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Conformational analysis of isopropylidene-protected *C*-glycosyl derivatives of 3-deoxy-D-*manno*-2-octulosonic acid (Kdo) in the solid state and in solution

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ABSTRACT

The favoured conformations of a series of *C*-glycosyl derivatives of 4,5:7,8-di-*O*-isopropylidene-3-deoxy-D-*manno*-2-octulosonic acid (Kdo) esters were analyzed by n.m.r. spectroscopy and in one instance by X-ray crystallography. The Kdo derivatives were found to adopt a skew-boat conformation ($B_{3,6}$ + $^{O}S_{3}$) in solution which corresponds well to the solid-state conformation. The skew-boat conformation of the pyranose ring appeared to be imposed solely by the 4,5-dioxolane ring. Molecular-mechanics calculations [MM2(85)] on a model compound identified two low-energy conformations of equal steric energy, namely a skew-boat conformation almost identical to the experimentally observed conformation, and a chair conformation ($^{5}C_{2}$).

INTRODUCTION

In the search for potential inhibitors of lipopolysaccharide biosynthesis in Gram-negative bacteria, we have explored the chemistry of various protected analogues of 3-deoxy-D-*manno*-2-octulosonic acid (Kdo)[1-4]. Of special interest have been 4,5:7,8-diisopropylidene-protected analogues of Kdo, for example, compounds **2**–**14**, synthesized *via* an enolate reaction from protected "2-deoxy-Kdo" (**1**). This reaction turned out to be quite stereoselective in that it mainly gave rise to *β*-*C*-glycosyl derivatives (*α* and *β* refer to the relative orientation of the displaced anomeric oxygen). The conformation of an enolate is generally the major factor that determines the stereochemistry of the product by directing the incoming electrophile to the least sterically hindered side[5]. However, analysis of steric interactions in the *α*- and *β*-forms of these Kdo analogues might also contribute to an understanding of the stereoselectivity in the enolate reaction.

It is noteworthy that a conformational influence on stereoselectivity has been observed in a radical reaction where a diisopropylidene-protected thioglycoside of Kdo

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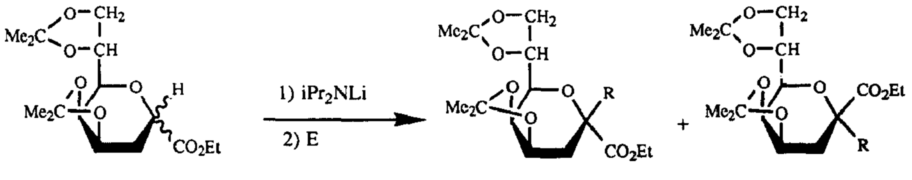
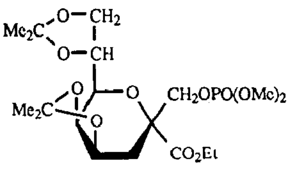


1 **2-10,12** **13**

^{a}	*E*	*R*	*R*
2	$(CN)_2$	CN	
3	CH_2O	CH_2OH	**13** CH_2OH
4	CH_3I	CH_3	
5	$CH_2{=}CHCH_2Br$	$CH_2CH{=}CH_2$	
6	$HC{\equiv}CCH_2Br$	$CH_2C{\equiv}CH$	
7	$PhCH_2Br$	CH_2Ph	
8	$BrCH_2CO_2CMe_3$	$CH_2CO_2CMe_3$	
9	$CH_2{=}CHCO_2Me$	$(CH_2)_2CO_2Me$	
10	$CF_3SO_3CH_2PO(OEt_2)$	$CH_2PO(OEt)_2$	
12	$(CN)_2$	CN	

^{a} Methyl ester



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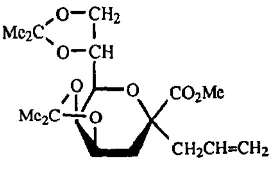

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gave the α- and β-anomeric products in equal amounts, whereas its tetraacetyl-protected counterpart favoured the formation of the α-anomer[3]. The result may be explained by assuming that the diisopropylidene derivative and its radical favour a boat conformation, whereas the acetyl-protected thioglycoside should adopt a chair conformation.

It has been known since the work of Cone and Hough that the pyranose ring in some 1,2:3,4-diisopropylidene-protected galactose derivatives adopt a skew-boat conformation[6] ($B_{2,5}$ + $^{O}S_2$). However, galactose derivatives containing only the 1,2-*O*-isopropylidene group favour a distorted chair conformation (see later)[7,8]. The skew-boat conformation has also been observed in studies of some diisopropylidene-protected analogues of Kdo having the anomeric β-hydroxyl group exchanged by hydrogen[4] or fluorine[9]. However, the conformation of Kdo derivatives having considerably larger 2-substituents has not been determined. In order for the same conformation ($B_{3,6}$ + $^{O}S_3$)

to be favoured also for isopropylidene-protected Kdo derivatives, steric interactions between the 2-substituent and the 4,5-dioxolane ring would have to be overcome.

As conformational aspects are of great importance in the reactions of Kdo derivatives and since the influence of fused dioxolane rings on the pyranose-ring conformation is also of theoretical interest, we have studied a series of Kdo derivatives (**2**–**14**) by n.m.r. spectroscopy, by molecular-mechanics calculations, and in one instance by X-ray crystallography. The present report also includes assignments of all ^{1}H- and ^{13}C-n.m.r. signals of the derivatives. The molecular-mechanics method (or the force-field method) is a standard method for calculation of molecular structure and steric energies. Whereas n.m.r.-spectroscopy and X-ray crystallography give data on the most favoured conformations in solution and in the solid state, respectively, computational methods allow estimation of the energies of many additional conformers of a molecule.

EXPERIMENTAL

Materials. — Compounds **2**–**4**, **6**–**9**, **12**, and **13** were synthesized *via* an enolate reaction as previously described[2]. Reactive electrophiles were added to the enolate prepared from **1** and lithium diisopropylamide in THF at $-75°$. Compounds **5** (ref. 3) and **10** (ref. 1) were prepared by the same method, and compound **11** (ref. 1) was synthesized from **3** and phosphorus oxychloride. Compound **14** (ref. 3) was synthesized *via* a photoinitiated radical-reaction using a phenyl thioglycoside of protected Kdo and allyltributyltin.

