Carbohydrate Research, 77 (1979) 37–50

HUDSON'S RULES OF ISOROTATION AS APPLIED TO FURANOSIDES, AND THE CONFORMATIONS OF METHYL ALDOFURANOSIDES

STEPHEN J. ANGYAL
School of Chemistry, University of New South Wales, Kensington, NSW 2033 (Australia)
(Received May 21st, 1979; accepted for publication, June 25th, 1979)

ABSTRACT

Molecular rotations and molecular-rotation differences are tabulated for the methyl furanosides of all of the aldopentoses, aldohexoses, and hexuloses. The n.m.r. spectra of most of the methyl aldofuranosides have been determined and analyzed, and from the data, the conformations of the glycosides have been deduced. In the D series, the β-pentofuranosides are found to be in the $^3T_2$ form, with the methoxyl group *quasi*-axial and the side-chain *quasi*-equatorial. The α-D-pentofuranosides are mixtures of two twist forms, or assume an envelope conformation. The correlation between conformation and optical rotation of the methyl furanosides is discussed.

INTRODUCTION

Hudson's Rules of Isorotation[1], although fundamentally unsound, have, over many years, proved of great value in assigning structures and configurations to glycosides and other sugar derivatives[2]. Although exceptions to the rules have been found when the aglycon is a heterocycle[3] or an *o*-nitro-substituted phenyl group[4], they seem to be reliable when the aglycon is an alkyl group.

Most of the discussions and applications of the rules had related to pyranosides; on only a few occasions have they been applied to furanosides[5,6], but, as we have recently synthesized[7–10] a substantial number of new methyl glycofuranosides, the opportunity is now being taken to survey the specific rotations and molecular-rotation differences of the methyl furanosides of all of the aldo- and keto-pentoses and -hexoses. The only methyl furanosides still unknown amongst these were those of D-altrose, and we have now synthesized them in the conventional way (with methanol and hydrogen chloride) and have included them in order to obtain a complete set of data.

DISCUSSION

Molecular-rotation differences

Table I shows the molecular rotations and rotation differences of the methyl

TABLE I

MOLECULAR ROTATIONS AND MOLECULAR-ROTATION DIFFERENCES OF METHYL GLYCOFURANOSIDES[a]

Methyl furanoside	$[M]_S$ *(degrees)*	$[M]_R$ *(degrees)*	$[M]_S - [M]_R$ *(degrees)*	*Methyl furanoside*	$[M]_S$ *(degrees)*	$[M]_R$ *(degrees)*	$[M]_S - [M]_R$ *(degrees)*
D-Erythro-	188, α	−194, β	382	L-Threo-*	259, β	−130, α	389
L-Lyxo-*	184, β	−212, α[b]	396	D-Xylo-[k]	297, α	−131, β	428
L-Manno-[c]*	213, β	−215, α	428	D-Gluco-[e]	221, α	−153, β	374
L-Rhamno-[d]	202, β	−189, α	391	L-Ido-[l]	171, β	−147, α	318
D-Gulo-*	186, α[e]	−210, β	396				
D-*glycero*-D-*gulo*-Hepto-[e]	166, α	−202, β	368	L-Arabino-[k]*	192, β	−202, α	394
				L-Altro-[m]*	183, β	−198, α	381
D-Ribo-	239, α	−82, β[f]	321	D-Galacto-	202, α	−217, β	419
D-Allo-[g]	248, α	−111, β	359	D-Fuco-*	192, α	−201, β	394
L-Talo-[e]*	219, β	−72, α	291				
				3-*C*-(Hydroxymethyl)-L-threo-[h]	180, β	−113, α	294
3-*C*-(Hydroxymethyl)-D-erythro-[h]	221, α	−167, β	388				
				D-*threo*-Pentulo-[i]	141, β	−120, α	261
D-*erythro*-Pentulo-[i]	69, α	−179, β	248	D-Sorbo-[n]*	180, α	−111, β	291
L-Tagato-[h]	84, β	−165, α	249	L-Fructo-[n]	89, β	−178, α	267
D-Psico-[j]	136, α	−76, β	212				

[a] $[M]_S$ and $[M]_R$ are the molecular rotations in water of the anomers in which the anomeric center is *S* and *R*, respectively. Data are taken from ref. 14, unless otherwise stated. An asterisk marks those cases where the rotation was actually determined on the enantiomer of the compound listed. [b]Ref. 8. The value of 160° for the rotation ($[M] = +262°$) given in ref. 22 for the enantiomer seems to be erroneous. [c]V. Smirnyagin and C. T. Bishop, *Can. J. Chem.*, 46 (1968) 3085-3090. [d]Calculated from the rotation of the ethyl glycosides. [e]Ref. 8. [f]The value of −63° given for the rotation in ref. 22 seems to be erroneous. [g]Ref. 7. [h]Ref. 10. [i]L. Stankovič, K. Linek, and M. Fedoroňko, *Carbohydr. Res.*, 35 (1974) 242-246. [j]P. C. M. Herve du Penhoat, Ph.D. Thesis, McGill University, Montreal, Canada, 1973. [k]Ref. 22. [l]Ref. 9. [m]Present work. [n]S. J. Angyal and G. S. Bethell, *Aust. J. Chem.*, 29 (1976) 1249-1265.

furanosides, all determined in aqueous solution. To facilitate comparisons, the compounds are arranged in homomorphous groups; they are headed by the D-erythrofuranosides and the L-threofuranosides, therefore all of the compounds have the same configuration of C-2 (or C-3 in the case of the ketoses). The glycosides in each column have the same configuration of the anomeric center. This arrangement means that D and L could not be used as a basis of the classification, because not all homomorphs carry the same prefix; nor could α and β be used for the classification, because the meaning of these symbols depends on the D and L notation. Thus, α-D-glucofuranose and β-L-idofuranose are placed in the same column because they are homomorphs, that is, they have the same configuration of every carbon atom in the ring. The rotations are arranged in columns according to the absolute configuration of the anomeric center, expressed by the *R* and *S* notation; to facilitate reference to the data, it is also indicated in each case whether the anomer is α or β. For several of the glycosides, the rotation actually determined was that of the enantiomer of the listed compound; for these, marked by an asterisk, the sign of the rotation was reversed for listing in the Table.

