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THE REVERSE ANOMERIC EFFECT: FURTHER OBSERVATIONS ON *N*-GLYCOSYLIMIDAZOLES*

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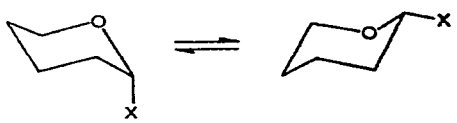
ABSTRACT

The conformational analysis of a number of *N*-hexopyranosylimidazoles and their tetra-*O*-acetyl derivatives has been carried out using ^{1}H-n.m.r. data obtained after computer simulation of spectra. Evidence is presented that, for some compounds, mixtures of $^4C_1$ and $^1C_4$ conformers are present in solution, and the possible contributions of steric effects and polar, reverse anomeric effects are discussed. It is concluded that the results can in large part be accounted for by steric factors, but that the operation of additional polar factors is likely. Present rationalisations of the reverse anomeric effect are discussed and a stereoelectronic interpretation is presented. The conformations of the exocyclic hydroxymethyl groups are analysed and shown to give additional information about the presence of alternative chair conformations.

INTRODUCTION

The reverse anomeric effect is a particular manifestation of the interaction between atoms carrying unshared electron pairs and vicinal polar bonds (as in **1a** and **1b**, where *X* is electronegative or electropositive) and was first recognised by Lemieux



1a **1b**

and Morgan[1], who found that *N*-(tetra-*O*-acetyl-α-D-glucopyranosyl)-4-methylpyridinium bromide (**2**) adopts conformations in solution[1], and in the solid state[2], in which the 4-methylpyridinium group attains an equatorial orientation with respect to the pyranose ring. In later work[3,4], Lemieux and Saluja observed conformations

*Dedicated to the memory of Professor Edward J. Bourne.

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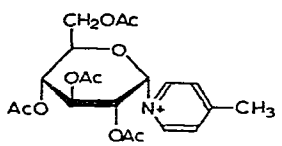
quite distinct from the normal $^4C_1$ (as in **1a**) for *N*-(tetra-*O*-acetyl-α-D-*gluco*)- (**3**, $R^1 = H$, $R^2 = OAc$, $R^3 = H$ or Me) and (-*manno*)- (**3**, $R^1 = OAc$, $R^2 = H$, $R^3 = H$ or Me)-pyranosylimidazolium salts. These authors associated the conformational changes with the presence of a quaternary nitrogen in compounds **2** and **3** which adopt conformations (possibly boat forms[5,6]) in which the heterocyclic substituent takes up a non-axial orientation. More recently, Paulsen and his co-workers have reported[7] conformational studies of a range of per-*O*-acetyl-*N*-substituted *N*-pentopyranosyl compounds in which the charge on the nitrogen atom varied from formal negative ($-\overset{-}{N}-\overset{+}{P}Ph_3$) to formal positive ($-\overset{+}{N}HPPh_3$). Again, the operation of the reverse anomeric effect was detected through conformational analysis of imidazolium and pyridinium compounds for which substantial proportions of the $^1C_4$ conformation were observed, and these authors noted that a predominant influence is the magnitude and sign of the dipole of the C-1–N-1′ bond. The reverse anomeric effect has been interpreted in terms of dipole interactions[4], by analogy with the anomeric effect[5], which has received more detailed investigation by *ab initio* calculations[8,9]. The anomeric effect has also been discussed in terms of orbital interactions between the lone-pair orbitals of the ring oxygen and the empty σ* C-1–X orbital[9–13]. David *et al.*[13] concluded that this latter approach also offers some rationalisation of the reverse anomeric effect if X is less electronegative than hydrogen.



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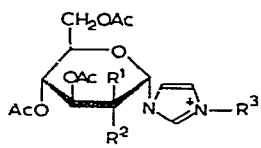

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Conformational inversion has also been observed in 7-(tetra-*O*-acetyl-α-D-mannopyranosyl)theophylline[14] and other α-glycopyranosyl nucleoside analogues[15–17] in which a substantial relief of steric strain must accompany the adoption of an equatorial orientation by the large heterocyclic moiety.

In connection with investigations into the chemistry of action of glycosidases[18,19], we have synthesised a number of *N*-hexopyranosylimidazoles and their tetra-acetates and have examined them by ^{1}H-n.m.r. spectroscopy. The ^{1}H-n.m.r. parameters have been refined by computer simulation of spectra and used to analyse the conformations of the sugar rings and the exocyclic hydroxymethyl groups. We confirm that a conformational inversion occurs in neutral as well as positively charged *N*-(tetra-*O*-acetyl-α-D-mannopyranosyl)imidazole, observe a conformational inversion in (unacetylated) *N*-α-D-mannopyranosylimidazole in D_2O solution, and present a rationalisation for the reverse anomeric effect based on orbital rather than dipolar interactions.