X-Ray crystallography. — The selected colourless needle-shaped crystal of **2** ($C_{16}H_{23}NO_7$, $M_w = 341.36$, $D_c = 1.30\ g\cdot cm^{-3}$), which crystallized from hexane–diethyl ether with the approximate dimensions $0.032 \times 0.480 \times 0.176$ mm, was mounted on a computer-controlled Philips PW1100 diffractometer. The intensities of 1696 unique reflections ($\lambda = 1.5418$ Å, $\theta_{max} = 67°$) were collected at room temperature. Lorentz and polarisation corrections were applied during the data reduction, but the rather low absorption effects ($\mu_{X\text{-ray,calc}} = 8.2\ cm^{-1}$) were neglected. The unit cell was monoclinic ($P2_1$) with $a = 14.680(5)$, $b = 6.951(1)$, $c = 8.573(7)$ Å, $\beta = 94.99(2)°$, and $Z = 2$. The cell parameters were refined by least-squares fitting against 29 accurately measured line-positions ($11.5° < 2\theta < 57.5°$) from a Guinier powder photograph. Direct methods using the MULTAN[10] system gave reasonable positions for all non-hydrogen atoms but one. This model was then extended and refined with the programs of the SHELX[11] system. The hydrogen atomic positions were calculated after each cycle of the refinement using geometrical evidence (C–H = 1.08 Å). The methyl groups were treated as if they were rigid. In the last refinement, the positions of the non-hydrogen atoms were refined, together with their anisotropic thermal parameters, and the three group isotropic temperature-factors were refined for the hydrogen atoms*. The largest parameter

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* Tables of anisotropic thermal parameters and calculated structure factors are deposited with and can be obtained from Elsevier Science Publishers B.V., B.B.A. Data Deposition, P.O. Box 1527, Amsterdam, The Netherlands. When applying please quote No. BBA/DD/455/*Carbohydr. Res.*, 211 (1991) 1–16

TABLE I

Fractional atomic parameters ($\times$ 10^4) and equivalent isotropic temperature factors ($\times$ 10^3) for non-hydrogen atoms of compound **2**, with e.s.d.'s in parentheses.

Atom	*X*	*Y*	*Z*	U_{eq}(Å^2)^a
C-1	4932(3)	4617(10)	7485(6)	50(2)
C-2	3991(3)	5038(9)	8077(5)	40(2)
C-3	3861(3)	3866(8)	9565(5)	42(1)
C-4	2875(3)	3788(8)	9973(5)	42(1)
C-5	2196(3)	3456(8)	8516(5)	38(1)
C-6	2688(3)	3106(8)	7051(5)	34(1)
C-7	2043(3)	3082(8)	5564(5)	38(1)
C-8	2525(3)	2541(9)	4125(5)	50(2)
C-9	3941(3)	7149(9)	8370(6)	50(2)
C-10	5803(4)	2210(14)	6424(8)	91(3)
C-11	1640(4)	8203(9)	9678(7)	64(2)
C-12	1720(3)	6049(8)	9874(5)	47(2)
C-13	983(3)	5182(10)	10 804(6)	62(2)
C-14	419(3)	76(11)	3676(6)	72(2)
C-15	1389(3)	354(9)	4369(5)	47(2)
C-16	1867(4)	−1486(9)	4879(7)	74(2)
N-17	3920(3)	8743(9)	8561(7)	76(2)
O-18	3311(2)	4648(0)	6814(3)	40(1)
O-19	5531(3)	5748(9)	7475(5)	90(2)
O-20	4958(2)	2822(8)	7015(5)	72(2)
O-21	2614(2)	5592(7)	10 570(3)	47(1)
O-22	1690(2)	5207(7)	8362(3)	48(1)
O-23	1386(2)	1610(7)	5688(3)	50(1)
O-24	1877(2)	1364(7)	3257(4)	55(1)

^{a} $U_{eq} = \frac{1}{3} \Sigma_i \Sigma_j U_{ij} \cdot a^*_i \cdot a^*_j \cdot a_i \cdot a_j$

shift was less than 0.28 times its e.s.d. when the final linear *R* value of 0.038 was reached for 1239 structure factors, all with unit weights and $F > 6\,\sigma(F)$. The molecule has the absolute configuration shown in Fig. 1 and Table I lists the final atomic coordinates, which refer to the correct enantiomer.

N.m.r. spectroscopy. — ^{1}H-N.m.r. spectra were recorded at 22° with a Bruker AM-500 spectrometer at 500 MHz using a sweep width of 5000 Hz, 32 K data points, and a recycle time of 3.3 s. The ^{1}H-n.m.r. spectra were analyzed by first-order approximations; coupling constants were measured from expanded spectra and were refined by use of the Jeol FASNO 5 n.m.r. spectrum simulation-program.

^{13}C-N.m.r. spectra were recorded at 22° with a Jeol FX-90Q spectrometer at 22.61 MHz using a sweep width of 4600 Hz, 16 K data points, and a recycle time of 3.0 s. Spectra were proton noise-decoupled. All ^{13}C-n.m.r. signals of **2**–**4** and **13** were assigned by use of a graphical method involving proton off-resonance spin-decoupled spectra[12,13]. The ^{13}C-n.m.r. spectra of the remaining compounds were assigned by analogy. Signals due to C-4 and C-6 were unambiguously assigned by use of ^{13}C-[^{1}H] selective decoupling.

Chemical shifts were referenced to tetramethylsilane (Me_4Si).

^{31}P-N.m.r. spectra were recorded at 22° with a Jeol FX-90Q spectrometer at 36.21 MHz by use of a sweep width of 3627 Hz, 8 K data points, a recycle time of 1.6 s, and 10% H_3PO_4 (δ 0 p.p.m.) as the external reference. Data from ^{31}P-n.m.r. spectra are presented in the footnotes of Tables VI and VII.