The first conclusion that emerges from Table I is that, for the methyl furanosides, all α anomers of the D series are dextrorotatory, and all β anomers of the D-series are levorotatory. (This is not true for all methyl pyranosides: both of the D-arabinopyranosides are levorotatory.) The sign of the rotation of a methyl furanoside can, therefore, be safely used to assign the configuration of its anomeric center. This correlation is due to the fact that the configuration of the anomeric carbon atom makes a greater contribution to the optical rotation than that of all of the other asymmetric centers.

The molecular-rotation difference for the methyl pyranosides is $\sim 400°$ when OH-2 is equatorial, and $\sim 280°$ when it is axial. Table I shows that most of the methyl aldofuranosides have molecular-rotation differences of $400 \pm 25°$, but a few have much lower values. An explanation was sought for these values.

The basis of the validity of Hudson's Rule for the aldopyranosides is the fact that the two anomers have the same conformation (except, possibly, for the idosides). Hence, the only change common to all sugars on going from the α to the β anomer is the change of configuration of C-1. When the conformations of the α and β anomers are different, as they are for the hexulopyranosides, Hudson's Rule is not valid. In order to ascertain the applicability of Hudson's Rule to the furanosides it was, therefore, necessary to study their conformations.

Conformations

The conformations of furanosides have been studied[11-13] and reviewed[14-16] by several authors. These studies were mostly conducted on the pentoses, and dealt with acylated derivatives in organic solvents. For the present purpose, the conformations of the free glycofuranosides in water were of interest, and we extended our investigation to cover most of the hexosides. It is well known from studies on the pyranosides that the free sugars in water do not always have the same conformation

TABLE II

PROTON CHEMICAL-SHIFT DATA FOR METHYL GLYCOFURANOSIDES IN DEUTERIUM OXIDE

Methyl furanoside	*Chemical shifts (δ)*							
	H-1	*H-2*	*H-3*	*H-4*	*H-5*	*H-6*	*H-6'*	*Me*
α-D-Erythro-	4.88	4.10	4.22	4.11, 3.85				3.38
β-L-Lyxo-*	4.90	4.19	4.24	4.17	3.83, 3.71			3.39
β-L-Manno-*	4.87	4.20	4.28	3.98	—	3.68	—	3.37
α-D-*glycero*-D-*gulo*-Hepto-	4.91	4.21	4.26	4.15	3.93	—	3.65 (H-7)	3.42
α-D-Ribo-	4.98	4.10	4.03	4.09	3.72, 3.66			3.42
α-D-Allo-	4.96	4.07	4.13	4.04	3.79	3.69	3.59	3.41
β-L-Talo-*	4.97	~4.15	~4.15	~3.92	~3.80	~3.66	3.60	3.42
β-D-Erythro-	4.91	4.04	4.36	4.12, 3.81				3.39
α-L-Lyxo-*	4.94	4.11	4.32	4.24	3.80, 3.73			3.43
α-L-Manno-*	4.93	4.12	4.31	3.97	—	—	—	3.43
β-D-*glycero*-D-*gulo*-Hepto-	4.94	4.09	4.41	4.31	3.87	—		3.43
β-D-Ribo-	4.89	4.02	4.14	4.00	3.78, 3.59			3.39
β-D-Allo-	4.87	4.04	4.35	3.90	~3.75	~3.75	3.62	3.38
α-L-Talo-*	4.87	4.02	4.25	3.91	~3.71	~3.71	3.61	3.40
β-D-Xylo-	4.89	4.11	4.21	4.33	3.84, 3.73			3.39
β-D-Gluco-	4.87	4.13	4.23	4.17	3.94	3.85	3.69	3.35
α-L-Ido-	4.89	4.14	4.16	4.18	3.94	3.73	3.61	3.41
β-L-Altro-*	4.85	4.10	4.20	3.78?	3.73?	~3.76	3.61	3.38
α-D-Galacto-	4.86	4.07–4.14			3.66–3.79		3.58	3.41
α-D-Xylo-	4.99	4.14	4.29	4.25	3.76, 3.69			3.44
α-D-Gluco-	5.06	4.15	4.28	4.08	3.86	3.78	3.64	3.44
β-L-Ido-	5.00	4.19	4.29	4.16	3.90	3.66	3.60	3.44
α-L-Arabino-*	4.91	4.04	3.93	4.03	3.80, 3.68			3.40
α-L-Altro-*	4.89	4.05	4.13	3.95	3.86	3.75	3.61	3.38
β-D-Galacto-	4.89	~4.03		3.93	3.80	3.69	3.63	3.39

as their acylated derivatives in organic solvents[16]. We have now found that the length and the configuration of the sidechain can also affect the conformation of the furanosides.