RESULTS AND DISCUSSION

The conformations of the sugar rings

Deductions about the conformations of the sugar rings are based on consideration of the vicinal coupling constants $J_{1,2}$–$J_{4,5}$ given in Table I. Examination of the magnitudes of these constants shows that, as anticipated, the *N*-glycopyranosyl ring in cases I, II, VII–X, XII, and XIX–XXI adopts the normal $^4C_1$ conformation, and there are no reasons for supposing that this conformation is not also adopted in III, IV, XI, and XIV. However, in the remaining cases (V, VI, XIII, XV–XVIII), definite indications of distortions from the normal conformation are revealed by deviation of the $J_{ax,ax}$ values from the expected[20] value of ~10 Hz. The low value of $J_{1,2}$ for the β-D-*manno* compound (VII) is readily explained by the fact that, in the $^4C_1$ conformation, H-1 and H-2 are both antiparallel to electronegative substituents[21,22], but the lower values of $J_{3,4}$ and $J_{4,5}$ for the α-D-*manno* compound (V and VI) as compared to those for the β-D-*manno* anomer (VII) must indicate a distortion of the ring. Although more difficult to interpret, the magnitudes of $J_{1,2}$ for V and VI support this view, as α-mannopyranose derivatives often have $J_{1,2}$ = 1–1.5 Hz[23]. The relatively minor influence of protonation (*cf.* V and VI) is partially explained by the fact that, because of their p*K* values (*e.g.*, *N*-methylimidazole[24], p*K* = 7.2), imidazole derivatives will exist partially in the conjugate acid form in neutral, aqueous solution. These results point to the operation of a reverse anomeric effect in the highly polar and solvating solvent water, which normally favours the operation of "steric" rather than opposing "polar" factors[4,16]. As shown by Lemieux[4], the protonated *N*-(tetra-*O*-acetyl-α-D-*gluco*- and *manno*-pyranosyl)-imidazoles (cases XIII, XVI, and XVIII) show evidence of considerable distortion from the normal $^4C_1$ conformation. It is clear, however, from comparison of the coupling constants for the β-D-*manno* and α-D-*manno* compounds (cases XX and XV, XIX and XVII), that the unprotonated compounds also do not adopt a $^4C_1$ conformation. The question then arises of the nature of these unusual solution conformations. Lemieux[6,25] has postulated a $B_{2,5}$ form as in **4**, but in our view the magnitudes of the $J_{4,5}$ coupling constants make this unlikely. Paulsen *et al.*[7] interpreted the n.m.r. parameters for the *N*-(tetra-*O*-acetyl-α-D-xylopyranosyl)imidazoles in terms of equilibrium mixtures of $^4C_1$ and $^1C_4$ conformations, and have reported that *N*-(tri-*O*-acetyl-α-D-xylopyranosyl)pyridinium chloride[7] and *N*-(tri-*O*-acetyl-α-D-xylopyranosyl)imidazole[26] adopt the $^1C_4$ conformation in the crystalline state. Assuming an equilibrium mixture of $^4C_1$ and $^1C_4$ forms, the proportion of each form present for each compound can be calculated from the observed coupling constants with the aid of limiting values of the vicinal coupling constants for each conformation. The majority of previous determinations of conformational populations by this method of averaging of coupling constants (*e.g.*, Refs. 7, 16, 27–29) have relied on one vicinal coupling constant only, often $J_{4,5}$. In this work, we have calculated conformational populations from three coupling constants, in order to assess the accuracy of the method and the validity of the assumption that the compounds

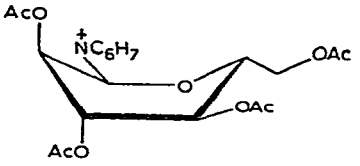
TABLE I

^{1}H-N.M.R. COUPLING CONSTANTS (Hz) OF *N*-GLYCOPYRANOSYLIMIDAZOLES

Case no.	*Glycon residue*	*Solvent*	$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$	$J_{5,6a}$	$J_{5,6b}$	$J_{6a,6b}$
I	α-D-*gluco*	D_2O	5.50	10.00	8.80	10.00	2.70	4.80	12.50
II	α-D-*gluco*	D_2O+TFA[a]	5.10	10.10	8.90	10.10	2.40	5.00	12.50
III	β-D-*gluco*	D_2O	8.2	[b]	[b]	[b]	[b]	[b]	[b]
IV	β-D-*gluco*	D_2O+TFA	~7.5	[b]	[b]	[b]	[b]	[b]	[b]
V	α-D-*manno*	D_2O	3.69	3.55	6,96	7.36	7.16	2.50	12.59
VI	α-D-*manno*	D_2O+TFA	4.12	3.05	6.96	7.67	7.17	2.53	12.59
VII	β-D-*manno*	D_2O	0.52	2.70	9.63	9.63	1.98	5.57	12.14
VIII	α-D-*galacto*	D_2O	5.54	10.33	3.15	0.94	8.00	3.75	11.87
IX	α-D-*galacto*	D_2O+TFA	4.70	9.35	3.10	0.40	7.95	3.15	12.00
X	β-D-*galacto*	D_2O	9.2	8.7	3.3	~0	[b]	[b]	[b]
XI	β-D-*galacto*	D_2O+TFA	7.6	[b]	[b]	[b]	[b]	[b]	[b]
XII	Tetra-*O*-acetyl-α-D-*gluco*	$CDCl_3$	5.5	10.25	8.5	10.0	4.5	2.5	12.25
XIII	Tetra-*O*-acetyl-α-D-*gluco*	$CDCl_3$+TFA	3.12	8.03	7.39	7.38	6.37	2.40	12.37
XIV	Tetra-*O*-acetyl-β-D-*gluco*	$CDCl_3$	[b]	[b]	[b]	~7	4.4	2.6	12.36
XV	Tetra-*O*-acetyl-α-D-*manno*	$CDCl_3$	5.1	2.2	7.75	7.09	7.10	2.95	12.1
XVI	Tetra-*O*-acetyl-α-D-*manno*	$CDCl_3$+TFA	6.48	3.08	5.92	4.42	9.01	3.06	13.14
XVII	Tetra-*O*-acetyl-α-D-*manno*	$(CD_3)_2CO$	5.2	3.1	6.9	5.8	7.4	3.2	12.4
XVIII	Tetra-*O*-acetyl-α-D-*manno*	$(CD_3)_2CO$+TFA	7.0	3.0	5.5	4.2	7.5	3.5	12.1
XIX	Tetra-*O*-acetyl-β-D-*manno*	$(CD_3)_2CO$	1.35	3.02	10.04	9.60	6.20	2.00	12.83
XX	Tetra-*O*-acetyl-β-D-*manno*	$CDCl_3$	1.31	2.94	10.16	9.78	5.78	3.00	12.64
XXI	Tetra-*O*-acetyl-β-D-*galacto*	$CDCl_3$	9.08	10.24	3.02	0.0	[b]	[b]	[b]