Molecular-mechanics calculations. — Force-field calculations [MM2(85)][14] on model compound **15**, a substituted 3,7,9-trioxabicyclo[4,3,0]nonane, were performed on a Microvax II computer by use of the interactive graphics program MIMIC[15]. The lack of reliable parameters (for example torsion-angle parameters for $O–C_{sp^3}–C_{sp}–N_{sp}$ and $O–C_{sp^3}–C_{sp^2}–O$) prevented us from using compounds **2**–**14** in the calculations. To span the conformational space of the pyranose ring, 18 different starting geometries were selected. These included the two chair conformations $^5C_2$ and $^2C_5$, all conformations on the boat–skew-boat pseudorotational itinerary[16], and also the half-chairs $^OH_6$ and $^5H_6$ and half-boats ^5E and E_6. The starting geometries of the 4,5-dioxolane ring and the C-6 exocyclic side-chain were taken from X-ray diffraction data.

RESULTS AND DISCUSSION

X-Ray crystallography of compound **2**. — The molecular structure of compound **2** is shown in Fig. 1. The pyranose ring adopts a conformation close to a boat ($B_{3,6}$). The r.m.s. torsion angle is 40.9°. The ring-puckering parameters, calculated according to Cremer and Pople[17], are Q = 0.045(6) Å, θ = 86.1(5)°, and Φ = 299.1(5)°. The cyanide group is quasi-axially and the methyl ester group is quasi-equatorially oriented. The r.m.s. torsion angle is 23.6° for the five-membered ring at C-6, and 25.5° for the fused ring at C-4–C-5. The calculated ring-puckering parameters for these two rings are Q = 0.302(5) and 0.316(5) Å, and Φ = −118.1(8) and 118.3(8)°, respectively. The bond

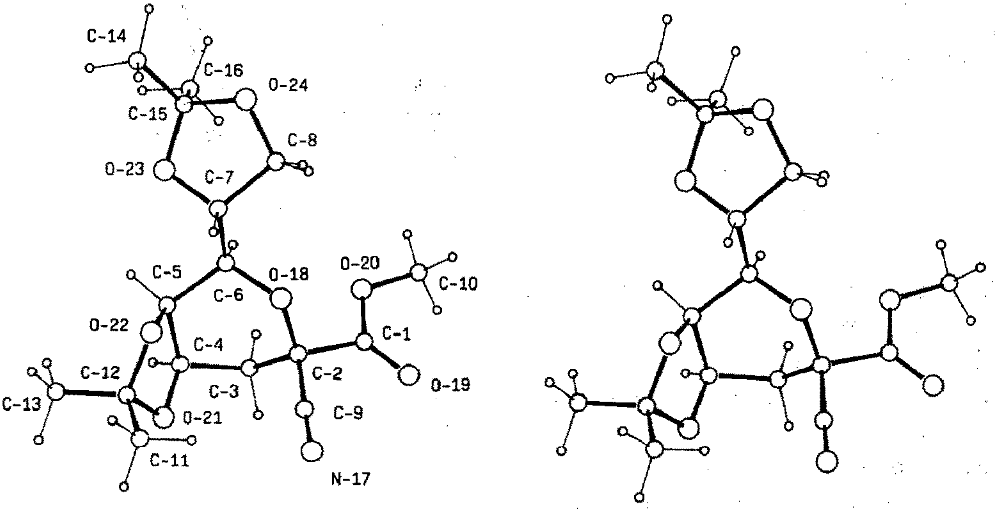


Fig. 1. Molecular structure of compound **2** obtained from X-ray crystallography.

TABLE II

Intramolecular bond lengths (Å) and bond angles (°) of compound **2** involving the non-hydrogen atoms, with e.s.d.'s in parentheses.

Distances (Å)

C-1–C-2	1.541(7)	C-7–C-8	1.521(6)
C-1–O-19	1.180(8)	C-7–O-23	1.420(6)
C-1–O-20	1.313(8)	C-8–O-24	1.416(6)
C-2–C-3	1.539(7)	C-9–N-17	1.121(9)
C-2–C-9	1.492(9)	C-10–O-20	1.443(8)
C-2–O-18	1.434(5)	C-11–C-12	1.510(9)
C-3–C-4	1.520(6)	C-12–C-13	1.522(8)
C-4–C-5	1.546(6)	C-12–O-21	1.429(6)
C-4–O-21	1.420(7)	C-12–O-22	1.420(6)
C-5–C-6	1.522(6)	C-14–C-15	1.506(7)
C-5–O-22	1.426(7)	C-15–C-16	1.505(9)
C-6–C-7	1.520(6)	C-15–O-23	1.429(6)
C-6–O-18	1.434(5)	C-15–O-24	1.426(6)

Angles (°)

C-2–C-1–O-19	124.4(6)	C-8–C-7–O-23	104.5(4)
C-2–C-1–O-20	109.4(4)	C-7–C-8–O-24	103.3(4)
O-19–C-1–O-20	126.1(5)	C-2–C-9–N-17	178.1(6)
C-1–C-2–C-3	110.6(4)	C-11–C-12–C-13	113.5(5)
C-1–C-2–C-9	107.5(5)	C-11–C-12–O-21	109.1(4)
C-1–C-2–O-18	107.5(4)	C-11–C-12–O-22	108.1(4)
C-3–C-2–C-9	111.7(4)	C-13–C-12–O-21	111.2(4)
C-3–C-2–O-18	113.4(3)	C-13–C-12–O-22	110.3(4)
C-9–C-2–O-18	105.8(4)	O-21–C-12–O-22	104.2(4)
C-2–C-3–C-4	113.5(4)	C-14–C-15–C-16	114.0(5)
C-3–C-4–C-5	112.2(4)	C-14–C-15–O-23	108.8(4)
C-3–C-4–O-21	110.1(4)	C-14–C-15–O-24	108.2(4)
C-5–C-4–O-21	104.4(4)	C-16–C-15–O-23	108.8(4)
C-4–C-5–C-6	111.9(4)	C-16–C-15–O-24	111.4(4)
C-4–C-5–O-22	104.0(4)	O-23–C-15–O-24	105.3(4)
C-6–C-5–O-22	109.9(4)	C-2–O-18–C-6	116.4(3)
C-5–C-6–C-7	112.8(3)	C-1–O-20–C-10	115.9(5)
C-5–C-6–O-18	110.6(4)	C-4–O-21–C-12	108.2(4)
C-7–C-6–O-18	104.3(3)	C-5–O-22–C-12	107.0(4)
C-6–C-7–C-8	112.5(4)	C-7–O-23–C-15	109.5(4)
C-6–C-7–O-23	108.9(4)	C-8–O-24–C-15	106.7(4)

lengths and bond angles in the molecule generally conform to expected values (Table II).