We studied the conformations, as have others before us, by examination of the n.m.r. spectra of the furanosides. The spectra were first recorded at 100 MHz, but in only a few cases could they be analyzed and coupling constants determined. The spectra (except those of the mannosides) were then recorded at 270 MHz, and, in all but three instances, those of methyl β-D-talofuranoside, methyl α-D-galacto-

TABLE III

PROTON–PROTON, SPIN-COUPLING DATA FOR METHYL GLYCOFURANOSIDES IN DEUTERIUM OXIDE

Methyl furanoside	*First-order couplings*[a] *(Hz)*								
	$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$	$J_{4,5'}$	$J_{5,6}$	$J_{5,6'}$	J_{gem}	*Conformation*
α-D-Erythro-	4.6	5.5	2.1	5.3($J_{3,4'}$)				−10.3	^2E (D)
β-L-Lyxo-*	4.9	5.0	4.4	4.4	7.6			−11.6	$^2T_3$ (L)
β-L-Manno-*	4.5	5.0	3.6	8.5		—	5.5	−12	$^2T_3$ (L)
α-D-*glycero*-D-*gulo*-Hepto-	4.7	5.0	4.1	6.0		6.0	7.4 ($J_{6,7}$)	−12.3	$^2T_3$ (D)
α-D-Ribo-	4.3	6.3	3.4	3.4	4.4			−12.3	$^0T_1$ (D)?
α-D-Allo-	4.3	6.4	2.9	4.5		3.9	7.2	−11.9	$^0T_1$ (D)?
β-L-Talo-*	4.2	6.2	2.6	2.6		5.1	7.2	−11.5	$^0T_1$ (L)?
β-D-Erythro-	2.7	4.6	3.5	4.7($J_{3,4'}$)				−9.8	$^2T_3$ ($^3T_2$) (D)
α-L-Lyxo-*	3.5	4.7	4.4	4.4	6.6			−11.8	E_3 ($^3T_2$) (L)
α-L-Manno-*	4.25	4.5	2.7	8.5		2.8	5.7	−12	E_3 (L)
β-D-*glycero*-D-*gulo*-Hepto-	3.2	4.9	4.7	4.4		6.8			E_3 ($^3T_2$) (D)
β-D-Ribo-	0.8	4.6	7.0	3.2	6.4			−12.4	$^3T_2$ (D)
β-D-Allo-	1.2	4.9	6.0	6.3		~2.8	~8.0	−12.5	$^3T_2$ (D)
α-L-Talo-*	0.8	4.6	7.2	4.8		4.0?	8.8	−12.5	$^3T_2$ (L)
β-D-Xylo-	~0	1.7	5.0	4.2	7.6	2.9	6.0	−11.9	$^3T_2$ (D)
β-D-Gluco-	~0	0.6	4.6	8.8		2.9	6.0	−11.8	$^3T_2$ (D)
α-L-Ido-	~0	0.7	4.2	6.0		3.7	6.5	−11.8	$^3T_2$ (L)
β-L-Altro-*	4.6	7.7	5.9	7.0?		2.7?	5.8	−11.3	$^2T_3$ (L)
α-D-Galacto-	~4.0	—	—	—		—	8.2	−12.5	
α-D-Xylo-	4.4	5.5	5.8	3.5	5.7			−12.1	$^2T_3$ ($^3T_2$) (D)
α-D-Gluco-	4.4	3.6	4.6	7.7		3.0	6.3	−11.8	($^2T_3$) $^3T_2$ (D)
β-L-Ido-	4.4	5.5	6.4	4.2		4.7	7.1	−11.6	$^2T_3$ ($^3T_2$) (D)
α-L-Arabino-*	1.8	3.2	5.5	3.4	5.7			−12.2	E_0 (L)
α-L-Altro-*	1.3	2.4	4.8	5.5		3.6	6.8	−12.0	E_0 (L)
β-D-Galacto-	~2	—	5.6	4.2		4.3	7.4	−11.6	E_0 (D)

[a]Most of the spacings were measured on expanded, 270-MHz spectra, and a few on 100-MHz spectra. When second-order effects were evident, the coupling constant is shown to be only approximate. *Data determined on the enantiomer.

furanoside, and methyl β-D-altrofuranoside, first-order spectra were obtained. The coupling constants of the first of these compounds were determined by the use of complexing with cations[17]: gradual addition of praseodymium nitrate to its solution shifted some of the signals until they were well separated. This method could not be applied to the other two glycosides, as they form no complexes with cations, and some of their chemical shifts and coupling constants remain uncertain.

The chemical shifts of the methyl furanosides are assembled in Table II, and the coupling constants in Table III. These Tables include a few data that have already been published (particularly concerning the anomeric hydrogen atom). The data for the D-erythrosides are taken from a forthcoming paper[18]. The compounds are arranged in the same way as in Table I, in homomorphous groups, and it is apparent that most, but not all, homomorphs have the same conformation. Data are available, or have been obtained, on some acetylated furanosides; these have not been included in the Tables, but will be mentioned where relevant.

In using n.m.r. data for the determination of the conformation of furanosides in solution, two difficulties are encountered: one of principle and one of method. Because the free-energy difference between the various twist and envelope forms of furanoses is small, a furanose in solution will not be in a single conformation but will occupy a segment of the pseudorotational itinerary[15]. Hence, when it is concluded that a furanoside has, for example, the ${}^3T_2$ conformation, this statement means that it will be found mainly in the ${}^1T_2 \rightleftharpoons E_2 \rightleftharpoons {}^3T_2 \rightleftharpoons {}^3E \rightleftharpoons {}^3T_4$ segment of the itinerary, with ${}^3T_2$ being the predominant, or the average, conformation. A closer definition cannot be given for the conformation in solution.