[a]TFA = trifluoroacetic acid. [b]Complex multiplet.

considered exist as mixtures of chair conformers only. Of course, the accuracy of the results depends critically on the validity of the limiting values of the coupling constants chosen for the pure conformers, as well as on a linear relation between coupling constant and conformational population. The limiting values used (Table II) were obtained in this and other work[5,7,30] for conformationally homogeneous molecules. The calculated, percentage conformational populations for cases V, VI, XIII, and XV–XVIII are shown in Table III. With three exceptions, consistent results are obtained, and we propose that, in all cases, mixtures of chair conformers are present. The relative proportions of the conformers follow general expectations, in that the amount of the $^1C_4$ form is (*a*) greater for the α-D-*manno* than the α-D-*gluco* compounds, (*b*) greater for acetylated compounds, (*c*) increased on protonation, and (*d*) smaller for the α-D-*gluco* compound (XII and XIII) than was observed[7] for the corresponding α-*xylo* derivative in which the acetoxymethyl substituent is replaced by hydrogen. Attempts were made to observe a "conformational freeze-out"[27,29] in cases XIII and XVI, but only a progressive broadening of the spectral features was observed until, at −60°, the solutions solidified.



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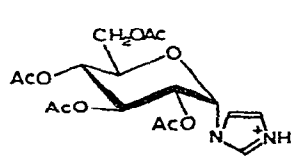
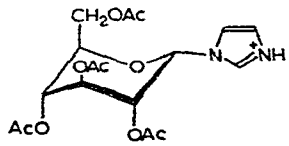
As Saluja[3] has pointed out, it is important to try to distinguish between steric and polar effects in order to establish the existence of the (polar) reverse anomeric effect. It has been argued[3,4,7] that protonation of the imidazole ring does not significantly alter its steric influence and that therefore any conformational change on protonation can be attributed to polar effects. While this argument seems likely, it should not be accepted without reservation, as the association of a counterion may affect the A-value of the imidazolium group. An alternative approach is to calculate the value of the reverse anomeric effect by an empirical method. Such methods[31] have been successful in predicting the conformational free energies of aldopyranoses in aqueous solution, but rather less successful with acylated aldopyranose derivatives[27]. For *N*-α-D-mannopyranosylimidazole in D_2O (V and VI), the difference between the conformational free energies (in kcal.mol^{-1}) of the two chair forms can be predicted to be 3.05 (the difference between the calculated[31] values for the $^4C_1$ and $^1C_4$ forms of α-D-mannopyranose) minus 2.13 (the difference between the A-values[32] for a phenyl substituent and a hydroxyl substituent) minus 0.55 (the anomeric effect of a hydroxyl group[31]) plus the anomeric effect of an imidazole or imidazolium group. The observed value (Table III) is ~0.5 kcal.mol^{-1}, which leads to a positive anomeric effect of ~0.1 kcal.mol^{-1}. Thus, the observation of a conformational equilibrium in cases V and VI could apparently be the result of the operation of steric

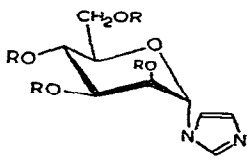
TABLE II

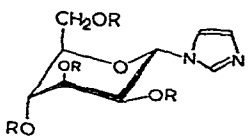
LIMITING VALUES OF COUPLING CONSTANTS (Hz) USED IN CALCULATIONS OF CONFORMATIONAL POPULATIONS





	$^4C_1$	α-D-*gluco*	$^1C_4$
$J_{1,2}$	5.5		1.31
$J_{2,3}$	10.25		3.0[a]
$J_{3,4}$	8.5		2.8[a]
$J_{4,5}$	10.0		1.8[a]





	$^4C_1$		α-D-*manno*	$^1C_4$	
	R = Ac	R = H		R = Ac	R = H
$J_{1,2}$	0.5[a]	1.7[b]		9.5[a]	8.2
$J_{2,3}$	2.94	2.70		3.2[a]	3.1[b]
$J_{3,4}$	10.16	9.63		3.8[a]	1.5[c]
$J_{4,5}$	9.78	9.63		1.8[a]	1.5[c]

[a]Ref. 7. [b]Ref. 30. [c]Ref. 5.