The crystal packing of **2** is illustrated in Fig. 2. Most of the intermolecular distances less than 3.6 Å, involving non-hydrogen atoms, were observed between a heteroatom and a carbon atom (Table III). This observation may indicate that the crystal structure is stabilized not only by conventional van der Waals forces but also by favourable electrostatic interactions.

Molecular-mechanics calculations on compound **15**. — The energy-minimization process starting from the pyranose-ring conformations $B_{3,6}$, $^{2,5}B$, $^{4,O}B$, $^{2}S_{6}$, $^{O}S_{3}$, ^{5}E, $^{5}H_{6}$,

TABLE III

Intermolecular distances in the crystal of compound **2** less than 3.6 Å between the non-hydrogen atoms, with e.s.d.'s in parentheses.

Atom A	*Atom B*	*Distance (Å)*
C-3	O-19[a]	3.397(7)
C-8	O-19[b]	3.502(7)
O-21	C-10[c]	3.502(8)
C-3	N-17[a]	3.505(7)
N-17	O-20[d]	3.531(8)
C-13	O-24[e]	3.565(8)

Symmetry operations: [a] $-x-1, y-0.5, -z$. [b] $-x-1, y-0.5, -z-1$. [c] $-x-1, y+0.5, -z$. [d] $x, y+1, z$. [e] $x, y, z+1$.

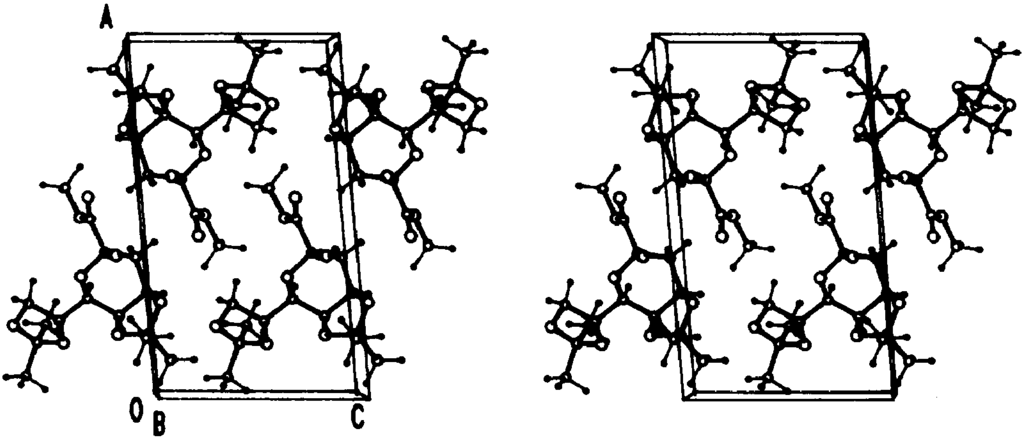


Fig. 2. A crystal-packing illustration of the unit cell for the nitrile **2**.

and $^{O}H_6$ led to a skew-boat conformation ($B_{3,6}$ + $^{O}S_3$, Fig. 3a), whereas $^{4}S_2$, $^{5}C_2$, and E_6 resulted in a chair conformation ($^{5}C_2$, Fig. 3b). These two conformations had no significant difference in steric energy. Torsion angles for the ring atoms of the two low-energy conformations are found in Table VIII. Energy minimization of the remaining starting geometries ($B_{4,O}$, $^{3,6}B$, $B_{2,5}$, $^{2}S_4$, $^{3}S_o$, $^{6}S_2$ and $^{2}C_5$ conformations) led to insignificantly populated conformations having relative steric energies > 5 kcal/mol.

The solid-state conformation of **2** is very similar to the MM2-minimized skew-boat conformation (Tables IV and VIII); a best fit of the pyranose-ring atoms of these compounds gave an average distance of 0.074 Å.

N.m.r. spectroscopy of compounds **2–14**. — ^{1}H- And ^{13}C-n.m.r. chemical shifts and $^{3}J_{H,H}$ coupling constants for **2–14** are listed in Tables V–VII.

For compound **2**, ^{1}H-n.m.r. spectroscopic data were compared with data from X-ray crystallography. Torsion angles from the X-ray structure were used to calculate approximate $^{3}J_{H,H}$ coupling constants according to a modified Karplus equation[18]

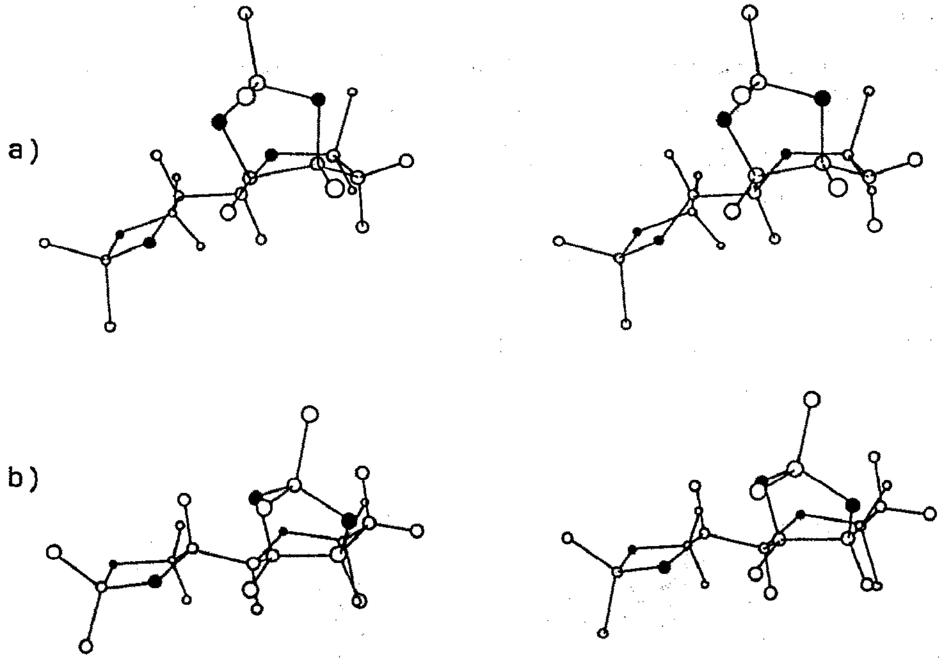


Fig. 3. Stereo views of the MM2(85) minimized (a) *skew-boat* and (b) *chair* conformations of the model compound **15**. The hydrogen atoms, except those bonded to the pyranose rings, are omitted.