For the present purpose (the interpretation of optical rotation), this does not matter very much. The conformations can be classified into two groups. It has been pointed out[11,19] that puckering of the furanose ring will preferably occur in such a way that C-2 or C-3, or both, are displaced from the plane of the ring; in this way, the maximum extent of eclipsing will occur at the bonds of the ring-oxygen atom, where there are no *cis*-1,2, nonbonded interactions[15]. Pseudorotation permits ${}^1T_2 \rightleftharpoons E_2 \rightleftharpoons {}^3T_2 \rightleftharpoons {}^3E \rightleftharpoons {}^3T_4$ and ${}^2T_1 \rightleftharpoons {}^2E \rightleftharpoons {}^2T_3 \rightleftharpoons E_3 \rightleftharpoons {}^4T_3$ to occur without any 1,2-eclipsing interaction being involved in these interconversions[13]. Two *cis*-substituents on C-2 and C-3 will have a positive dihedral angle in the first example, and a negative one in the second; it is the sign of these angles that affects the optical rotation, the exact value of the angle being of comparatively little importance. We therefore classify the conformations into those in which C-3 is above C-2, and those in which C-2 is above C-3; within each group, the variation of the optical rotation will be small.

Secondly, as conformational inversions at room temperature are very fast on the n.m.r. scale, the n.m.r. data only give information for the average conformation. At temperatures that can be used with aqueous solutions, there is no way of deciding whether the coupling constants represent a single conformation, or the average of two or more conformations. This does not matter when all of the conformations are in a narrow segment of the pseudorotational itinerary, because an uncertainty exists there in any case; but it is also possible that two such segments are populated. The decision as to the conclusions that may be drawn from the n.m.r. spectrum may involve considerable guess-work.

The favored conformation of furanosides will be determined by three criteria: (*i*) the anomeric methoxyl group will tend to take up a *quasi*-axial position; (*ii*) the bulky sidechain will tend to be located in a *quasi*-equatorial orientation; and (*iii*)

substituents will be staggered insofar as possible. [When two vicinal carbon atoms carry *cis* substituents, the coupling constants between the respective hydrogen atoms are <6.0 Hz, which corresponds to a dihedral angle of $>35°$, indicating that the ring is fully puckered to avoid eclipsing. The only exceptions are $J_{2,3}$ (6.3 Hz) for methyl α-D-ribofuranoside and its homomorphs, and $J_{3,4}$ (6.4 Hz) for methyl β-L-idofuranoside, compounds having unfavorable conformations that will be discussed further.]

Furanosides in which O-1 and C-5 are cis*-oriented.* — In these compounds, the foregoing three criteria are all satisfied by the $^3T_2$(D) or $^2T_3$(L) conformation, and, in fact, the n.m.r. spectra indicate that methyl β-D-xylofuranoside, β-D-ribofuranoside, β-L-arabinofuranoside, and β-L-lyxofuranoside mainly adopt this conformation. Consideration of the coupling constants leaves no doubt for the first two compounds. For the xyloside, the small values of $J_{1,2}$ and $J_{2,3}$ indicate that O-1, O-2, and O-3 are *quasi*-axial; for the riboside, the small $J_{1,2}$ value and the large $J_{3,4}$ value show that O-1 and O-2 are *quasi*-axial, and O-3 and C-5 are *quasi*-equatorial. We have not investigated the arabinoside, but the homomorphous methyl β-L-altrofuranoside is undoubtedly in the $^2T_3$(L) conformation. The coupling constants of methyl β-L-lyxofuranoside do not allow an unambiguous assignment of conformation. They indicate, however, maximum staggering between the substituents, all of which are *cis* to each other, and this excludes all other conformations but $^3T_2$, which is most unlikely, having a *quasi*-axial side-chain and a *quasi*-equatorial anomeric group. Moreover, the chemical shifts of H-1 (δ 4.90) and of the methyl group (δ 3.39) seem to be, respectively, typical of an equatorial, anomeric hydrogen atom and of a methyl group on an axial oxygen atom. Both δ values are higher for the reverse case. Also, the chemical shifts and the coupling constants of H-5 and H-5′ in methyl β-L-lyxofuranoside are the same as for those in methyl β-D-xylofuranoside, suggesting that the orientation of the hydroxymethyl group is the same in these two compounds.

All of the homomorphs of these four pentofuranosides have the same [$^2T_3$(L) or $^3T_2$(D)] conformation. So as to avoid 1,3-parallel interactions as far as possible, the arrangement in the side-chains changes into a sickle form[20], if necessary, but another (unexpected) effect was noticed. When the methoxyl group is *quasi*-axial and the side-chain is *quasi*-equatorial, as they are in these compounds, there is a tendency to avoid the conformation (see Fig. 1) in which the substituent on C-5 is connected by a bond that is parallel to the C-1–O-1 bond. The explanation of this effect is obscure. It is noticeable for methyl β-D-allofuranoside, the side-chain of which is mainly in the zigzag form ($J_{4,5}$ large), despite an interaction between O-3

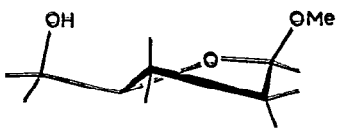

Fig. 1. Conformation of a methyl furanoside in which the substituent on C-5 is connected by a bond parallel to the C-1–O-1 bond.

and O-5; and for methyl α-L-talofuranoside, the side-chain of which is not wholly in the zigzag form, but partially in a sickle form having an unfavorable steric interaction, to avoid the foregoing effect. Also, it occurs in methyl β-L-altrofuranoside, the side-chain of which is mainly in the zigzag form, despite an unfavorable interaction between O-3 and O-5. The side-chains of methyl β-D-glucofuranoside and β-L-mannofuranoside are zigzags, as expected; those of methyl α-L-idofuranoside and α-D-gulofuranoside are mainly in sickle forms, to avoid C-5–O-5 being parallel to C-3–O-3 and C-1–O-1. Methyl α-D-galactofuranoside, the spectrum of which we could not analyze, would be expected to be in the $^2T_3$ form, with the side-chain partially in the sickle conformation.

