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Note

Structural and conformational studies of 2,7-anhydro-L-*glycero*-β-D-*manno*-octulopyranose and its per-*O*-acetyl derivative*

Michael G. Ambrose, Alexander J. Fatiadi, and Bruce Coxon
Center for Analytical Chemistry, National Institute of Standards and Technology, Gaithersburg, Maryland 20899 (U.S.A.)

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The physiological properties of the higher monosaccharides and their derivatives (for example, the sialic acids) make them attractive targets for synthetic modification and structural studies. The products of such investigations could be useful in determining correlations between molecular structure and biological function. Thus, the synthesis of such higher-carbon sugars as heptoses[1,2], heptitols[3], octoses[4,5], nonoses[6], and decoses[7,8] has recently received considerable attention. Higher-carbon sugars have been used in the synthesis of mycin-type antibiotics[4,9,10] and chiral segments of macrolides[11]. Thus far, conformational analysis of higher-carbon sugars has been very limited. Angyal and co-workers[12,13] have studied the conformations of heptitols; however, there appear to be no reports of similar studies of octitols, octuloses, or other higher-carbon sugars.

The aim of this paper is to discuss, at length, the structures and conformations of 2,7-anhydro-L-*glycero*-β-D-*manno*-octulopyranose (**3**) and 1,3,4,5,8-penta-*O*-acetyl-2,7-anhydro-L-*glycero*-β-D-*manno*-octulopyranose (**4**). Richtmyer reported the preparation of **3** from D-*erythro*-D-*galacto*-octitol (**1**) which had been isolated from avocado[14,15]. Oxidation of **1** with *Acetobacter suboxydans*, followed by treatment of the resulting syrupy L-*glycero*-D-*manno*-octulose (**2**) with methanol in the presence of a cation-exchange resin, yielded a product that was presumed to be **3** on the basis of the mass spectrum of its per-*O*-trimethylsilyl derivative (molecular ion at *m/z* 582) and the absence of formaldehyde on treatment of the product with periodate[14]. Our examination of **3** and **4**, using both ^{1}H- and ^{13}C-n.m.r. spectroscopy, has confirmed the structure originally assigned by Richtmyer.

The ^{1}H-n.m.r. spectrum of the penta-acetate **4** in chloroform-*d* at 400 MHz displayed five resonances for acetyl methyl protons and a well dispersed, sugar-chain proton region, first-order analysis of which yielded the chemical shifts reported in Table

* Dedicated to Professor Leslie Hough in the year of his 65th birthday.

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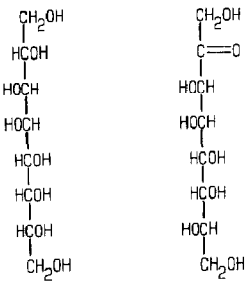

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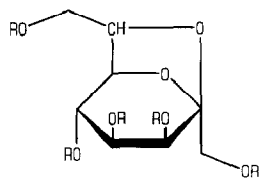


3 R = H

4 R = Ac

TABLE I

^1H and ^{13}C chemical shifts[a] of 2,7-anhydro-L-*glycero*-β-D-*manno*-octulopyranose (**3**) and its 1,3,4,5,8-penta-O-acetyl derivative (**4**)

Derivative	*Parameter*	*Position*									
		1	*1'*	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*8'*
3[b]	δ_H	3.58	3.32	—	3.63	3.68	3.61	4.10	4.13	3.28	3.15
	δ_C	61.10	—	107.75	64.54	70.94	72.23	78.64	75.55	62.59	—
4[c,d]	δ_H	4.50	4.02	—	5.22	5.34	4.89	4.49	4.61	4.18	3.98
	δ_C	61.60	—	106.18	65.43	67.90	71.53	77.53	74.43	63.96	—

[a] In p.p.m. from internal tetramethylsilane. The resonances of H-1 and H-8 are at lower field than those of H-1' and H-8', respectively. [b] In $(CD_3)_2SO$ solution. A trace of trifluoroacetic acid was present in the solution that was used for ^{13}C-n.m.r. spectroscopy; hydroxyl protons HO-1, HO-3, HO-4, HO-5, and HO-8 had δ_H 4.66, 4.40, 4.62, 5.06, and 4.65, respectively. [c] In $CDCl_3$ solution. [d] Acetyl methyl groups had δ_H 2.18, 2.16, 2.10, 2.09, 2.03, and δ_C 20.86, 20.72, 20.75, 20.55, 20.38. Acetyl C=O groups had δ_C 170.55, 170.01, 169.71, 169.46, 169.33.