TABLE IV

Observed and calculated values of vicinal coupling-constants for ring protons in compound **2** and low-energy conformations of model compound **15**, indicating that **2** adopts a skew-boat conformation both in solution and in the solid state. In addition calculated proton torsion angles are given.

Compound	*Coupling constants (Hz)*				
	$J_{3_1,4}$	$J_{3_2,4}$	$J_{4,5}$	$J_{5,6}$	$J_{6,7}$
2[a]	2.4	3.1	8.3	1.6	8.6
2 *X-Ray*[b,c]	2.1 (−74)	3.9 (45)	7.6 (4)	1.0 (−57)	9.6 (−178)
15 *Skew-boat*[b,d]	3.4 (−63.4)	3.1 (50.7)	7.6 (−4.2)	1.0 (−57.8)	9.4 (−176.6)
15 *Chair*[b,d]	9.5 (−158.5)	6.9 (−41.8)	4.9 (37.5)	1.9 (−48.9)	9.6 (−178.8)

[a] Observed coupling constants. [b] Calculated coupling constants by use of parameter set D and E, ref. 18. [c] Torsion angles (H_x-C-C-H_y) calculated from X-ray data are given in parentheses, estimated uncertainty ±3°. [d] MM2(85)-calculated torsion angles (H_x-C-C-H_y) are given in parantheses.

TABLE V

^{1}H-N.m.r. chemical shifts for **2–14** in $CDCl_3$

Compd. R	*Shift values (δ)*																	
											Ethyl ester			*Isopropylidene*				
	$H\text{-}3_1$	$H\text{-}3_2$	*H-4*	*H-5*	*H-6*	*H-7*	$H\text{-}8_1$	$H\text{-}8_2$	$H\text{-}9_1$	$H\text{-}9_2$	CHH'-	CHH'-	CH_3-	CH_3-				
2 β-CN[a]	2.13	2.68	4.67	4.40	3.51	4.27	4.11	4.18						1.61	1.41	1.40	1.37	
3 β-CH_2OH	1.99	2.24	4.55	4.30	3.45	4.27	4.09	4.39	3.75	3.93	4.22	4.28	1.36	1.51	1.42	1.37[b]		
4 β-CH_3	2.04	2.10	4.52	4.25	3.36	4.26	4.10	4.28	1.52		4.18	4.23	1.30	1.51	1.41	1.37[b]		
5 β-$CH_2CH{=}CH_2$[c]	2.04	2.08	4.49	4.24	3.39	4.27	4.09	4.16	2.51	2.77	4.13	4.21	1.29	1.51	1.41	1.40[b]		
6 β-$CH_2C{\equiv}CH$[d]	2.18	2.25	4.57	4.26	3.36	4.25	4.08	4.17	2.82	2.87	4.22	4.26	1.31	1.50	1.41	1.35[b]		
7 β-CH_2Ph[e]	2.10		4.50	4.24	3.42	4.30	4.05	4.17	3.03	3.35	4.02	4.07	1.15	1.55	1.38	1.38	1.36	
8 β-$CH_2CO_2CMe_3$[f]	1.98	2.18	4.58	4.29	3.52	4.22	4.04	4.30	2.88	3.12	4.22	4.23	1.31	1.53	1.41	1.36[b]		
9 β-$(CH_2)_2CO_2Me$[g]	2.02	2.07	4.48	4.24	3.42	4.24	4.07	4.32	2.10	2.22	4.18	4.22	1.30	1.50	1.41	1.37	1.36	
10 β-$CH_2PO(OEt)_2$[h]	2.00	2.26	4.59	4.29	3.53	4.24	4.05	4.37	2.48	2.84	4.22	4.26	1.33	1.53	1.42	1.37	1.36	
11 β-$CH_2OPO(OMe)_2$[i]	1.96	2.13	4.54	4.31	3.44	4.25	4.06	4.36	4.19	4.57	4.23	4.25	1.32	1.54	1.42	1.36	1.36	
12 β-CN	2.13	2.68	4.66	4.39	3.51	4.28	4.11	4.18			4.34			1.36	1.61	1.41	1.40	1.37
13 α-CH_2OH[j]	1.77	2.66	4.55	4.26	3.50	4.34	4.07	4.14	3.65			4.16	4.25	1.29	1.44	1.43	1.38	1.32
14 α-$CH_2CH{=}CH_2$[k]	1.77	2.75	4.52	4.28	3.35	4.33	4.04	4.13	2.42	2.53				1.43	1.42	1.36	1.32	

[a] Methyl ester 3.89. [b] Overlapping peaks. [c] $CH_2CH{=}CH_2$ 5.74; $CH_2CH{=}CHH'$ 5.01–5.11. [d] $C{\equiv}CH$ 2.00. [e] Aromatic 7.14–7.26. [f] CMe_3 1.40. [g] $CCH_2CHH'CO_2$ 2.42–2.49. [h] $POCH_2CH_3$ 4.00–4.09; $POCH_2CH_3$ 1.28, 1.29. [i] $POCH_3$ 3.73, 3.73. [j] OH 2.25. [k] Methyl ester 3.70; $CH_2CH{=}CH_2$ 5.77; $CH_2CH{=}CHH'$ 5.08–5.17.