Methyl α-D-erythrofuranoside, which has no side-chain, also assumes a similar conformation; the coupling constants suggest that it may be closer to the ^2E than to the $^2T_3$ conformer; the anomeric group is *quasi*-axial. Surprisingly, however, methyl β-D-erythrofuranoside appears to be a mixture of the $^2T_3$ and $^3T_2$ forms, with the former preponderating.

Furanosides having O-*1 and C-5* trans-*oriented.* — The three criteria mentioned cannot all be satisfied; hence, there is no particularly favored conformation, and the compounds may populate conformations from two different segments of the pseudorotational itinerary.

The $J_{2,3}$ value (5.5 Hz) of methyl α-D-xylofuranoside shows that it is mainly, but not wholly, in the $^2T_3$ form, with the side-chain *quasi*-axial; some of the $^3T_2$ form seems to be present, too. Methyl β-L-idofuranoside is conformationally similar, but O-3 and C-5 are closer to eclipsing ($J_{3,4}$ 6.4 Hz), in order to move the (bulkier) side-chain a bit farther from the *quasi*-axial position. The side-chain is mainly zigzag; it is to be noted that, with O-1 *trans* to C-5, there is no impediment to O-5 pointing "inwards".

On the other hand, the homomorphous methyl α-D-glucofuranoside has a considerably smaller $J_{2,3}$ value, indicating a substantial presence of the $^3T_2$ form. The side-chain is a zigzag ($J_{4,5}$ 7.7 Hz), which would encounter parallel interaction in the $^2T_3$ form. This is an example where homomorphs do not present the same conformational mixture. The difference is further accentuated for the peracetates, that of the glucoside having a $J_{2,3}$ value[21] of 3.0 Hz, and that of the idoside, 8.0 Hz; the xyloside has the intermediate value of 6.4 Hz. Accordingly, the side-chains in the acetates are closer to zigzags, $J_{4,5}$ being 8.9 and 2.0 Hz, respectively.

The $J_{1,2}$ value shows that methyl α-L-lyxofuranoside is a conformational mixture of the $^3T_2$ and $^2T_3$ forms (or, more probably, the E_3 form, which allows maximum staggering of the three *cis*-substituents), with the latter preponderating. The β-D-gulofuranoside exists as a similar mixture, the side-chain being mainly in the zigzag form. However, methyl α-L-mannofuranoside ($J_{1,2}$ 4.25) is almost completely in the E_3 form, with the anomeric group in the *quasi*-equatorial location; this conformation allows an unhindered, zigzag side-chain which is, indeed, found to be present ($J_{4,5}$ 8.5 Hz). The tetraacetate of methyl α-L-mannofuranoside, however, with $J_{1,2}$ 3.0, is partly in the $^3T_2$ form, probably owing to the larger anomeric effect.

The conformation of methyl α-L-altrofuranoside appears to be different. The small $J_{1,2}$ value indicates that the anomeric group is *quasi*-axial; however, the $^3T_2$ conformation would require a similarly small value for $J_{3,4}$. The side-chain is, to a considerable extent, in the sickle form, and this must be due to an interaction between O-5 and O-3. Therefore, O-3 must be *quasi*-equatorial. The conformation accommodating all these facts is E_O. Apparently, with all substituents *trans* to their neighbors, eclipsing does not introduce prohibitive interactions, and the two first criteria will be satisfied at the expense of the third: in the E_O form, the methoxyl group is *quasi*-axial and the sidechain *quasi*-equatorial, but C-2 and C-3 are eclipsed. Methyl β-D-galactofuranoside seems to have the same conformation, with the side-chain in the zigzag form.

The conformation of methyl α-D-ribofuranoside and its homomorphs is more difficult to assign. The value of $J_{2,3}$ (6.3 Hz) is too large for the $^2T_3$ or $^3T_2$ conformations, and it indicates partial eclipsing. Because the value of $J_{3,4}$ (2.6–3.4 Hz) cannot correspond to an angle of $<60°$, it indicates an angle close to 120°, that is, also close to eclipsing. The side-chain of the β-L-talofuranoside is zigzag, and that of the α-D-allofuranoside is mainly a sickle; this indicates, as in the previous example, the presence of a *quasi*-equatorial hydroxyl group on C-3. Again, the tendency of the anomeric group and the side-chain to become respectively axial and equatorial seems to overcome the tendency to staggering. The ^OE conformation would, however, entail complete eclipsing of the *cis*-hydroxyl groups on C-2 and C-3. A slight pseudorotation results in the $^OT_1$ conformation, which seems to fit the experimental data best, but should not be regarded as definitely proved.