TABLE II

^1H-N.m.r. coupling constants (Hz) of 2,7-anhydro-L-*glycero*-β-D-*manno*-octulopyranose (**3**) and its 1,3,4,5,8-penta-*O*-acetyl derivative (**4**)

Derivative	$J_{1,1'}$	$J_{3,4}$	$J_{4,5}$	$J_{4,6}$	$J_{5,6}$	$J_{6,7}$	$J_{7,8}$	$J_{7,8'}$	$J_{8,8'}$
3[a]	11.7	5.5	~1.8	1.8	2.0	≤0.9	5.0	8.0	10.7
4	12.2	5.6	1.6	1.6	1.7	0.8	5.7	6.8	11.3

[a] $J_{1,HO-1}$ 6.8, $J_{1',HO-1}$ 5.6, $J_{3,HO-3}$ 8.4, $J_{4,HO-4}$ 3.5, $J_{5,HO-5}$ 4.8, $J_{8,HO-8}$ 5.3, $J_{8',HO-8}$ 6.1 Hz.

I, and the ^1H–^1H coupling constants shown in Table II. A series of selective homonuclear decoupling experiments was used to confirm the ^1H assignments for **4**.

The ^1H-n.m.r. spectrum of the anhydro-octulose **3** in $(CD_3)_2SO$ was more complex, owing to the presence of spin couplings to several hydroxyl protons. In this case, the ^1H-n.m.r. assignments were confirmed by two-dimensional (2D) homonuclear

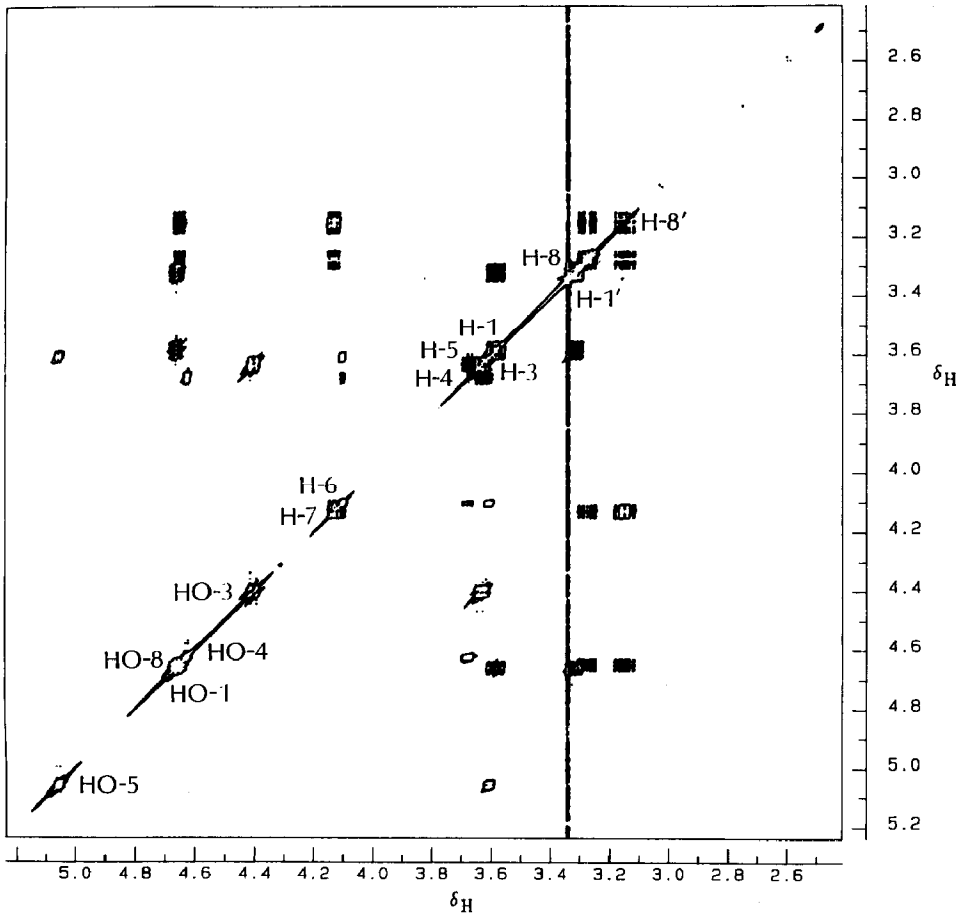
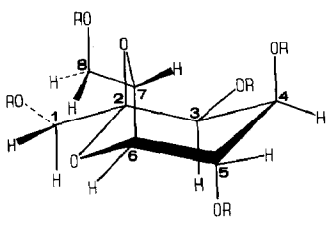


Fig. 1 Contour plot of 2D-COSY ^{1}H-n.m.r. spectrum of 2,7-anhydro-L-*glycero*-β-D-*manno*-octulopyranose (**3**) in $(CD_3)_2SO$ solution at 400 MHz.