TABLE III

CALCULATED PERCENTAGES OF $^1C_4$ CONFORMERS

Case no.[a]	*Percent of* $^1C_4$ *form based on individual J values*				*Average % of* $^1C_4$ *form*
	$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$	
V	30.6		32.8	27.9	30.4
VI	37.2		32.8	24.1	31.3
XIII		30.6	19.5	32.0	27.4
XVI	66.7		67.0	67.4	67.0
XVII	52.2		51.25	49.9	51.1
XVIII	72.2		73.3	69.9	71.8

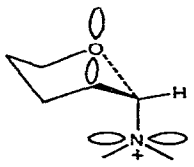
[a]See Table I.

factors (A-values) rather than a reverse (negative) anomeric effect. Calculations of this type are approximate and, in this particular case, a big approximation is the equating of the A-value of an imidazole group in D_2O with that of a phenyl group in an organic solvent[32], *viz.*, 3.0 kcal.mol^{-1}. Similar calculations were not carried out with the acetylated derivatives because of the poor correlations observed previously with a number of acylated compounds[27]. However, the greater amount of conformational inversion observed for the tetra-*O*-acetyl compounds (*cf.* V and XV, Table III) is not inconsistent with a steric interpretation, as the A-value of an acetoxyl group has been reported[32–34] to be smaller than that of a hydroxyl group in protonic solvents[32]. The greater degree of conformational inversion observed for the α-D-*manno* configuration (V and VI) in comparison with the α-D-*galacto* configuration (VIII and IX) is to be expected, as any positive or negative anomeric effect will be greater if the substituent on C-2 is axial; this will disfavour the $^1C_4$ form in the *galacto* series if the anomeric effect is positive, and disfavour the $^4C_1$ form in the *manno* series if the anomeric effect is negative (reverse effect). In the absence of more-precise data on the steric contribution toward conformational inversion, the most convincing evidence of a polar, reverse anomeric effect is the observation of conformational inversion attendant on the development of a positive charge on the nitrogen atom adjacent to the anomeric carbon atom in the protonated imidazole compounds and the *N*-(tri-*O*-acetyl-α-D-lyxopyranosyl)triphenylphosphinimide hydrochloride studied by Paulsen and his co-workers[7]. Unlike the pyridinium compounds (*e.g.*, **2**), the imidazolium compounds do not develop a full, positive charge on this nitrogen atom because of delocalisation as represented in **5**. The calculations of Jordan[35] indicate

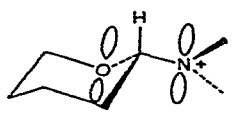
5

that, for unprotonated glycosylimidazoles, the glycosyl–nitrogen bond is polarised in the manner C($\delta+$)–N($\delta-$), and clearly protonation of the imidazole ring will significantly alter the extent, and possibly reverse the direction, of polarisation. However, Romers *et al.*[11] have argued that dipolar interaction energies may not be of sufficient magnitude to effect conformational inversion, although energies of 1–2 kcal.mol^{-1}, which would be sufficient to account for the effects of protonation observed in this work, could be generated by this type of interaction[11,38]. An alternative rationalisation[10,11] of the anomeric effect involves overlap of the axial lone-pair of the ring-oxygen atom with the C-1–X σ^* antibonding orbital. In a quantitative extension of this idea, David *et al.*[13] suggested that, where X is less electronegative than H, interactions between the ring-oxygen (s- and p-type) lone-pairs and the C-1–X and C-1–H σ^* antibonding orbitals favour equatorial X, as in **1b**. This suggestion appears to depend crucially on the dependence of the energies of the C-1–X and C-1–X σ^* orbitals on the nature of X, but it is not clear how the electro-

negativity of X can be the controlling factor. In the compounds in which the reverse anomeric effect has been proposed to operate, $X = \overset{+}{N}R_3$, and one would suppose that the nitrogen atom in such a group would be more, rather than less, electronegative than hydrogen. By means of ^{1}H-n.m.r. measurements[36,37] on *N*-methyl- and *N*-ethyl-imidazole, we find the electronegativities of the imidazole and imidazolium groups to be 3.6 (in CCl_4) and 3.75 (in D_2O*), respectively, on a scale in which the electronegativity of hydrogen is 2.1 and that of fluorine is 3.94. An alternative picture of the stabilisation of the structure **1b** with equatorial X, when X is pyridinium or imidazolium, is provided by an interaction between the p-type lone-pair of the ring-oxygen atom and the e_{2u} π^* antibonding orbital of the aromatic system in the conformation shown in **6b**, in which the aromatic ring and the C-1–O-5 bond are



6a



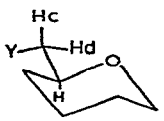
6b

coplanar; such an arrangement is not possible in the alternative conformation **6a**. In addition to offering a stereoelectronic interpretation of the reverse anomeric effect, this proposal predicts a glycosyl–nitrogen torsion angle† of 0° or 180° in compounds in which this interaction occurs. For (unprotonated) *N*-(tri-*O*-acetyl-α-D-xylopyranosyl)imidazole in the crystalline state[26], this angle is 45.3°. However, for crystalline *N*-(tri-*O*-acetyl-α-D-xylopyranosyl)pyridinium chloride[7], the angle is 22.6°, and for *N*-(tetra-*O*-acetyl-α-D-glucopyranosyl)-4-methylpyridinium bromide, it is similar[46]. Quantum mechanical calculations and experimental observations[35,36] on nucleosides show that, in the favoured (syn and anti[37]) conformations, the angle between the plane of the aromatic substituent and the C-1–O-4 bond is in the range 0–70°. In two crystalline salts which have been examined, the angle is 0.0° (deoxycytidine hydrochloride[37]) and 19° (puromycin dihydrochloride pentahydrate[39]).