To summarize: when the methoxyl group and the side-chain are *trans*, the former can be *quasi*-axial and the latter *quasi*-equatorial in the ^OE form only (in the D series). This form involves considerable eclipsing of the ring-carbon atoms, but this does not matter when all of the substituents are *trans* to their neighbors. Even with *cis*-hydroxyl groups on the ring, a closely related twist form ($^OT_1$) seems to provide sufficient eclipsing. But, when the side-chain and O-3 are *cis*, maximum puckering of the ring is required in this region, and either the side-chain will be *quasi*-axial, or the anomeric group, *quasi*-equatorial.

For most of the furanosides, the conformations now proposed are similar to those deduced by Stevens and Fletcher[12] for the aldopentofuranose perbenzoates, the only exception being the perbenzoate of α-D-lyxofuranose, which they found to be in the $^4T_3$ (or, possibly, E_3) form. There is, however, poor agreement with the conformations proposed for the methyl pentofuranosides by Bishop and Cooper[22] on the basis of nonbonded interactions.

Calculation of optical rotations

In order to understand the correlations between conformation and optical rotation, the molecular rotations of several methyl furanosides were obtained by calculation. Empirical rules for performing such calculations for sugars were first suggested by Whiffen[23], and were later generalized by Brewster[24]. A more detailed

method of calculation for sugar derivatives was given by Lemieux and Martin[25]. In these methods, partial contributions to the rotatory power are attributed to asymmetrical, conformational units consisting of four carbon and oxygen atoms in a *gauche* relationship. These units were represented by the symbols C/C, O/C, or O/O when the bridging atoms are both carbon, and by C/C_o and O/C_o when one is oxygen; O_r represents the oxygen atom in the ring. The rotational contribution is positive when the arrangement of the four atoms forms a right-handed screw. The sum of these contributions is the calculated molecular rotation.

There is considerable uncertainty regarding the values to be used for the various contributions. Lemieux and Brewer[26] later modified some of the constants; we mainly used these modified values, except that, for O/O, we retained the value of 45°, well proved for cyclitols and methyl glycopyranosides[27], and we used Brewster's value[24] of 50° for O/C. There are no agreed values for C/C and C/C_o; Paulsen and Friedmann[28] used 5° and 70°, respectively, but gave no justification for their choice. We used 40° for both. We also assumed that $C/O_r = O/O_r$, as C/O and O/O are almost equal.

Such calculations have apparently not yet been made for furanosides, but they have been applied to skew forms of pyranosides[28]. In them, as in furanosides, dihedral angles other than staggered ones occur; the rotational contributions were taken to be proportional to the sine function of the dihedral angles[24]. Two examples of the calculations are given in the Experimental part.

The optical rotations of the methyl pentofuranosides, including those of the apiosides, were thus calculated. Owing to the uncertainty of the exact dihedral angles in these molecules and of the contribution of minor conformations, these values must be regarded as approximate; in some instances, they differ by as much as 50° from the experimental values. The data obtained for the conformations shown in Table III are: methyl D-xylofuranosides: α +356° (for $^2T_3$), +262° (for $^3T_2$); β, −99°; L-arabinofuranosides: α, −195; β +199°; L-lyxofuranosides: α, −272; β, +160°; D-ribofuranosides: α, +243; β, −48°; 3-*C*-(hydroxymethyl)-D-erythrofuranosides: α, +245; β, −205°; 3-*C*-(hydroxymethyl)-L-threofuranosides: α, −88; β, +273°. For the last compound, the E_2 form gave a better value (+239°); this form allows more staggering of O-1 and O-2 than the $^3T_2$ form.

It may be noted that the values calculated for almost all of the compounds in the $^3T_2$ form are too high, and that those for the $^2T_3$ forms are too low. The twist form itself is chiral; and better calculated values would be obtained were a value of $\sim$+25° to be added for the chirality of the $^2T_3$ form, and $\sim$−25° for that of the $^3T_2$ form. Moreover, although $O/C_r = 115°$ is a suitable value to account for the interaction between the anomeric methoxyl group and the ring-oxygen atom when the methoxyl group is axial, it gives results that are too high when it is equatorial[23]; apparently, there is a greater distribution amongst rotamers in the latter case. Therefore, the calculated rotation is probably too low for methyl 3-*C*-(hydroxymethyl)-β-D-erythrofuranoside, and too high for methyl 3-*C*-(hydroxymethyl)-β-L-threofuranoside, both of which have *quasi*-equatorial, anomeric groups.

The data show that the apparent validity of Hudson's rule for the furanosides is due more to chance and to cancellation of various interactions than to systematic factors. Where the anomers of a sugar have the same conformation, the result is predictable: when OH-2 is *quasi*-equatorial, the molecular-rotation difference is ~400°, and when it is *quasi*-axial, it is ~280°, as it is with the pyranosides. Examples are the apiosides and the lyxosides. (The optical rotation of methyl α-L-lyxofuranoside is rather insensitive to conformational inversion: the rotation calculated for the $^2T_3$ form is −291°, and for the $^3T_2$ form, −317°.) For the arabinofuranosides, despite a change in the conformation, the molecular-rotation difference calculated happens to be very close to 400°. In the β-ribofuranosides and β-lyxofuranosides, O-2 is *quasi*-axial; if the α form had the same conformation, the change in rotation would be ~280°. However, the α-xylofuranoside is mainly in the $^2T_3$ form, and the change from $^3T_2$ to $^2T_3$ increases the rotation by nearly 100°; the difference is, therefore, again close to 400°. The α-ribofuranoside, like the α-lyxofuranoside, is rather insensitive to conformational inversion, owing to the presence of three *cis* groups, and the rotational difference is close to 300°.

