned in the H<sub>3</sub> multiplet of XXIV (Fig. 3a), because of broadening by the nitrogen quadrupole.

In this series, the ranges of values were  $J_{1,2} = 3.3$ – $3.5$ ,  $J_{1,3} < 0.5$ ,  $J_{2,3} = 3.9$ – $4.4$ ,  $J_{3,4} = 3.9$ – $4.2$  c/s.



The conformations which are possible for these  $\alpha$ -D-allopyranosides are the chair (F), the classical boats (G) and (H), and the twist boat (I), and the idealized proton dihedral angles for their pyranose rings are shown in Table 5. The values of the vicinal coupling constants  $J_{1,2}$ ,  $J_{2,3}$ , and  $J_{3,4}$  are all characteristic of protons in approximately *gauche* orientation, and do not in themselves definitely distinguish between the chair conformation (F) and the twist boat (I). Since  $J_{2,3}$  and  $J_{3,4}$  are both greater than  $J_{1,2}$ , application of the Karplus equation<sup>35</sup> would imply that  $\phi_{2,3}$  and  $\phi_{3,4}$  are both less

than  $\phi_{1,3}$ , in accordance with conformation I (Table 5). However, the fact that one of the compounds shows a long range coupling of  $H_1$  and  $H_3$  supports the chair (F), since this is the only conformation in which both of these protons are equatorial.

*Methyl 4,6-O-benzylidene- $\alpha$ -D-glucopyranosides* (XXVI-XXXIV). The chemical shifts and coupling constants for these derivatives are displayed in Table 6 together with for convenience those of the related 2-deoxy- $\alpha$ -D-arabinohexopyranosides (XXXV and XXXVI). In the  $\alpha$ -D-glucopyranosides (XXVI-XXXIV) the resonance due to  $H_1$  was usually a sharp doublet, and that of  $H_2$  a sharp quartet, except that in the case of the 2-acetamido-3-O-acetyl-2-deoxy derivative (XXXIV),  $H_2$  appeared as an octet because of coupling with NH. However the triplet due to  $H_3$  in these compounds was frequently severely broadened, or extra lines were present, as in the spectrum (Fig. 4a) of the di-O-acetyl derivative (XXVIII) in pyridine. Since the extra splitting in  $H_3$  was most apparent when  $H_1$  and  $H_2$  were strongly coupled it was therefore assigned to virtual long range coupling of  $H_3$  with  $H_1$ . Treating  $H_3$ ,  $H_2$  and  $H_1$  as a linear 3-spin sub-system, the conditions of Musher and Corey<sup>43</sup> may be restated for this system as follows: The  $H_3$  multiplet is reduced to that of the 1st order case (extra splittings  $< 0.1 J_{2,3}$ ) if (a)

$$|\nu_2 - \nu_1| \geq 2 J_{2,3} \quad \text{and} \quad |\nu_2 - \nu_1| \geq J_{1,2},$$

or if (b)

$$|\nu_2 - \nu_1| \approx J_{2,3} \quad \text{and} \quad |\nu_2 - \nu_1| \geq \frac{1}{2} J_{1,2}.$$

Alternatively, the general condition for virtual coupling may be stated; i.e. the lines in the 1st order  $H_3$  multiplet will show extra splitting greater than  $0.1 J_{2,3}$  if (c)

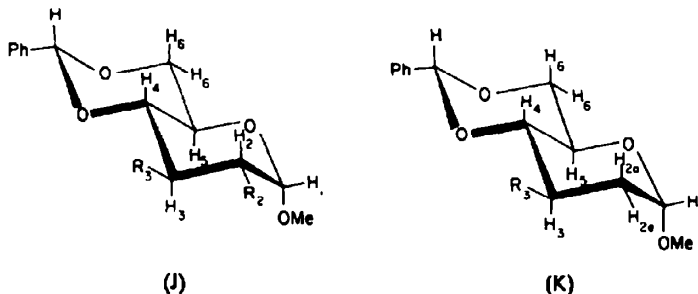
$$\{(|\nu_2 - \nu_1| + \frac{1}{2} J_{2,3})^2 + J_{1,2}^2\}^{\frac{1}{2}} - \{(|\nu_2 - \nu_1| - \frac{1}{2} J_{2,3})^2 + J_{1,2}^2\}^{\frac{1}{2}} = E \leq 0.8 J_{2,3}.$$

For the di-O-acetate (XXVIII) in pyridine,  $|\nu_2 - \nu_1| \approx 5.4$ ,  $J_{1,2} = 3.6$ , and  $J_{2,3} = 9.8$  c/s and neither condition (a) nor condition (b) is satisfied. However condition (c) is true in this case since the expression E has the value 7.3 c/s, and also  $0.8 J_{2,3} = 7.8$  c/s. Since  $0.1 J_{2,3} = 1.0$  c/s, therefore observable virtual coupling is expected for  $H_3$  in XXVIII (Fig. 4a).

The di-O-benzoyl derivative (XXIX) in a 1:1 mixture of deuteriochloroform and pyridine, yielded a spectrum (Fig. 4b) in which the  $H_2$  quartet was completely resolved between the  $H_1$  doublet and the singlet due to the benzylic methine proton, rather than overlapping with either one signal or the other as occurred in spectra measured in the separate pure solvents. Under these conditions compound (XXIX) showed  $|\nu_2 - \nu_1| = 12$ ,  $J_{1,2} = 3.6$ , and  $J_{2,3} = 9.5$  c/s, and hence  $E = 9.0$ , and  $0.8 J_{2,3} = 7.6$  c/s. Condition (b) is satisfied by these parameters but (a) is not, and since  $E \approx 0.8 J_{2,3}$ , this therefore represents a border line case in which some broadening of the  $H_3$  triplet is to be expected (Fig. 4b).