TABLE VI

Coupling constants for **2–14**

Compd. R	*J (Hz)*										*Ester*	
	$^2J_{3_1,3_2}$	$^3J_{3_1,4}$	$^3J_{3_2,4}$	$^3J_{4,5}$	$^3J_{5,6}$	$^3J_{6,7}$	$^3J_{7,8_1}$	$^3J_{7,8_2}$	$^2J_{8_1,8_2}$	$^2J_{9_1,9_2}$	$^2J_{CHH'}$	$^3J_{CH_2,CH_3}$
2 β-CN[a]	−15.5	2.4	3.1	8.3	1.6	8.6	6.1	3.6	−8.9			
3 β-CH_2OH	−15.8	3.4	3.4	7.7	1.8	8.8	6.2	3.4	−8.6	−11.1	−10.9	7.2
4 β-CH_3	−15.1	4.7	4.0	7.2	2.0	8.6	5.8	3.7	−8.3		−10.8	7.2
5 β-$CH_2CH=CH_2$[b]	−15.2	4.9	4.4	7.1	1.7	8.4	nd[c]	nd[c]	nd[c]	−13.8	nd[c]	7.1
6 β-$CH_2C\equiv CH$[d]	−15.5	3.7	4.2	7.4	2.0	8.5	6.2	3.8	−8.7	−16.4	−10.8	7.1
7 β-CH_2Ph	nd[c]	[e]	[e]	6.9	1.9	8.4	6.2	4.1	−8.7	−13.5	−10.7	7.1
8 β-$CH_2CO_2C(Me_3)$	−15.5	3.3	3.6	7.7	1.9	8.7	6.2	4.0	−8.5	−14.7	nd[c]	7.2
9 β-$CH_2CH_2CO_2Me$[f]	−15.2	4.1	4.5	7.2	2.0	8.6	6.2	3.9	−8.6	nd[c]	−10.8	7.1
10 β-$CH_2PO(OEt)_2$[g]	−15.5	3.1	3.7	7.6	1.8	8.8	6.3	3.7	−8.6	−15.2	−10.7	7.1
11 β-$CH_2OPO(OMe)_2$[h]	−15.9	3.1	3.4	7.7	1.5	8.7	6.4	3.7	−8.5	−10.1		7.2
12 β-CN	−15.5	2.4	3.2	8.2	1.6	8.6	6.2	3.7	−8.8			7.1
13 α-CH_2OH	−15.3	2.2	3.2	8.1	1.7	7.0	4.9	6.3	−8.8	nd[c]	−10.8	7.1
14 α-$CH_2CH=CH_2$[a,i]	−15.4	2.1	3.4	8.1	1.8	8.2	3.8	6.1	−8.9	nd[c]		

[a] Methyl ester. [b] $^3J_{9_1,CH=CH_2} = 8.2$; $^3J_{9_2,CH=CH_2} = 6.4$; $^2J_{CH=CHH'}$, $^3J_{CH=CHH}$ and $^3J_{CH=CHH'}$ nd. [c] nd = not determined. [d] $^4J_{9_1,C\equiv CH} = -2.5$; $^4J_{9_2,C\equiv CH} = -2.7$. [e] $^3J_{3_1,4} + {}^3J_{3_2,4} = 9.6$. [f] $^3J_{9,CH_2CO_2}$ and $^2J_{CHH'CO_2}$ nd. [g] $^4J_{3_1,P} = 4.5$; $^4J_{3_2,P} = 1.3$; $^2J_{9_1,P} = 19.0$; $^2J_{9_2,P} = 17.6$; sign not determined for $^2J_{H,P}$ and $^4J_{H,P}$; phosphate ester $^2J_{POCHH'}$, $^3J_{POCH_2}$ nd; $^3J_{POCH_2,POCH_3} = 7.0$. [h] $^3J_{9_1,P} = 6.0$; $^3J_{9_2,P} = 6.5$; $^3J_{POCH_3} = 11.1$. [i] Coupling constants for the $CH_2CH=CH_2$ residue nd.

TABLE VII

^{13}C-N.m.r. chemical shifts

	Chemical shifts (δ)												
										Ester		*Isopropylidene*	
Compd. R	*C-1*	*C-2*	*C-3*	*C-4*	*C-5*	*C-6*	*C-7*	*C-8*	*C-9*	CH_2	CH_3	$\mathit{C}(CH_3)_2$	$C(\mathit{CH}_3)_2$
2 β-$CN^{2,a}$	167.10	69.30	30.69	68.52	70.91	73.63	72.90	66.72	116.77			110.01, 109.33	26.94, 25.48, 24.90, 24.56
3 β-CH_2OH^2	172.95	78.88	27.80	70.04	71.65	73.81	73.69	66.77	68.44	61.46	14.21	109.33, 109.14	27.18, 26.25, 25.08, 24.83
4 β-$CH_3{}^2$	174.58	75.92	32.25	70.89	71.49	73.93	73.78	67.00	27.17	61.12	14.21	109.27, 109.12	27.17, 26.72, 25.72[b]
5 β-$CH_2CH{=}CH_2{}^{3,c}$	173.26	80.54	31.19	70.87	71.67	73.91	73.76	67.03	44.90	61.10	14.39	109.25[b]	27.15, 26.95, 25.45, 25.31
6 β-$CH_2C{\equiv}CH^{2,d}$	172.09	70.99	30.06	70.69	71.64	74.08	73.68	66.95	29.01	61.52	14.26	109.37, 109.27	27.12, 26.57, 25.17, 25.08
7 β-$CH_2Ph^{1,e}$	173.03	79.21	31.76	70.84	71.59	73.97	73.68	67.02	46.51	60.92	14.04	109.22[b]	27.02[b], 25.42, 25.32
8 β-CH_2CO_2*t*-$Bu^{1,f}$	172.78[m]	75.82	30.06	70.74	71.79	73.63	73.43	66.85	45.81	61.12	14.16	109.32[b]	27.07, 26.22, 25.17, 25.03
9 β-$(CH_2)_2CO_2Me^{1,g}$	173.43	77.47	32.05	70.79	71.64	73.98	73.68	66.90	35.39	61.27	14.26	109.32, 109.22	27.22, 26.72, 25.27[b]
10 β-$CH_2PO(OEt)_2{}^{1,h}$	172.60	75.46	31.34	70.74	71.59	73.76	73.66	66.85	36.87	61.47	14.13	109.40, 109.30	27.14, 26.25, 25.20, 24.88
11 β-$CH_2OPO(OMe)_2{}^{1,i}$	171.59	77.19	27.72	69.89	71.74	73.83	73.63	66.85	72.08	61.62	14.13	109.37[b]	27.17, 26.12, 25.12, 24.83
12 β-CN^2	167.19	69.72	30.76	68.75	71.16	73.75	73.19	66.83	117.17	63.62	14.02	110.32, 109.70	27.05, 25.63, 25.02, 24.71
13 α-CH_2OH^2	169.01	77.08	28.09	69.90	72.31	72.47	74.44	66.88	67.43	61.50	14.25	109.74, 109.09	26.91, 25.43, 25.09, 24.63
14 α-$CH_2CH{=}CH_2{}^{3,j}$	174.06	nd	31.69	69.97	72.32	72.46	74.01	67.28	43.60			109.50, 109.25	27.15, 25.21, 25.01, 24.66
α-$(CH_2)_2CO_2Me^{2,k}$	172.78[l]	75.77	32.40	69.89	72.08	72.33	74.93	67.20	33.70	61.17	14.21	109.52, 109.12	26.97, 25.22, 25.02, 24.62
α-CN^2	164.86	69.18	32.5	71.09	72.27	73.38	74.43	66.96	116.43	63.50	14.21	110.07, 109.39	26.93, 26.00, 25.20[b]