On going from pentofuranosides to the homomorphous hexofuranosides, there is usually not much change in the molecular rotation. The O/O unit containing O-5 and the ring-oxygen atom disappears. Models show that, in the D series, addition of a sixth D carbon atom (*e.g.*, D-lyxose→D-mannose) introduces no additional, optically active unit if the side-chain is zigzag, but that an additional +O/O appears if it is sickle. Conversely, addition of an L carbon atom (*e.g.*, D-lyxose→L-gulose) introduces a +O/O unit if the sidechain is sickle, but none if it is zigzag. The rotations of the β anomers conform well with this general observation, but, amongst the α anomers, owing to changes in conformation, exceptions are found. The substantial drop in the rotation on going from methyl α-D-xylofuranoside to methyl α-D-glucofuranoside is due to the conformational change from $^2T_3$ to $^3T_2$ (see the preceding). However, the larger drop on going to methyl β-L-idofuranoside is not explained. Possibly, the rotation recorded[9] is erroneous; the compound has not been obtained crystalline.

For methyl β-D-erythrofuranoside in the $^3T_2$ form, the calculated rotation is −152°, and for the $^2T_3$ form, −103°. The observed molecular rotation being −194°, the former conformation seems to preponderate, in accordance with the n.m.r. data. For the α anomer, and for the two threosides, the calculated values do not differ sufficiently to allow conclusions about the prevalence of the $^2T_3$ or the $^3T_2$ conformation.

The molecular-rotation differences for the ketofuranosides are considerably less than those for the aldofuranosides, and this is readily explained by means of the Lemieux–Martin type of calculations. When a hydroxymethyl group is added to β-D-xylofuranoside and β-D-ribofuranoside, which have a *quasi*-axial hydroxyl group on C-2, to give the homomorphous β-D-sorbofuranoside and β-D-psicofuranoside, respectively, there are created a +O/C and a $-C/C_o$ unit that just about cancel each other out, and there is no substantial change in the rotation. But, when OH-2 is

quasi-equatorial, as in β-L-arabinofuranoside and β-L-lyxofuranoside, the resulting β-L-fructofuranoside and β-L-tagatofuranoside will have new —O/C and —C/C_o units, and the rotation will decrease by ~100°. Conversely, amongst the α anomers, the hexulosides derived from D-xyloside and D-riboside will have rotations decreased by ~100°, and those of those from L-arabinoside and L-lyxoside will have changed but little. In every instance, therefore, the difference of the rotations will be ~100° less. Here, again, the psicosides, homomorphs of the ribosides, have the smallest difference.

EXPERIMENTAL

General. — Most of the methyl furanosides were available from previous investigations; references to their preparation are given in Table I. 100-MHz, n.m.r. spectra were recorded with a JEOL JNM-4H-100S spectrometer, operating at 25°, for solutions in deuterium oxide; *tert*-butanol (δ 1.23) was used as the internal reference standard. The 270-MHz spectra were recorded at 23° with a Bruker HX-270 spectrometer at the National NMR Centre in Canberra.

In the n.m.r. spectrum of methyl β-D-talofuranoside, H-2 and H-3 resonate at the same frequency; therefore, even at 270 MHz, the signals of H-1 and H-4 are complex, due to "virtual coupling", and do not provide any coupling constants. Several aliquots of praseodymium nitrate were added to the solution in deuterium oxide, and the spectra were recorded at 100 MHz. The signals of H-2 and H-3 shifted downfield, and those of the other protons shifted upfield, as has been observed in similar cases[17]. After the addition of 0.12 equiv. of the salt, H-2 and H-3 were not yet separated, but the signals of H-1 (at δ 4.63) and H-4 (δ 3.88) were of first order, and yielded the respective coupling-constants. With 0.31 equiv. of the salt, H-3 (δ 4.61), H-2 (δ 4.38), and H-1 (δ 4.14) were all well separated, and of first order.

The methyl D-*altrofuranosides.* — D-Altrose (2.6 g) was added to methanol (40 mL) in which acetyl chloride (14 μL) had been dissolved. The mixture was boiled under reflux for 3 h, cooled, made neutral with sodium hydrogencarbonate, filtered, and evaporated. The residue was fractionated on a column of Bio Rad AG-1 X-2 (OH^-) resin (200–400 mesh), with water as the eluant.

The last fraction (dextrorotatory) contained methyl α-D-altrofuranoside, crystals from ethyl acetate; m.p. 100°, $[\alpha]_D^{25}$ +102.2° (*c* 1.1, water).

Anal. Calc. for $C_7H_{14}O_6$: C, 43.29; H, 7.27. Found: C, 43.12; H, 7.40.

The penultimate fraction (levorotatory) contained methyl β-D-altrofuranoside, crystals from ethyl acetate; m.p. 98–100°, $[\alpha]_D^{25}$ —94.5° (*c* 1.0, water).

Anal. Calc. for $C_7H_{14}O_6$: C, 43.29; H, 7.27. Found: C, 42.86; H, 7.28.

Calculations of optical rotations. — We followed the method of Lemieux and Martin[25], using the following values for the asymmetrical, conformational units: O/O 45, O/C 50, O/C_o 115, C/C = C/C_o 40, and O/O_r = O/C_r 90°. These values apply to dihedral angles of 60°; for other angles, the values were calculated on the assumption that they are proportional to the sine function of the dihedral angle.

The dihedral angles within the furanose ring in the twist conformations were taken as 15, 35, 40, 35, and 15°; these are close to the average values found by Sundaralingam[19] for furanoses in the crystalline state. For the envelope forms, the internal dihedral angles were taken as 40, 20, 0, 20, and 40°.