In deuteriochloroform, the 2-O-tosyl-3-O-benzoyl derivative (XXX) gave the spectrum in Fig. 4c which yielded  $|\nu_2 - \nu_1| = 21.6$ ,  $J_{1,2} = 3.7$ ,  $J_{2,3} = 9.6$ ,  $E = 9.5$ , and  $0.8 J_{2,3} = 7.7$  c/s. Since both conditions (a) and (b) are satisfied by these parameters and E is now appreciably greater than  $0.8 J_{2,3}$ , little virtual coupling is expected for  $H_3$ , and its signal appears as a reasonably sharp triplet (Fig. 4c). Figures 4a through 4c therefore show how virtual coupling of  $H_3$  decreases, as the chemical shift between  $H_1$  and  $H_2$  increases. Since in these examples, the chemical shifts of  $H_4$  and  $H_5$  have

not been determined, there could possibly be some contribution to virtual coupling of  $H_3$  from these protons if they happened to be strongly coupled.



For the series XXVI-XXXIV the values obtained were  $J_{1,2} = 3.5-3.7$ ,  $J_{2,3} = 9.2-9.8$  and  $J_{2,4} = 8.5-9.5$  c/s, and these are consistent with only the chair conformation (J) for which  $\phi_{1,2} \approx 60^\circ$ , and  $\phi_{2,3} \approx \phi_{3,4} \approx 180^\circ$ . Similar values of  $J_{1,2}$  in some methyl 3-aryazo-4,6-O-benzylidene-3-deoxy- $\alpha$ -D-glucopyranosides, and related derivatives, have previously been reported by Guthrie *et al.*<sup>50</sup>

In order to assess the effect on the  $H_1$ ,  $H_2$ ,  $H_3$  couplings in these compounds, of the absence of an electronegative substituent at  $C_2$ , the spectra of methyl 4,6-O-benzylidene-2-deoxy- $\alpha$ -D-arabinohexopyranoside (XXXV) and of its 3-O-acetyl derivative (XXXVI) were measured in deuteriochloroform solution. The  $H_1$  signals appeared as quartets at  $\tau$  5.31 and 5.22 respectively, and the protons at  $C_2$  each as well resolved octets at high field. In the spectrum (Fig. 5) of the acetate (XXXVI), the resonance of the acetoxy methyl protons occurred conveniently between the two  $H_2$  octets, and that of  $H_3$  as an octet near to the singlet of the benzylic proton. The hydroxyl proton of the alcohol (XXXV) was *not* decoupled by chemical exchange since its signal occurred as a sharp doublet ( $J_{3,OH} = 2.9$  c/s) at  $\tau$  6.9. The remainder of the derived chemical shifts and coupling constants are presented at the end of Table 6, and are consistent with the expected chair conformation (K) since large values 11.4-11.5, and 9.4 c/s were obtained for the diaxial couplings  $J_{2a,3}$  and  $J_{3,4}$ , and smaller values 5.0-5.3, 3.8 and 1.1 c/s respectively for the *gauche* couplings  $J_{2e,3}$ ,  $J_{1,2a}$  and  $J_{1,2e}$ . First order coupling constants measured from deuterium oxide solutions have previously been reported for 2-deoxy- $\alpha$ -D-arabinohexopyranose by Lenz and Heeschen,<sup>36</sup> and for methyl 2-deoxy  $\alpha$ - and  $\beta$ -D-arabinohexopyranosides and methyl 2-deoxy-2-deuterio  $\alpha$ - and  $\beta$ -D-glucopyranosides by Lemieux and Levine.<sup>16</sup>

For the purpose of checking the validity of first order analyses of the spectra of the benzylidene derivatives (XXXV and XXXVI), somewhat more precise analyses were obtained; firstly by removal of the  $H_3$  couplings from the  $H_{2e}$  and  $H_{2a}$  octets<sup>51</sup> followed by analysis of the remaining signals of  $H_{2e}$ ,  $H_{2a}$  and  $H_1$  as an ABX system,<sup>52</sup> and secondly by removal of the  $H_1$  couplings from the  $H_{2e}$  and  $H_{2a}$  octets and then analysis of  $H_{2e}$ ,  $H_{2a}$ , and  $H_3$  as an ABX arrangement. Refinement of the values of the 1st order coupling constants in this manner (Table 6) served merely to increase slightly the effective differences between  $J_{1,2a}$  (3.7  $\rightarrow$  3.8 c/s) and  $J_{1,2e}$  (1.2  $\rightarrow$  1.1 c/s),

<sup>50</sup> R. D. Guthrie and (in part) L. F. Johnson, *J. Chem. Soc.* 4166 (1961); G. J. F. Chittenden and R. D. Guthrie, *Ibid.* 1045 (1964).

<sup>51</sup> cf. R. J. Abraham and K. A. McLauchlan, *Mol. Phys.* 5, 195 (1962).