The conformations of the exocyclic hydroxymethyl groups

The average rotamer conformation or rotamer population distribution for an exocyclic hydroxymethyl substituent can be deduced from ^{1}H-n.m.r. coupling constants by applying three criteria (*1*) the value of $J_{5,6}$ for an anti-periplanar arrangement of H-5 and H-6 (rotamer **7a**, $J_{5,6c}$) is much greater (~9 Hz) than that 2–5 Hz) for a syn-clinal arrangement (rotamer **7a**, $J_{5,6d}$); (*2*) for syn-clinal arrangements of H-5 and H-6, the value of $J_{5,6}$ is reduced by the presence of an electronegative substituent in an antiperiplanar arrangement with either hydrogen[21,22]

*These measurements were made by Mr. B. M. Cockerill.
†Angles defined according to Ref. 35.



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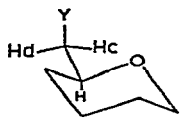

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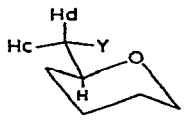
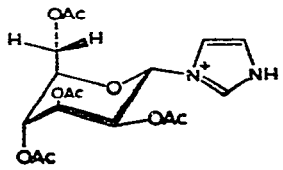


7c

(rotamer **7b**, $J_{5,6d} < J_{5,6c}$); (*3*) the value of the geminal coupling constant ($J_{6c,6d}$ is smallest for the rotamer (**7a**) in which H-6c and H-6d are both syn-clinal to O-5[5,22]. Inspection of the results (Table I) shows clearly that the conformations of the exocyclic hydroxymethyl groups fall into two broad groups, namely, I, II, VII, XII, and XIV, in which the $J_{5,6}$ values are both small; and V, VI, VIII, IX, XIII, and XV–XX in which $J_{5,6a}$ is substantially greater than $J_{5,6b}$. The first group clearly exhibit a preponderance of rotamer **7b**, and the magnitudes of the chemical shifts (see Table IV) of H-6a and H-6b in cases I, II, and VII are in agreement with this conclusion, as the low-field (due to deshielding by HO-4) signal is associated with the smaller coupling (proton anti-periplanar to O-5)[40]. In cases XII and XIV, this situation is reversed ($J_{5,6a} > J_{5,6b}$) and it appears that an acetoxyl substituent on C-4 results in a relative shielding of the 1,3-diparallel proton on C-6. The relative instability of rotamer **7b** in *galacto* compounds (VIII and IX) has been noted previously[41] and ascribed to unfavourable 1,3-diparallel interactions between the axial C-4 substituent and the C-6 substituent. In both rotamers **7a** and **7c**, the larger $J_{5,6}$ coupling will be associated with the low-field signal due to deshielding by HO-4, but a decision may be reached in favour of **7a** based on the low values of the geminal couplings $J_{6a,6b}$. For other cases in the second group, the magnitudes of the $J_{5,6}$ couplings indicate the presence of substantial proportions of rotamers **7a** or **7c**. A clear distinction is possible for XVI, in which the low value of $J_{5,6b}$ (3.06 Hz) and the large value of $J_{6a,6b}$ (13.14 Hz) indicate a substantial proportion of rotamer **7c**, and possibly this is also the favoured rotamer in the other cases. For XIII and XV–XVIII, an unusual feature is that the C-6 proton having the larger $J_{5,6}$ coupling is strongly deshielded with respect to the other C-6 proton. A possible origin of this effect lies in the interaction of the *pro*-6-*R* hydrogen with the axial AcO-3 in the $^1C_4$ conformation, as in **8**. Certainly the five



8

cases in which this large (0.31–0.77 p.p.m.) shift-difference is observed are those in which there is good evidence (see above) for a distortion of the sugar ring from the $^4C_1$ conformation. In general, it appears that rotamer **7b** is favoured (α-D-*gluco* compounds) unless destabilised by steric interactions with other axial groups (*galacto*

compounds, cases VIII and IX; and tetra-*O*-acetyl-β-D-*manno* compounds, cases XIX and XX) or by ring inversion (α-D-*manno* compounds and protonated tetra-*O*-acetyl-α-D-*gluco* compound, case XIII). In other studies on acetyl derivatives of hexopyranoses, Hall and Manville[41] concluded that rotamer **7b** is favoured in *gluco* derivatives and rotamer **7a** in *galacto* derivatives, while Streefkerk *et al.*[42] concluded that *gluco* and *manno* derivatives adopted mainly rotamer **7b**, with a lesser proportion of rotamer **7c**, and a galactose derivative adopted rotamer **7a** almost exclusively. Pullman and his co-workers[43] have reported that quantum mechanical calculations predict that the favoured conformation in purine and pyrimidine nucleosides and nucleotides is rotamer **7b**, and have noted that experimental observations are in good agreement with this prediction.