The partial contribution of the hydroxymethyl group in pentofuranosides to the optical rotation will depend on the relative population of its three staggered rotamers, which was estimated from consideration of steric interactions and of the coupling constants of the methylene hydrogen atoms[26]. The values used ranged from 10 to 45°.

Two examples of the calculations are given next; the first row under the symbols contains the dihedral angles between the atoms shown in the symbols, and the second row gives the contributions to the optical rotation. Interactions of the substituents along the O-1–C-1 bond are given first, followed by those along the C-1–C-2 bond, and so on, around the ring.

O/C_o	O/O	O/O_r	O/C	O/O	O/C	O/C	O/O_r	O/C	C/C	O/O	C/C_o	O/C_o	
Methyl β-D-xylofuranoside-$^3T_2$													
−60	−155	+85	+85	+160	−80	−80	+85	−35	−155	+60	+135	−105°	
−115	−22	+102	+57	+18	−57	−57	+102	−33	−20	+20	+33	−127	Total −99°
Methyl α-D-xylofuranoside-$^2T_3$													
+60	+35	+155	−85	+80	−160	−160	+155	+35	−85	+60	+105	+105°	
+115	+30	+44	−57	+51	−20	−20	+44	+33	−45	+10	+44	+127	Total +356°

ACKNOWLEDGMENTS

This research was supported by a grant from the Australian Research Grants Committee. The author thanks the staff of the National NMR Centre, Canberra, for recording the 270-MHz, n.m.r. spectra, and Mrs. Donna Range for synthesizing some of the methyl furanosides.

REFERENCES

1 C. S. Hudson, *J. Am. Chem. Soc.*, 31 (1909) 66–86.
2 J. Staněk, M. Černý, J. Kocourek, and J. Pacák, *The Monosaccharides*, Czech. Acad. Sci., Prague, 1963, pp. 50–55.
3 R. U. Lemieux and M. Hoffer, *Can. J. Chem.*, 39 (1961) 110–115.
4 S. Guberman and D. Horton, *J. Org. Chem.*, 32 (1967) 294–296.
5 W. N. Haworth and C. R. Porter, *J. Chem. Soc.*, (1929) 2796–2806; J. W. Green and E. Pacsu, *J. Am. Chem. Soc.*, 59 (1937) 1205–1210; 60 (1938) 2056–2057; A. Scattergood and E. Pacsu, *ibid.*, 62 (1940) 903–910.
6 A. K. Bhattacharya, R. K. Ness, and H. G. Fletcher, Jr., *J. Org. Chem.*, 28 (1963) 428–435.
7 M. E. Evans and S. J. Angyal, *Carbohydr. Res.*, 25 (1972) 43–48.
8 S. J. Angyal, C. L. Bodkin, and F. W. Parrish, *Aust. J. Chem.*, 28 (1975) 1541–1549.
9 F. W. Parrish, S. J. Angyal, M. E. Evans, and J. A. Mills, *Carbohydr. Res.*, 45 (1975) 73–83.
10 S. J. Angyal, C. L. Bodkin, J. A. Mills, and P. M. Pojer, *Aust. J. Chem.*, 30 (1977) 1259–1268.
11 R. U. Lemieux and R. Nagarajan, *Can. J. Chem.*, 42 (1964) 1270–1278.

12 J. D. STEVENS AND H. G. FLETCHER, JR., *J. Org. Chem.*, 33 (1968) 1799–1805.
13 L. D. HALL, P. R. STEINER, AND C. PEDERSEN, *Can. J. Chem.*, 48 (1970) 1155–1165.
14 J. W. GREEN, *Adv. Carbohydr. Chem.*, 21 (1966) 95–142.
15 J. F. STODDART, *Stereochemistry of Carbohydrates*, Wiley–Interscience, New York, 1971, pp. 97–102.
16 P. L. DURETTE AND D. HORTON, *Adv. Carbohydr. Chem. Biochem.*, 26 (1971) 109–113.
17 S. J. ANGYAL, D. GREEVES, L. LITTLEMORE, AND V. A. PICKLES, *Aust. J. Chem.*, 29 (1976) 1231–1237.
18 S. J. ANGYAL AND R. G. WHEEN, *Aust. J. Chem.*, 33 (1980), in press.
19 M. SUNDARALINGAM, *J. Am. Chem. Soc.*, 87 (1965) 599–606.
20 S. J. ANGYAL, D. GREEVES, AND J. A. MILLS, *Aust. J. Chem.*, 27 (1974) 1447–1456.
21 DR. J. D. STEVENS, personal communication.
22 C. T. BISHOP AND F. P. COOPER, *Can. J. Chem.*, 41 (1963) 2743–2758.
23 D. H. WHIFFEN, *Chem. Ind. (London)*, (1956) 964–968.
24 J. H. BREWSTER, *J. Am. Chem. Soc.*, 81 (1959) 5475–5483, 5483–5493.
25 R. U. LEMIEUX AND J. C. MARTIN, *Carbohydr. Res.*, 13 (1970) 139–161.
26 R. U. LEMIEUX AND J. T. BREWER, *Adv. Chem. Ser.*, 117 (1973) 121–146.
27 E. L. ELIEL, N. A. ALLINGER, S. J. ANGYAL, AND G. A. MORRISON, *Conformational Analysis*, Interscience, New York, 1965, pp. 385–389.
28 H. PAULSEN AND M. FRIEDMANN, *Chem. Ber.*, 105 (1972) 718–730.