<sup>52</sup> J. A. Pople, W. G. Schneider and H. J. Bernstein, *High Resolution Nuclear Magnetic Resonance* p. 132. McGraw-Hill, New York (1959).

and between  $J_{2a,3}$  (11.0–11.3  $\rightarrow$  11.4–11.5 c/s) and  $J_{2e,3}$  (5.4–5.5  $\rightarrow$  5.0–5.3 c/s). Because of the lack of an electronegative substituent at  $C_2$ , the coupling constants  $J_{2a,3}$  and  $J_{2e,3}$  are appreciably larger than are the corresponding couplings in the  $\alpha$ -D-glucopyranosides and  $\alpha$ -D-mannopyranosides respectively. However, the differences between  $J_{1,2a}$  in the 2-deoxy- $\alpha$ -D-arabino-hexopyranosides (XXXV and XXXVI), and the corresponding couplings in the  $\alpha$ -D-glucopyranosides, and between the values of  $J_{1,2e}$  in XXXV and XXXVI, and those in the  $\alpha$ -D-altropyranosides, and  $\alpha$ -D-mannopyranosides, are rather less marked, probably because of the combined overriding influences of the electronegative ring oxygen and methoxyl groups at  $C_1$ . From the ABX analyses the chemical shift  $\nu_{2c} - \nu_{2a}$  ( $\delta_{AB}$ ) in the 3-O-acetate (XXXVI) was determined to be 35.7 c/s, and is considerably greater than that (26.4 c/s) found in the alcohol (XXXV), due presumably to the larger diamagnetic anisotropy of the acetoxy group.

In those compounds in which the substituents  $R_2$  and  $R_3$  were both identical, and possessed the same orientation, that is either both equatorial, as in the  $\alpha$ -D-glucopyranosides, or both axial, as in the  $\alpha$ -D-altropyranosides, then the signal due to  $H_3$  invariably occurred at lower field than that due to  $H_2$ . Although this difference may in the case of the  $\alpha$ -D-glucopyranosides, be explained in terms of deshielding of the axial  $H_3$  by the axially opposed oxygen of the methoxyl substituent at  $C_1$ ,<sup>5,53</sup> the presence of it for equatorial  $H_2$  and  $H_3$  in the  $\alpha$ -D-altropyranosides suggests that additional factors such as long range deshielding by the phenyl ring may be in operation.

In all five configurations which were studied it appears that the combination of the usual stability of chair conformations (as compared with the flexible forms) with the anomeric effect<sup>54</sup> tending to maintain the  $C_1$  methoxyl group in an axial conformation, is sufficient to ensure that the pyranose rings in these compounds exist exclusively in the C1 chair conformation. Even in the apparently unfavourable case of the  $\alpha$ -D-altropyranosides, these factors evidently outweigh the effect of the presence of three axial substituents, and a 1:3 diaxial interaction, although the chair conformation (A) has a further energetic advantage for those examples which do not contain substituents capable of hydrogen bonding, in that the repulsive interactions between the vicinal electronegative substituents  $R_2$  and methoxyl, and between  $R_2$  and  $R_3$ , are at a minimum. Similar advantages are present in the preferred conformation of 4-O-acetyl-2,3-O-isopropylidene diethylsulphonyl ( $\alpha$ -D-lyxopyranosyl) methane, and in those of the 1,2-O-alkylidene- $\alpha$ -D-glucopyranose, and 1,2:3,4-di-O-isopropylidene- $\alpha$ -D-galactopyranose derivatives mentioned above.

By comparison of the Tables (1, 3, 4 and 6) of 1st order coupling constants with the preferred conformations (A, E, F, J and K) of the benzylidene derivatives, it may be seen that a small coupling  $J_{1,2} = 0.6$ – $1.7$  c/s is characteristic of an equatorial  $H_1$ –equatorial  $H_2$  proton arrangement (in the  $\alpha$ -D-altro-,  $\alpha$ -D-manno-, and 2-deoxy- $\alpha$ -D-arabino-hexopyranosides, whereas a larger coupling  $J_{1,2} = 3.3$ – $3.8$  c/s is characteristic

<sup>53</sup> J. D. Stevens and R. U. Lemieux. 45th National Meeting of the Chemical Institute of Canada, Edmonton, Alberta, May (1962); cf. N. S. Bhacca and D. H. Williams in *Applications of NMR Spectroscopy in Organic Chemistry. Illustrations from the steroid field* p. 190. Holden-Day, San Francisco (1964).

<sup>54</sup> 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); C. B. Anderson and D. T. Sepp, *Chem. & Ind.* 2054 (1964).

TABLE 1. CHEMICAL SHIFTS ( $\tau$  VALUES) AND 1ST ORDER COUPLING CONSTANTS (C/S) OF METHYL 4,6-O-BENZYLIDENE- $\alpha$ -D-ALTROPYRANOSIDES