TABLE IV

CHEMICAL SHIFTS (δ) OF METHINE AND METHYLENE PROTONS OF *N*-GLYCOPYRANOSYLIMIDAZOLES

Case no.[a]	*Solvent*	*H-1*	*H-2*	*H-3*	*H-4*	*H-5*	*H-6a*	*H-6b*
I[b]	D_2O	6.15	4.19	4.05	3.63	3.38	3.85	3.80
II[c]	D_2O+TFA[d]	6.20	4.21	3.84	3.62	3.36	3.86	3.79
III[c]	D_2O	5.83	[e]	[e]	[e]	[e]	[e]	[e]
IV[c]	D_2O+TFA	6.03	[e]	[e]	[e]	[e]	[e]	[e]
V[b]	D_2O	5.82	4.59	3.92	3.85	3.53	3.92	3.86
VI[b]	D_2O+TFA	5.89	4.58	3.91	3.87	3.60	3.94	3.85
VII[b]	D_2O	5.73	4.20	3.87	3.75	3.65	3.99	3.83
VIII[b]	D_2O	6.08	4.36	4.16	4.05	3.60	3.76	3.70
IX[b]	D_2O+TFA	6.25	4.46	4.04	4.08	3.66	3.87	3.76
X[b]	D_2O	5.31	4.03	[e]	3.86	[e]	[e]	[e]
XI[b]	D_2O+TFA	5.44	[e]	[e]	[e]	[e]	[e]	[e]
XII[f]	$CDCl_3$	6.11	5.39	5.68	5.19	3.60	4.28	4.06
XIII[f]	$CDCl_3$+TFA	6.30	5.46	5.42	5.08	3.99	4.45	4.14
XIV[f]	$CDCl_3$	5.3[e]	5.3[e]	5.3[e]	5.3[e]	3.95	4.29	4.16
XV[f]	$CDCl_3$	5.79	5.78	5.28	5.24	3.87	4.60	4.07
XVI[f]	$CDCl_3$+TFA	6.01	5.65	5.37	5.14	~3.1	4.82	3.05
XVII[f]	$(CD_3)_2CO$	6.01	5.75	5.34	5.22	3.99	4.63	4.19
XVIII[f]	$(CD_3)_2CO$+TFA	6.49	5.85	5.57	5.33	4.48	4.83	4.40
XIX[f]	$(CD_3)_2CO$	6.1	5.57	5.38	5.35	4.16	4.25	4.22
XX[f]	$CDCl_3$	5.61	5.51	5.19	5.31	3.88	4.27	4.20
XXI[f]	$CDCl_3$	5.30	5.52[e]	5.19	5.52[e]	4.15[e]	4.15[e]	4.15[e]

[a]See Table I. [b]Internal standard, TSP. [c]External standard, Me_4Si. [d]TFA = trifluoroacetic acid. [e]Complex multiplet. [f]Internal standard, Me_4Si.

EXPERIMENTAL

The *N*-glycosylimidazoles and their tetra-*O*-acetyl derivatives were prepared as described previously[18] for *N*-α- and β-D-glucopyranosylimidazoles and their 2,3,4,6-tetra-acetates. ^{1}H-n.m.r. spectra were recorded at 100 and 220 MHz at PCMU, Harwell, and first-order assignments were checked by spin-decoupling experiments. Spectral parameters were checked and refined by spectrum simulation using program-

mes UEA NMR BASIC and UEA NMR ITERATIVE filed at the University of London Computer Centre in conjunction with a plotting routine LIBRARY RHC PLOT developed at Royal Holloway College Computer Services. Computed and simulated spectra were compared visually, and long-range coupling was ignored. Paper chromatography was performed with butan-1-ol–ethanol–water (40:11:19) as irrigant.

N-(*2,3,4,6-Tetra-O-acetyl-α-D-mannopyranosyl*)*imidazole.* — A mixture of tetra-*O*-acetyl-α-D-mannopyranosyl bromide[43] (32.9 g), imidazole (12 g, 2 mol. eq.), and *p*-dioxane (80 ml, dried over sodium) was heated under reflux for 4 h. After removal of solvent, the syrup (27 g) was taken up in chloroform, and the solution was washed with water, dried (Na_2SO_4), and concentrated to a syrup (9 g) which was applied to a column (100 × 4 cm) of silica gel and eluted with benzene–methanol (9:1). Fractions containing a faster-moving (t.l.c.) component were concentrated, and the material obtained was further purified by chromatography on silica gel (elution with ethyl acetate) to give the chromatographically homogeneous title compound (1.5 g, 4.7%) which resisted attempts at cyrstallisation; $[\alpha]_D^{21}$ +38° (*c* 1.35, chloroform), lit.[3] 35°; λ_{max}^{EtOH} 225 nm (log ε 3.15) (Found: C, 51.5, H, 5.7; N, 6.8. $C_{17}H_{22}N_2O_9$ calc.: C, 51.3; H, 5.6; N, 7.0%).

N-(*2,3,4,6-Tetra-O-acetyl-β-D-mannopyranosyl*)*imidazole.* — Fractions containing the slower-moving component obtained in the preparation of the α-anomer (above) were combined and concentrated. The resulting syrup solidified under high vacuum to give a solid (2.7 g, 8.5%) which could not be crystallised; $[\alpha]_D^{21}$ −15° (*c* 0.985, chloroform), lit.[3] −16°; λ_{max}^{MeOH} 225 nm (log ε 3.25) (Found: C, 51.4; H, 5.7; N, 6.8. $C_{17}H_{22}N_2O_9$ calc.: C, 51.3; H, 5.6; N, 7.0%).