[a] $CO_2\mathit{C}H_3$ 53.88. [b] Overlapping peaks. [c] $CH_2\mathit{C}H{=}CH_2$ 132.34; $CH_2CH{=}\mathit{C}H_2$ 118.43. [d] $CH_2\mathit{C}{\equiv}CH$ 78.86; $CH_2C{\equiv}\mathit{C}H$ 77.56. [e] Phenyl carbons *C'-1* 135.94; *C'-2, C'-3, C'-5, C'-6* 130.31, 127.81; *C'-4* 126.72. [f] $CH_2\mathit{C}O_2C$ 168.85[m]; $\mathit{C}(CH_3)_3$ 80.61; $C(\mathit{C}H_3)_3$ 27.92. [g] $CH_2\mathit{C}H_2CO_2$ 28.71; $CH_2CH_2\mathit{C}O_2$ 173.43; $CO_2\mathit{C}H_3$ 51.50. [h] $PO\mathit{C}H_2$ 61.60; 61.23; ($^2J_{POCH_2}$ = 6.4 Hz, sign not determined); $POCH_2\mathit{C}H_3$ 16.39; 16.32; ($^3J_{POCH_2CH_3}$ = 6.4 Hz); $^3J_{1,P}$ = 2.6 Hz; $^2J_{2,P}$ = 3.9 Hz, sign not determined; $^3J_{3,P}$ = 12.4 Hz; $^1J_{9,P}$ = 181 Hz; $^{31}P(\delta)$ 25.28. [i] $PO\mathit{C}H_3$ 54.26; 54.16; ($^2J_{POCH_3}$ = 5.7 Hz, sign not determined); $^3J_{2,P}$ = 7.9 Hz; $^2J_{9,P}$ = 4.5 Hz, sign not determined; $^{31}P(\delta)$ 0.38. [j] $CH_2\mathit{C}H{=}CH_2$ 131.68; $CH_2CH{=}\mathit{C}H_2$ 119.22; $CO_2\mathit{C}H_3$ 52.08. [k] $CH_2\mathit{C}H_2CO_2$ 27.96; $CH_2CO_2\mathit{C}H_3$ 51.74; $CH_2\mathit{C}O_2Me$ 173.3. [l,m] Assignments may be reversed.

TABLE VIII

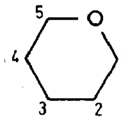
Comparison of X-ray crystallographic and n.m.r.-spectroscopic data of compounds **2** and **15** with selected compounds from the literature, and torsion angles for atoms in the pyranose ring of **2**, the two low-energy conformations of compound **15** obtained from molecular-mechanics calculations, and selected compounds from the literature

Torsion angle[a]	*Pyranose ring conformation*[a]							
	$B_{2,5}$	$B_{2,5} + {}^{O}S_2$			${}^{4}C_1$			
	Compound							
	2 *X-ray*	**15** *skew-boat*	α-**17**[9,b]	**19**[21]	**15** *chair*	**20**[7,c]	**22**[22]	**23**[23]
	Torsion angle (deg)							
O–C-1–C-2–C-3	−43.9	−30.6	−17.7	−34.7	55.4	37.5	58.8	59.3
C-1–C-2–C-3–C-4	42.6	45.1	37.4	50.9	−45.2	−42.9	−41.0	−46.6
C-2–C-3–C-4–C-5	5.2	−4.8	−5.5	−9.5	38.7	55.5	34.5	40.7
C-3–C-4–C-5–O	−54.8	−50.0	−45.6	−46.2	−42.5	−60.3	−43.2	−47.1
C-4–C-5–O–C-1	56.7	69.0	70.6	67.0	55.7	55.8	61.4	60.0
C-5–O–C-1–C-2	−6.8	−26.8	−36.1	−24.7	−62.3	−44.1	−70.5	−65.9

Vicinal coupling constants

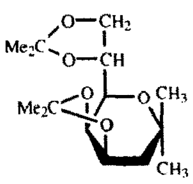
Compound	$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$	$J_{5,6}$
2		2.4;3.1	8.3	1.6	8.6
16[4]	5.8;11.6	2.8;2.7	8.0	1.5	4.3
α-**17**[9]		2.8;3.7	7.6	2.1	8.5
18[20]	5.0	2.4	7.9	1.6	nd[d]
19[20]	5.0	2.5	8.0	1.9	7.8
20[7]	4.6	7.4	3.0	2.4	6.5;6.8
21[8]	3.9	5.6	3.6	4.2;5.0	

[a] For convenience, the pyranose ring atoms are numbered in the same way; see additional formulas. [b] $B_{2,5}$ conformation according to the authors. [c] The crystal structure of **20** actually consists of two different, although very similar, conformations. [d] nd = not determined.



(Table IV). The calculated values for all coupling constants in the skew-boat conformation were in good agreement with the observed coupling constants (within ± 1 Hz, Table IV). This result indicates that **2** adopts a solution conformation very similar to that observed by X-ray crystallography.