Compound	Solvent	H <sub>1</sub>	H <sub>2</sub>	H <sub>3</sub>	H <sub>4</sub> , H <sub>5</sub> and 2H <sub>6</sub> <sup>a</sup>	R <sub>1</sub>	R <sub>2</sub>	R <sub>3</sub>	Ph	Benzyllic H.
(I) R <sub>1</sub> = R <sub>2</sub> = OH	CDCl <sub>3</sub>	5.32 J <sub>1,2</sub> $\approx$ J <sub>1,3</sub> < 0.8	5.51		6.21 <sup>a</sup>	7.48 <sup>b</sup>	7.03 d J = 5.5	2.53 m		4.33
(II) R <sub>1</sub> = R <sub>2</sub> = OD	CDCl <sub>3</sub> + D <sub>2</sub> O	5.38 t J <sub>1,2</sub> $\approx$ J <sub>1,3</sub> $\approx$ 0.8	5.57		6.27 <sup>b</sup>	—	—	2.61 m		4.40
(III) R <sub>1</sub> = R <sub>2</sub> = OAc	CDCl <sub>3</sub>	5.41 t J <sub>1,2</sub> = 0.9 J <sub>1,3</sub> = 0.9	4.97 q J <sub>2,3</sub> = 2.9 J <sub>3,4</sub> = 2.9	4.76 sx J <sub>2,3</sub> = 2.9 J <sub>3,4</sub> = 2.9	5.54-6.45	7.90 and	7.92	2.61 m		4.40
(IV) R <sub>1</sub> = R <sub>2</sub> = OBz	CDCl <sub>3</sub>	5.18 t J <sub>1,2</sub> = 0.8 J <sub>1,3</sub> = 0.7	4.55 q J <sub>2,3</sub> = 3.1	4.25 m <sup>c</sup>	5.28-6.29	1.86 m and	2.62 m	2.62 m		4.30
(V) R <sub>1</sub> = OMe	CDCl <sub>3</sub>	5.31 t J <sub>1,2</sub> = 1.0 J <sub>1,3</sub> = 0.9	6.54 q J <sub>2,3</sub> = 3.0	5.58	6.43 <sup>a</sup>	6.61	7.01	2.61 m		4.42
R <sub>2</sub> = OH	Pyridine	5.13 t J <sub>1,2</sub> = 0.8 J <sub>1,3</sub> $\approx$ 0.7	6.30 q J <sub>2,3</sub> = 2.9	5.25	6.16 <sup>a</sup>	6.64	4.03	— <sup>c</sup>		4.25
(VI) R <sub>1</sub> = OH R <sub>2</sub> = OMe	CDCl <sub>3</sub>	5.47 J <sub>1,2</sub> < 0.8	5.56		6.39 <sup>a</sup>	6.61	6.97 <sup>b</sup>	2.60 m		4.46
(VII) R <sub>1</sub> = R <sub>2</sub> = OMe	Pyridine	5.22 J <sub>1,2</sub> = 0.8 J <sub>1,3</sub> = 0.5	6.38 q J <sub>2,3</sub> = 2.8	6.15 sx J <sub>2,3</sub> = 2.8 J <sub>3,4</sub> = 2.8	5.38-6.26	6.62 and 6.68	6.52	— <sup>c</sup>		4.36
(VIII) R <sub>1</sub> = OMe R <sub>2</sub> = OTs	Pyridine	5.18 t J <sub>1,2</sub> = 0.8 J <sub>1,3</sub> = 0.7	6.09 q J <sub>2,3</sub> = 2.7	4.92 sx J <sub>2,3</sub> = 2.7 J <sub>3,4</sub> = 2.7	5.41-6.28	6.60 and 6.70	7.80, Me 2.22 m and 2.95 m <sup>d</sup>	2.66 m <sup>d</sup>		4.43



(IX)	R <sub>2</sub> = NH <sub>2</sub> R <sub>3</sub> = OH	CDCl <sub>3</sub>	5.49 J <sub>1,2</sub> = 0.8 <sup>a</sup>	6.76 q J <sub>2,3</sub> = 2.5 <sup>c</sup>	5.56 ----- 6.48 <sup>a</sup>	6.60	8.02 <sup>b</sup>	8.02 <sup>b</sup>	2.60 m	4.40
(X)	R <sub>2</sub> = OD R <sub>3</sub> = ND <sub>2</sub>	CDCl <sub>3</sub> + D <sub>2</sub> O	5.33 t J <sub>1,2</sub> ≈ J <sub>1,3</sub> ≈ 0.9	5.56-6.30 <sup>a</sup>	6.72 <sup>b</sup>	5.56-6.30	6.59	—	2.55 m	4.31
(XI)	R <sub>2</sub> = OH R <sub>3</sub> = NHAc	CDCl <sub>3</sub>	5.35	5.65-6.38 <sup>a</sup>	5.28 m <sup>b</sup>	5.65-6.38	6.62	4.90 d J <sub>2,OH</sub> = 3.9 3.40 d, <sup>b,c</sup> NH J <sub>2,NH</sub> = 9.2	2.63 m	4.53
(XII)	R <sub>2</sub> = OAc R <sub>3</sub> = NHAc	Pyridine	5.12 t J <sub>1,2</sub> = 1.0 J <sub>1,3</sub> = 0.9	4.62 q J <sub>2,3</sub> = 2.7	4.89 m <sup>b</sup>	5.44-6.34	6.68	7.94	2.71 m <sup>d</sup>	4.13
(XIII)	R <sub>2</sub> = OH R <sub>3</sub> = NHBz	CDCl <sub>3</sub>	5.27	5.50-6.36 <sup>a</sup>	4.86 m <sup>b</sup>	5.50-6.36	6.58	4.61 d J <sub>2,OH</sub> ≈ 3.8	2.66 m	4.54
(XIV)	R <sub>2</sub> = OH R <sub>3</sub> = NHC <sub>4</sub> H <sub>9</sub> (NO <sub>2</sub> ) <sub>2</sub>	CDCl <sub>3</sub>	5.24	5.40	5.40	6.17 <sup>a</sup>	6.41	7.54 d J <sub>2,OH</sub> = 5.7 0.85 d, 1.90 q 2.83 d J <sub>2,NH</sub> ≈ 7	2.78 m	4.40
(XV)	R <sub>2</sub> = OAc R <sub>3</sub> = NHC <sub>4</sub> H <sub>9</sub> (NO <sub>2</sub> ) <sub>2</sub>	CDCl <sub>3</sub>	5.18 t J <sub>1,2</sub> = 1.1 J <sub>1,3</sub> ≈ 0.6	4.90 q J <sub>2,3</sub> = 2.5	5.40	6.30 <sup>a</sup>	6.41	7.78	2.77	4.36
(XVI)	R <sub>2</sub> = OMe R <sub>3</sub> = NHC <sub>4</sub> H <sub>9</sub> (NO <sub>2</sub> ) <sub>2</sub>	Pyridine	4.98 J <sub>1,2</sub> = 0.9	6.23 q J <sub>2,3</sub> = 2.5	5.14 ----- 6.13 <sup>a</sup>	6.44 and 6.46	6.46	0.08 d, NH <sup>e</sup> 0.93 d, <sup>d</sup> 1.85 q, <sup>d</sup> 2.72 d <sup>d</sup> J <sub>2,NH</sub> = 8.4 <sup>e</sup>	2.75 <sup>e</sup>	4.24