N-α-D-*Mannopyranosylimidazole.* — Deacetylation of *N*-(2,3,4,6-tetra-*O*-acetyl-α-D-mannopyranosyl)imidazole (1.5 g) in methanolic ammonia at 0° gave a syrup (0.9) which solidified to a fine powder under high vacuum and was homogeneous in paper chromatography (R_F 0.24); $[\alpha]_D^{21}$ +64° (*c* 0.450, water), lit.[3] +66°; $\lambda_{max}^{H_2O}$ 215 nm (log ε 3.50) (Found: C, 46.7; H, 6.2; N, 12.0. $C_9H_{14}N_2O_5$ calc.: C, 47.0; H, 6.1; N, 12.2%).

N-β-D-*Mannopyranosylimidazole.* — Deacetylation of *N*-(2,3,4,6-tetra-*O*-acetyl-β-D-mannopyranosyl)imidazole (5 g) in methanolic ammonia at 0° gave a product (3 g) which could not be crystallised and which was homogeneous in paper chromatography (R_F 0.20); $[\alpha]_D^{21}$ +27.5° (*c* 0.607, water), lit.[3,44] +27°, $\lambda_{max}^{H_2O}$ 210 nm (log ε 3.00) (Found: C, 46.8; H, 6.1; N, 12.0. $C_9H_{14}N_2O_5$ calc.: C, 47.0; H, 6.1; N, 12.2%).

N-(*2,3,4,6-Tetra-O-acetyl-β-D-galactopyranosyl*)*imidazole.* — A mixture of tetra-*O*-acetyl-α-D-galactopyranosyl bromide[45] (82 g), imidazole (30 g, 2 mol. eq.), and dry *p*-dioxane was heated under reflux for 4 h. After working-up as described for the tetra-*O*-acetyl-*manno* compounds (above), the syrupy product (10 g) was applied to a column (100 × 4 cm) of silica gel and eluted with benzene–methanol (9:1). Fractions containing the slower-moving component were concentrated to give a syrup which solidified (3.1 g, 22% overall) under high vacuum, but resisted further attempts at crystallisation; $[\alpha]_D^{21}$ +11° (*c* 0.6, chloroform), lit.[44] 15°; λ_{max}^{MeOH} 225 nm

(log ε 2.96) (Found: C, 51.1; H, 5.5; N, 6.9. $C_{17}H_{22}N_2O_9$ calc.: C, 51.3; H, 5.6; N, 6.9%).

N-β-D-*Galactopyranosylimidazole.* — Deacetylation of *N*-(2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl)imidazole in methanolic ammonia at 0° gave a solid which could not be crystallised and was homogeneous in paper chromatography (R_F 0.29); $[\alpha]_D^{21}$ +51° (*c* 1.6, water), lit.[44] +35° (MeOH), $\lambda_{max}^{H_2O}$ 210 nm (log ε 3.00) (Found: C, 47.1; H, 6.3, N, 12.3. $C_9H_{14}N_2O_5$ calc.: C, 47.0; H, 6.1; N, 12.2%).

N-α-D-*Galactopyranosylimidazole.* — Fractions containing the faster-moving component obtained in the synthesis of *N*-(2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl)imidazole (above) were combined and concentrated to give a syrup (2 g) which was deacetylated with methanolic ammonia at 0°. Paper chromatography showed that the syrupy product was contaminated with D-galactose. Column chromatography on Dowex 1-x8 (OH) resin (elution with deionised, carbon dioxide-free water) gave the title compound as a solid (0.7 g, 5% overall) which resisted attempts at crystallisation and was homogeneous in paper chromatography (R_F 0.32); $[\alpha]_D^{21}$ +130° (*c* 0.6, water); $\lambda_{max}^{H_2O}$ 214 nm (log ε 3.53) (Found: C, 46.2; H, 6.2; N, 11.8. $C_9H_{14}N_2O_5$ calc.: C, 47.0, H, 6.1; N, 12.2%).

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REFERENCES

1 R. U. Lemieux and A. R. Morgan, *Can. J. Chem.*, 43 (1965) 2205–2213.
2 M. N. G. James, *Proc. Can. Fed. Biol. Soc.*, 13 (1969) 265.
3 S. S. Saluja, Ph.D. Thesis, University of Alberta, 1971.
4 R. U. Lemieux, *Pure Appl. Chem.*, 25 (1971) 527–548.
5 G. Kotowycz and R. U. Lemieux, *Chem. Rev.*, 73 (1973) 669–698.
6 R. U. Lemieux and S. Koto, *Tetrahedron*, 30 (1974) 1933–44.
7 H. Paulsen, Z. Gyorgydeak, and M. Friedmann, *Chem. Ber.*, 107 (1974) 1590–1613.
8 S. Wolfe, A. Rauk, L. M. Tel, and I. G. Csizmadia, *J. Chem. Soc., B*, (1971) 136–145.
9 L. Random, W. J. Hehre, and J. A. Pople, *J. Amer. Chem. Soc.*, 94 (1972) 2371–2381.
10 C. Altona, Ph.D. Thesis, University of Leiden, 1964, p. 117.
11 C. Romers, C. Altona, H. R. Buys, and E. Havinga, *Topics Stereochem.*, 4 (1969) 39–97.
12 G. A. Jeffrey, J. A. Pople, and L. Radom, *Carbohyd. Res.*, 25 (1972) 117–131.
13 S. David, O. Eisenstein, W. J. Hehre, L. Salem, and R. Hoffmann, *J. Amer. Chem. Soc.*, 95 (1973) 3806–3807.
14 K. Onodera, S. Hirano, F. Masuda, and N. Kashimura, *J. Org. Chem.*, 31 (1966)2403–240 6.
15 K. Onodera, S. Hirano, and F. Masuda, *Carbohyd. Res.*, 7 (1968) 27–37.
16 K. Onodera, *Conf. Anal. Pap. Int. Symp. 1969* (Pub. 1971), 191–202.