As mentioned earlier, the skew-boat conformation has been established for the Kdo analogue **16** and analogues thereof[4], as well as for the protected Kdo-fluorides[9] **17**. In addition, 1,2:3,4-di-*O*-isopropylidene-D-galactopyranose derivatives (such as **18** and **19**) are known to adopt a skew-boat conformation in solution[6,19–21], whereas in 1,2-*O*-isopropylidene-galactopyranose derivatives (such as **20** and **21**) a flattened-chair conformation appears more stable[7,8]. Interestingly, a distorted-chair conformation has been observed by X-ray crystallography of two 3,4-*O*-alkylidene-galactopyranose derivatives, compounds **22** (ref. 22), and **23** (ref. 23). However, it is important to note that



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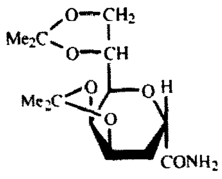

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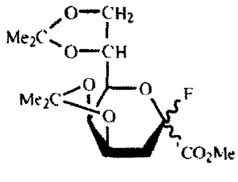

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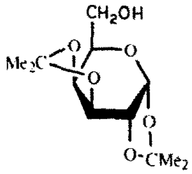

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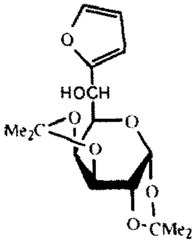

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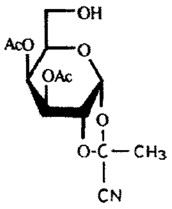

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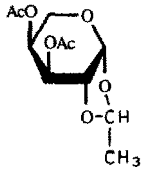

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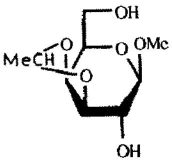

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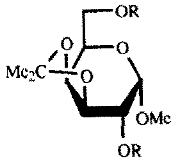
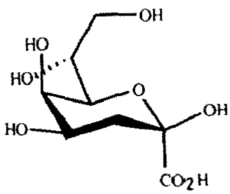


23

R= 2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl-



β-Kdo

the solid-state conformation(s) may differ considerably from favoured conformations in solution. Table VIII summarizes conformational data from the literature.

In the series of compounds studied in this paper, the observed coupling-constants are all of the same magnitude, which leads to the conclusion that all compounds adopt essentially the same conformation, namely the skew-boat conformation. The C-2 substituents in **2**–**12** and the ester functionality in **13** and **14** are thus quasi-axially disposed, in spite of unfavourable 1,3-*syn*-diaxial interactions with the dioxolane ring at C-4–C-5. The skew-boat conformation of **3** and **13** could be further confirmed by determination of the ${}^3J_{C,H}$ coupling constants between the ^{13}C-labeled hydroxymethyl group and the protons of the 3-methylene group*[2,24].

Some conformational flexibility was observed in compounds **4**, **5**, **7**, and **9**. The larger ${}^3J_{3,4}$ coupling constants in these compounds† might be explained by a change in the conformational distribution, with contributions of a small percentage of the low-energy chair conformation, which was also identified in the molecular-mechanics calculations (Table IV). The smaller value of the ${}^3J_{4,5}$ coupling constant observed in spectra of these compounds also support this interpretation.

The bulky C-7–C-8 side chain is equatorially oriented in all compounds. The ${}^3J_{6,7}$ coupling constant (ranging from 8.4 to 8.8 Hz) and the small ${}^3J_{5,6}$ coupling constant are in agreement with a preponderant *trans*-diaxial relationship between H-6 and H-7. The ${}^3J_{6,7}$ coupling constant in the α-glycosyl hydroxymethyl derivative (**13**), is considerably smaller (7.0 Hz) than that observed in any other compound, possibly because of intramolecular hydrogen bonding.

The 7,8-dioxolane ring appears to be more flexible than the rest of the molecule. The observed coupling-constants (${}^3J_{7,8_1}$ = 6.1 Hz and ${}^3J_{7,8_2}$ = 3.6 Hz) probably reflect an average of several different conformations in equilibrium. The size of these coupling constants varies only little in **2**–**12**. However, in the α derivatives **13** and **14**, these coupling constants are quite different, indicating that the side-chain conformation is affected by the C-2 substituents.

The ^{13}C-n.m.r. chemical shifts of **2**–**14** are listed in Table VII. Typically, the chemical shifts of C-2 were found between δ 75.5 and 80.5 p.p.m. The nitrile **2** and the propargyl derivative **6** show upfield shifts of C-2, an anisotropic effect attributable to shielding by the triple bonds. The C-2 substituents also appear to influence the chemical shifts of C-3, but the chemical shifts of the other carbon atoms in the pyranose ring are relatively independent of the C-2 substituent. ^{13}C-N.m.r. spectroscopic data do not provide any additional information on the pyranose-ring conformation; the data may, however, be useful when assigning spectra of similar compounds.

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* For the compounds studied, quasi-axial deoxy protons (H-3_1) appear upfield of quasi-equatorial deoxy protons (H-3_2). In compounds where the C-2 substituent is attached to the ring via a methylene group, the chemical-shift difference is significantly larger in the α derivatives (Δδ 0.89–1.08) than in the β derivatives (δ 0.00–0.26). This trend does not apply to compounds having an *sp*^{2} or *sp*-hybridized carbon atom directly attached to the ring (Table VI).

† In the spectrum of compound **7**, these coupling constants could not be determined directly. However, the sum of ${}^3J_{3_1,4}$ and ${}^3J_{3_2,4}$ (9.6 Hz) was larger (<8 Hz) than that of the other compounds.

CONCLUDING REMARKS

The data presented here show that the *C*-glycosylic ethyl and methyl 2,6-anhydro-3-deoxy-4,5:7,8-di-*O*-isopropylidene-D-*glycero*-D-*talo*- and -D-*galacto*-octonates (**2**–**14**), adopt an unusual pyranose-ring conformation ($B_{3,6}$ + $^{O}S_3$) in solution. This result is corroborated by force-field calculations on the model compound **15**, which provided a low-energy conformation close to the observed conformation of **2** in solution (by n.m.r. spectroscopy) and in the solid state (by X-ray crystallography). From the theoretical calculations, a minimum energy $^5C_2$ chair conformation was also obtained. N.m.r. data indicate the presence of minor amounts of this conformation of some compounds (**4**, **5**, **7**, and **9**) in solution.

An important conclusion to be drawn from the present work is that the 4,5-dioxolane ring in diisopropylidene-protected Kdo analogues imposes a skew-boat conformation on the pyranose ring, thereby completely overpowering the counteracting steric and electronic effects of the C-2 substituent.

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