<sup>a</sup> Incompletely resolved multiplet(s)

<sup>b</sup> Broad band

<sup>c</sup> Obscured by solvent resonances

<sup>d</sup> Measured in CDCl<sub>3</sub> solution

<sup>e</sup> Since the amino and hydroxyl proton resonances were coincident and not split these protons must therefore be decoupled from H<sub>2</sub> and H<sub>3</sub> respectively by exchange. Hence the splittings in the H<sub>2</sub> quartet were taken as J<sub>1,2</sub> and J<sub>2,3</sub>.

of the equatorial  $H_1$ -axial  $H_2$  arrangement ( $\alpha$ -D-*allo*-,  $\alpha$ -D-*gluco*-, and 2-deoxy- $\alpha$ -D-*arabino*hexo-pyranosides). Similar, but smaller differences are apparent in the couplings of  $H_2$  and  $H_3$  in *gauche* arrangement. Thus  $J_{2e,3e} = 2.5\text{--}3.1$  c/s in the  $\alpha$ -D-altropyranosides is smaller than both  $J_{2e,3a} = 3.3\text{--}3.6$  c/s in the  $\alpha$ -D-mannopyranosides, and  $J_{2a,3e} = 3.9\text{--}4.4$  c/s in the  $\alpha$ -D-allopyranosides. These differences between  $J_{ee}$ ,  $J_{ea}$ , and  $J_{ae}$  are of considerable interest, since if the pyranose chair conformation possessed idealized cyclohexane geometry<sup>46</sup> then  $\phi_{ee} = \phi_{ea} = \phi_{ae} = 60^\circ$  would obtain,

TABLE 2. PROTON DIHEDRAL ANGLES ( $\phi$ ) FOR THE POSSIBLE CONFORMATIONS OF THE PYRANOID RING IN METHYL 4,6-O-BENZYLIDENE- $\alpha$ -D-ALTROPYRANOSIDES (ASSUMING IDEALIZED CYCLOHEXANE GEOMETRY).

Conformation	$\phi_{1,2}$	$\phi_{2,3}$	$\phi_{3,4}$	$\phi_{4,5}$
Chair (A)	$60^\circ$	$60^\circ$	$60^\circ$	$180^\circ$
Boat (B)	$180^\circ$	$180^\circ$	$0^\circ$	$180^\circ$
Boat (C)	$180^\circ$	$120^\circ$	$60^\circ$	$180^\circ$
Skew Boat (D)	$169^\circ$	$153^\circ$	$33^\circ$	$169^\circ$

and application of the equation of Karplus<sup>35</sup> would suggest that these couplings should be equal in magnitude. That they are not equal may be due to one or more of several reasons. On the basis of the Karplus relationship Lemieux and Levine have suggested<sup>16</sup> that for methyl 2-deoxy- $\alpha$ -D-*arabino*hexopyranoside in which  $J_{1e,2e} \approx 1.4$  and  $J_{1e,2a} = 3.8$  c/s in deuterium oxide, the dihedral angle  $\phi_{1e,2a}$  is somewhat smaller than  $\phi_{1e,2e}$ , due to distortion of the pyranose ring caused by diaxial repulsions between the methoxyl oxygen at  $C_1$ , and axial  $H_3$  and  $H_5$ . Such distortion if present in the methyl 4,6-O-benzylidene- $\alpha$ -D-aldohexopyranosides however, would need to be already near to the maximum possible, in the 2-deoxy- $\alpha$ -D-*arabino*hexopyranosides (XXXV and XXXVI), since the successive introduction of larger axial substituents in place of the axial hydrogens at  $C_2$  and  $C_3$  as in the  $\alpha$ -D-mannopyranosides (one extra axial substituent), and  $\alpha$ -D-altropyranosides (two extra axial substituents), does not produce a further significant decrease in  $J_{1e,2e}$ , a result which might be anticipated from increasing 2:4 and 1:3 diaxial repulsions. In view of the small size of the hydrogen atom such maximal distortion in the 2-deoxy- $\alpha$ -D-*arabino*hexopyranosides would appear to be somewhat unlikely, suggesting that perhaps 1:3 diaxial repulsions are not the major cause of the observed differences between  $J_{ee}$ , and  $J_{ea}$  and  $J_{ae}$ . It is possible however, that the interaction between the axial methoxyl group and axial  $H_5$  will be greater than that between the methoxyl group and axial  $H_3$ , since the  $C_1$ -ring oxygen and  $C_5$ -ring oxygen bond lengths are likely to be shorter than those of  $C_1$ - $C_2$  and  $C_2$ - $C_3$ .<sup>55</sup> It was in fact suggested by Reeves<sup>17</sup> some years ago that such bond length differences would result in *cis* vicinal substituents on a pyranose ring being slightly closer together than *trans* vicinal groups, i.e.  $\phi_{ea} < \phi_{ee}$  would also in this way account for  $J_{ea} > J_{ee}$ . It was also claimed<sup>17</sup> that a ring oxygen valence angle *smaller* than the tetrahedral carbon angle would produce a similar geometrical effect, however more recent data from crystal-structure analyses<sup>55</sup> indicate that the ring-angle at oxygen is most frequently slightly greater than the carbon ring-angles, in both pyranoid,