17 A. J. FREESTONE, L. HOUGH, AND A. C. RICHARDSON, *Carbohyd. Res.*, 28 (1973) 378–386.
18 E. J. BOURNE, P. FINCH, AND A. G. NAGPURKAR, *J. Chem. Soc. Perkin I*, (1972) 2202–2205.
19 E. J. BOURNE, P. FINCH, AND A. G. NAGPURKAR, *Carbohyd. Res.*, 29 (1973) 492–496.
20 B. COXON, *Methods Carbohyd. Chem.*, 6 (1972) 513–539.
21 D. H. WILLIAMS AND N. S. BHACCA, *J. Amer. Chem. Soc.*, 86 (1964) 2742–2743.
22 L. D. HALL AND J. F. MANVILLE, *Advan. Chem. Ser.*, 74 (1968) 228–253.
23 R. U. LEMIEUX AND B. FRASER-REID, *Can. J. Chem.*, 42 (1964) 532–538.
24 N. C. LI, J. M. WHITE, AND E. DOODY, *J. Amer. Chem. Soc.*, 76 (1954) 6219–6223.
25 R. U. LEMIEUX AND S. S. SALUJA, *Abstr. Papers ACS–CIC Meeting (Toronto)*, (1970) C33.
26 P. LUGER, G. KOTHE, AND H. PAULSEN, *Chem. Ber.*, 107 (1974) 2626–2634.
27 P. L. DURETTE AND D. HORTON, *Adv. Carbohyd. Chem. Biochem.*, 26 (1972) 49–125, and refs. therein.
28 P. L. DURETTE AND D. HORTON, *J. Org. Chem.*, 36 (1971) 2658–2669.
29 P. L. DURETTE, D. HORTON, AND J. D. WANDER, *Advan. Chem. Ser.*, 117 (1973) 147–176.
30 R. U. LEMIEUX AND J. D. STEVENS, *Can. J. Chem.*, 44 (1966) 249–262.
31 S. J. ANGYAL, *Aust. J. Chem.*, 21 (1968) 2737–2746.
32 J. A. HIRSCH, *Topics Stereochem.*, 1 (1967) 199–222.
33 G. B. ANDERSON, D. T. SEPP, M. P. GEIS, AND A. A. ROBERTS, *Chem. Ind. (London)*, (1968) 1805–1806.
34 M. FUERTES, G. GARCÍA-MUÑOZ, F. G. DE LAS HERAS, R. MADRONERO, M. STUD, AND M. RICO, *J. Heterocycl. Chem.*, 10 (1973) 503–509.
35 F. JORDAN, *Biopolymers*, 12 (1973) 243–255.
36 (*a*) H. BERTHOD AND B. PULLMAN, *Biochim. Biophys. Acta*, 232 (1971) 595–606; (*b*) H. BERTHOD AND B. PULLMAN, *ibid.*, 246 (1971) 359–364; (*c*) A. SARAN, B. PULLMAN, AND D. PERAHIA, *ibid.*, 349 (1974) 189–203; (*d*) M. SUNDARALINGAM, *Biopolymers*, 7 (1969) 821–860; (*e*) G. A. JEFFREY AND M. SUNDARALINGAM, *Advan. Carbohyd. Chem. Biochem.*, 30 (1974) 445–466.
37 J. HUNT AND E. SUBRAMANIAN, *Abstr. Amer. Crystallogr. Assoc. Meeting, Tuscon, Arizona, February 4–7, 1968*, cited in Ref. 36 (*d*).
38 C. B. ANDERSON AND D. T. SEPP, *Tetrahedron*, 24 (1968) 1707–1716.
39 M. SUNDARALINGAM AND S. K. ARORA, *J. Mol. Biol.*, 71 (1972) 49–70.
40 R. U. LEMIEUX AND J. T. BREWER, *Advan. Chem. Ser.*, 117 (1973) 121–146.
41 L. D. HALL, J. F. MANVILLE, AND N. S. BHACCA, *Can. J. Chem.*, 47 (1969) 1–17.
42 D. G. STREEFKERK, M. J. A. DE BIE, AND J. F. G. VLIEGENTHART, *Tetrahedron*, 29 (1973) 833–844.
43 E. A. TALLELY, D. D. REYNOLDS, AND W. L. EVANS, *J. Amer. Chem. Soc.*, 65 (1943) 575–582.
44 J. JASIŃSKA AND J. SOKOLOWSKI, *Rocz. Chem.*, 43 (1969) 855–867.
45 R. U. LEMIEUX, *Methods Carbohyd. Chem.*, 2 (1963) 221–222.
46 R. U. LEMIEUX, Personal communication of unpublished work by Drs. M. N. G. JAMES AND L. T. J. DELBAERE.