<sup>46</sup> G. A. Jeffrey and R. D. Rosenstein, *Advances in Carbohydrate Chem.* **19**, 7 (1964).

TABLE 3. CHEMICAL SHIFTS ( $\tau$  VALUES) AND 1ST ORDER COUPLING CONSTANTS (C/S) OF METHYL 4,6-O-BENZYLIDENE- $\alpha$ -D-MANNOPYRANOSIDES

Compound	$R_1 = R_2 = OH$	Solvent	$H_1$	$H_2$	$H_3$	$H_4, H_5$ and $2H_6^a$	OMe	$R_3$	$R_4$	Ph	Benzyllic H.
(XVII)	$R_1 = R_2 = OH$ $J_{1,2} = 0.6$	$CDCl_3$	5.35 d	5.65	5.65	6.33 <sup>a</sup>	6.65	6.75	6.75	2.60 m	4.47
(XVIII)	$R_1 = R_2 = OAc$ $J_{1,2} = 1.2$	$CDCl_3$	5.34 d	4.47	4.70 m <sup>a</sup>	5.63-6.21	6.63	7.87	8.03	2.62 m	4.43
(XIX)	$R_1 = R_2 = OBz$ $J_{1,2} = 0.9$	$CDCl_3$	5.09 d	3.97	4.26 m <sup>a</sup>	5.37-6.13	6.58	1.91 m and 2.60 m	2.61 m	4.28	
(XX)	$R_1 = R_2 = OTs$ $J_{1,2} = 1.7$	Pyridine	4.83 d	4.62 q	4.85 q	5.53-6.33	6.78	7.86, Me and 7.74, Me 2.08 m, 2.41 m, 2.62 m and 3.04 m <sup>b</sup>	2.71 m <sup>b</sup>	4.53	
(XXI)	$R_1 = R_2 = ONs$ $J_{1,2} = 1.6$	$CDCl_3$	4.92 d	5.03 q	5.24 q	5.70-6.40	6.51	2.17 and 1.5-1.8 m	2.76 m	4.70	

<sup>a</sup> Unresolved<sup>b</sup> Measured in  $CDCl_3$  solution.

TABLE 4. CHEMICAL SHIFTS ( $\tau$  VALUES) AND 1ST ORDER COUPLING CONSTANTS ( $c/s$ ) OF METHYL 4,6-O-BENZYLIDENE- $\alpha$ -D-ALLOPYRANOSIDES

Compound	Solvent	H <sub>1</sub>	H <sub>2</sub>	H <sub>3</sub>	H <sub>4</sub> , H <sub>5</sub> and 2H <sub>6</sub> <sup>a</sup>	OMe	R <sub>2</sub>	R <sub>3</sub>	Ph	Benzyllic H.
(XXII) R <sub>2</sub> = OH	CDCl <sub>3</sub>	5.32 d J <sub>1,2</sub> = 3.3	5.57-6.70 <sup>a</sup>	5.14 m <sup>b</sup>	5.57-6.70	6.57	5.57-6.70 <sup>a</sup>	8.00, NAC 3.36 d, NH J <sub>2,3</sub> , NH = 9.4	2.60 m	4.51
R <sub>2</sub> = NHAc	Pyridine	5.03 d J <sub>1,2</sub> = 3.3	5.36-6.44 <sup>a</sup> J <sub>2,3</sub> = 3.9	4.60 qi J <sub>2,4</sub> = 3.9	5.36-6.44	6.57	3.94	8.15, NAC NH < 3.0 <sup>b</sup> J <sub>2,3</sub> , NH = 9.5	— <sup>b</sup>	4.26
(XXIII) R <sub>2</sub> = OD R <sub>3</sub> = NDAC	Pyridine	5.01 d J <sub>1,2</sub> = 3.4	5.34-6.40 <sup>a</sup> J <sub>2,3</sub> = 3.9	4.57 t J <sub>2,4</sub> = 3.9	5.34-6.40	6.57	—	8.15, NAC	— <sup>b</sup>	4.24
(XXIV) R <sub>2</sub> = OAc	CDCl <sub>3</sub>	4.75	—	—	5.54-6.47	6.56	7.93	8.00 NAC 3.36 d, NH J <sub>2,3</sub> , NH = 9.1	2.60 m	4.48
R <sub>2</sub> = NHAc	Pyridine	4.96 q J <sub>1,2</sub> = 3.5 J <sub>1,3</sub> = 0.5	4.73 q J <sub>2,3</sub> = 4.4	4.46 sx J <sub>2,4</sub> = 4.2	5.47-6.37	6.59	7.92	8.02, NAC NH < 3.0 <sup>b</sup> J <sub>2,3</sub> , NH = 9.6	— <sup>b</sup>	4.24
(XXV) R <sub>2</sub> = OAc R <sub>3</sub> = NDAC	Pyridine	4.98 d J <sub>1,2</sub> = 3.3	4.77 t J <sub>2,3</sub> = 4.0	4.51 t J <sub>2,4</sub> = 4.0	5.49-6.41	6.60	7.94	8.03, NAC	— <sup>b</sup>	4.28

<sup>a</sup> Unresolved<sup>b</sup> Obscured by the solvent.

and furanoid sugars. Indeed, it would be expected that the presence in a pyranose ring of a  $C_6-O-C_1$  angle larger than the carbon ring-angles would result in some flattening of the ring. Electron diffraction data obtained recently from cyclohexane, 1,4-dioxane, and piperazine suggest that the chair conformations of even unsubstituted six-membered rings are somewhat flatter than those based on the classical tetrahedral angle.<sup>58</sup>

Such fundamental flattening of six-membered rings if present also in solution, would, irrespective of the presence of large axial substituents, cause  $\phi_{ee}$  to be greater than  $\phi_{ea}$ , and hence  $J_{ee} < J_{ea}$ , and would also explain why the interactions between

TABLE 5. PROTON DIHEDRAL ANGLES ( $\phi$ ) FOR THE POSSIBLE CONFORMATIONS OF THE PYRANOID RING IN METHYL 4,6-O-BENZYLIDENE- $\alpha$ -D-ALLOPYRANOSIDES (ASSUMING IDEALIZED CYCLOHEXANE GEOMETRY)

Conformation	$\phi_{1,2}$	$\phi_{2,3}$	$\phi_{3,4}$	$\phi_{4,5}$
Chair (F)	60°	60°	60°	180°
Boat (G)	60°	60°	0°	180°
Boat (H)	60°	0°	60°	180°
Skew Boat (I)	71°	33°	33°	169°

1,3-diaxial substituents in the benzylidene derivatives do not appear to be as important as expected, since in a flattened pyranose chair conformation, these substituents are further apart. The relative importance of the effects of these minor geometrical factors on the coupling constants, as compared with the influence upon them of the orientation of the electronegative substituents,<sup>41,42</sup> is difficult to estimate.

Application of Booth's rationalization of electronegativity orientation<sup>42</sup> to a pyranoid chair conformation predicts that  $H_{2b}$  and  $H_{4e}$  would, if other factors were equal, tend to display small coupling constants, since the electronegative ring oxygen is *trans*-coplanar to these protons. Comparing the environments of  $H_{2b}$  and  $H_{2a}$  in the conformation (K) of the 2-deoxy- $\alpha$ -D-*arabino*hexopyranosides, it may be seen that  $H_{2b}$  is *trans*-coplanar to the ring oxygen ( $O_5$ ), and to  $C_4$ , whereas  $H_{2a}$  is *trans*-coplanar to the methoxyl oxygen ( $O_1$ ), and to  $H_3$ . Since  $C_4$  is probably more electronegative than  $H_3$ , therefore  $J_{1e,2e}$  is expected to be smaller than  $J_{1e,2a}$ , as indeed has been observed. Similarly,  $H_{2b}$  in the chair conformations (A) and (E) of the  $\alpha$ -D-*altro*- and  $\alpha$ -D-*manno*-pyranosides respectively is *trans*-coplanar to  $O_5$  and  $C_4$ , whereas  $H_{2a}$  in the  $\alpha$ -D-glucopyranosides (J) is *trans*-coplanar to  $O_1$  and  $H_3$ , and hence  $J_{1e,2e}$  in (A) and (E) is predicted to be less than  $J_{1e,2a}$  in (J). Additionally, substituent  $R_3$  which is *trans*-coplanar to  $H_{2a}$  in the  $\alpha$ -D-allopyranosides (F) is more electronegative than  $H_3$  in the  $\alpha$ -D-glucopyranosides (J), and hence  $J_{1e,2a}$  in the  $\alpha$ -D-allopyranosides is expected to be smaller than that in the  $\alpha$ -D-glucopyranosides (Found: 3.3-3.5 and 3.5-3.7 c/s respectively).

Such assessments of the total *trans*-coplanar electronegativity acting on a pair of coupled protons do not however, appear to explain all of the observed differences in the coupling constants; for instance because  $H_{2a}$  is *trans*-coplanar to both  $O_1$  and  $R_3$  (= NHAc or NDAc) in the  $\alpha$ -D-allopyranosides (F), it might be expected that  $J_{1e,2a}$

<sup>44</sup> M. Davis and O. Hassel, *Acta Chem. Scand.* 17, 1181 (1963).

TABLE 6. CHEMICAL SHIFTS ( $\tau$  VALUES) AND 1ST ORDER COUPLING CONSTANTS (C/S) OF METHYL 4,6-O-BENZYLIDENE- $\alpha$ -D-GLUCOPYRANOSIDES

Compound	Solvent	H <sub>1</sub>	H <sub>2</sub>	H <sub>3</sub>	H <sub>4</sub> , H <sub>5</sub> and 2H <sub>6</sub> <sup>a</sup>	OMe	R <sub>8</sub>	R <sub>9</sub>	Ph	Benzyllic H <sub>1</sub>
(XXVI) R <sub>1</sub> = R <sub>2</sub> = OH	Pyridine	4.95 d <sup>b</sup> J <sub>1,2</sub> = 3.5	5.36		6.36 <sup>a</sup>	6.60	5.13 <sup>c</sup>	5.13 <sup>c</sup>	— <sup>d</sup>	4.25
(XXVII) R <sub>1</sub> = R <sub>2</sub> = OD	CDCl <sub>3</sub> + D <sub>2</sub> O	5.35 d J <sub>1,2</sub> = 3.6	5.72		6.79 <sup>a</sup>	6.63	—	—	2.61 m	4.53
(XXVIII) R <sub>1</sub> = R <sub>2</sub> = OAc	Pyridine	4.86 d J <sub>1,2</sub> = 3.6	4.77 q J <sub>2,3</sub> = 9.8	4.03 m <sup>c</sup> J <sub>6,4</sub> ≈ 8.5	5.48–6.34	6.66	8.00	8.00	— <sup>d</sup>	4.29
(XXIX) R <sub>1</sub> = R <sub>2</sub> = OBz	CDCl <sub>3</sub> Pyridine 1:1 v/v	4.72 d J <sub>1,2</sub> = 3.6	4.52 q J <sub>2,3</sub> = 9.5	3.71 t <sup>c</sup> J <sub>6,4</sub> = 9.0	5.46–6.40	6.68	1.90 and <sup>d</sup>	1.90 and <sup>d</sup>	— <sup>d</sup>	4.35
(XXX) R <sub>1</sub> = OTs R <sub>2</sub> = OBz	CDCl <sub>3</sub>	4.96 d J <sub>1,2</sub> = 3.7	5.32 q J <sub>2,3</sub> = 9.6	4.17 t J <sub>6,4</sub> = 9.5	5.55–6.47	6.55	7.80, Me 2.36 m, 3.03 m	2.07–2.81	2.69 m	4.53
(XXXI) R <sub>1</sub> = R <sub>2</sub> = OTs	Pyridine	4.77 d J <sub>1,2</sub> = 3.6	5.08 q J <sub>2,3</sub> = 9.4	4.48 t J <sub>6,4</sub> = 9.0	5.50–6.57	6.71	7.86, Me 2.15 m, 3.04 m	7.74, Me 1.95 m and <sup>d</sup>	— <sup>d</sup>	4.53
(XXXII) R <sub>1</sub> = OAc R <sub>2</sub> = ONO <sub>2</sub>	CDCl <sub>3</sub>	4.94 d J <sub>1,2</sub> = 3.7	5.10 q J <sub>2,3</sub> = 9.6	4.28 t <sup>c</sup> J <sub>6,4</sub> = 9.5	5.50–6.41	6.56	7.90	—	2.30 m <sup>e</sup>	3.83
(XXXIII) R <sub>1</sub> = R <sub>2</sub> = OMe	CDCl <sub>3</sub>	5.18 d J <sub>1,2</sub> = 3.6	5.62		6.86 <sup>a</sup>		6.59, 6.48, and 6.37		2.61 m	4.48
(XXXIV) R <sub>1</sub> = NHAc R <sub>2</sub> = OAc	CDCl <sub>3</sub>	5.27 d J <sub>1,2</sub> = 3.5	5.62 o J <sub>2,3</sub> ≈ 9.2	4.66 t <sup>c</sup> J <sub>6,4</sub> ≈ 9.2	5.83–6.48	6.62	8.05, NAC 3.74 d, <sup>c</sup> NH J <sub>2,3</sub> , NH = 9.5	7.97	2.62 m	4.48
(XXXV) R <sub>1</sub> = H <sub>2</sub> e' <sup>f</sup> R <sub>2</sub> = OH	CDCl <sub>3</sub>	5.31 q J <sub>1,2</sub> = 3.7 (3.8)	8.38 o (H <sub>2</sub> a) J <sub>2,3</sub> = 11.0 (11.4) J <sub>2,3</sub> , H <sub>2</sub> = 13.4 (13.4)	ca. 6.02 m	5.71–6.70	6.73	7.88 o J <sub>1,2</sub> = 1.2 (1.1) J <sub>2,3</sub> = 5.4 (5.0)	6.90 d J <sub>2,3</sub> , OH = 2.9	2.61 m	4.50
(XXXVI) R <sub>1</sub> = H <sub>2</sub> e' <sup>f</sup> R <sub>2</sub> = OAc	CDCl <sub>3</sub>	5.22 q J <sub>1,2</sub> = 3.7 (3.8)	8.28 o (H <sub>2</sub> a) J <sub>2,3</sub> = 11.3 (11.5) J <sub>2,3</sub> , H <sub>2</sub> = 13.3 (13.3)	4.62 o J <sub>6,4</sub> = 9.4	5.62–6.53	6.68	7.67 o J <sub>1,2</sub> = 1.2 (1.1) J <sub>2,3</sub> = 5.5 (5.3)	8.00	2.58 m	4.45

<sup>a</sup> Unresolved.<sup>b</sup> Broad band.<sup>c</sup> C<sub>6</sub>H<sub>5</sub>NO<sub>2</sub>.<sup>d</sup> When observed in chloroform solution, this signal was unexpectedly degenerate.<sup>e</sup> Obscured by the solvent.<sup>f</sup> Coupling constants from ABX analyses are shown in parentheses after the 1st order values.

in these derivatives would be smaller than  $J_{1e,2e}$  in the  $\alpha$ -D-*altro*- and  $\alpha$ -D-*manno*-pyranosides, since  $R_3$  is more electronegative than  $C_4$ , whereas in fact, the reverse is true. It must be concluded therefore that other factors, such as the geometrical effects mentioned above, are important, and also that several of the factors discussed here may combine in the same direction to produce the obvious differences between  $J_{ee}$  and  $J_{ea}$ .

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