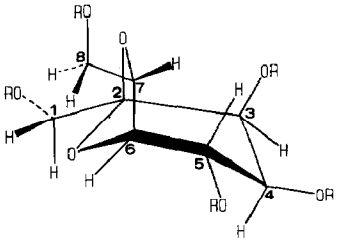
correlation spectroscopy (2D-COSY, see Fig. 1.). The H-4 signal of **4** in its resolution-enhanced 1D ^{1}H-n.m.r. spectrum appeared as a doublet of triplets, thus indicating the presence of three spin couplings to H-4. On the other hand, the resolution-enhanced H-4 signal of **3** in $(CD_3)_2SO$ was observed as a deceptively simple octet, analysis of which indicated the existence of four couplings to H-4, including one hydroxyl proton coupling that was removed by the addition of a trace of trifluoroacetic acid to the solution. A long-range coupling between H-4 and H-6 was confirmed for **4** by selective irradiation of H-6, and for **3**, by the observation of a cross-peak between H-4 and H-6 in the 2D-COSY spectrum (see Fig. 1.).

The significant downfield shifts (0.70–1.66 p.p.m., see Table I) of H-1, H-1', H-3, H-4, H-5, H-8, and H-8' upon acetylation of **3** support the 2,7-anhydro structure originally proposed by Richtmyer. Formation of 3,7- or 4,7-anhydro rings would have resulted in the absence of hydroxyl-proton spin coupling to H-3 and H-4, respectively, as well as the generation of formaldehyde on treatment of **3** with periodate[14].

The small values of the vicinal ^1H–^1H coupling constants of the pyranose ring protons (see Table II) indicate that **3** and **4** exist in chair-like conformations (**3a** and **4a**). In particular, the medium-sized values (5.5–5.6 Hz) for $J_{3,4}$ are appropriate for an axial/equatorial orientation of H-3/H-4, and the smaller values (1.6–2.0 Hz) for $J_{4,5}$ and $J_{5,6}$ are consistent[16] with equatorial/equatorial arrangements of H-4/H-5 and H-5/H-6. Further support for the assignment of chair conformations comes from the long-range coupling constants $J_{4,6}$ = 1.6–1.8 Hz, the magnitudes of which are appropriate[17] for the planar "W" arrangement of H-4 and H-6 in the fused, semi-rigid, bicyclic ring system of **3a** and **4a**.



3a R = H
4a R = Ac



3b R = H
4b R = Ac

The number of possible alternative boat conformations is restricted to such conformations as **3b** and **4b** by the bicyclic ring fusion. However, these slightly distorted boat conformations are unequivocally ruled out, because H-4 and H-5 are diaxial in these conformations and large values of $J_{4,5}$ would therefore be expected. Also, the boat conformations **3b** and **4b** do not contain a planar "W" grouping of H-4 and H-6. Molecular models of the chair conformations (**3a**, **4a**) and the boat conformations (**3b**, **4b**) suggest that the dihedral angle $\varphi_{6,7}$ is close to 90°; in agreement with this orientation, the value $J_{6,7} \leq 0.9$ Hz is small.

^{13}C-N.m.r. data for **3** and **4** have not been reported previously and were obtained for further confirmation of structure. The ^{13}C chemical shift assignments shown in Table I were determined by 2D heteronuclear (^{13}C–^1H) chemical shift correlation, based on the ^1H-n.m.r. assignments described heretofore. A contour plot and projections of the 2D heteronuclear shift correlation spectrum of **4** are shown in Fig. 2. The ^{13}C correlation peaks for the methylene carbons (C-1 and C-8) are characteristically split into AB quartets, since the**BI**linear **R**otation **D**ecoupling (BIRD), vicinal ^1H–^1H decoupling technique[18] that was used does not decouple the methylene protons from each other[19,20]. In agreement with the structure assigned to **4**, its ^{13}C-n.m.r. spectrum showed five acetyl methyl resonances and five carbonyl signals. Additionally, the ^{13}C-n.m.r. spectra of **3** and **4** show quaternary C-2 signals at 106–108 p.p.m. that were not detected by the 2D heteronuclear chemical shift correlation technique, which is based on transfer of polarization from the protons that are directly bonded to carbon atoms.

In summary, the structures and conformations of the anhydro-octulose deriv-

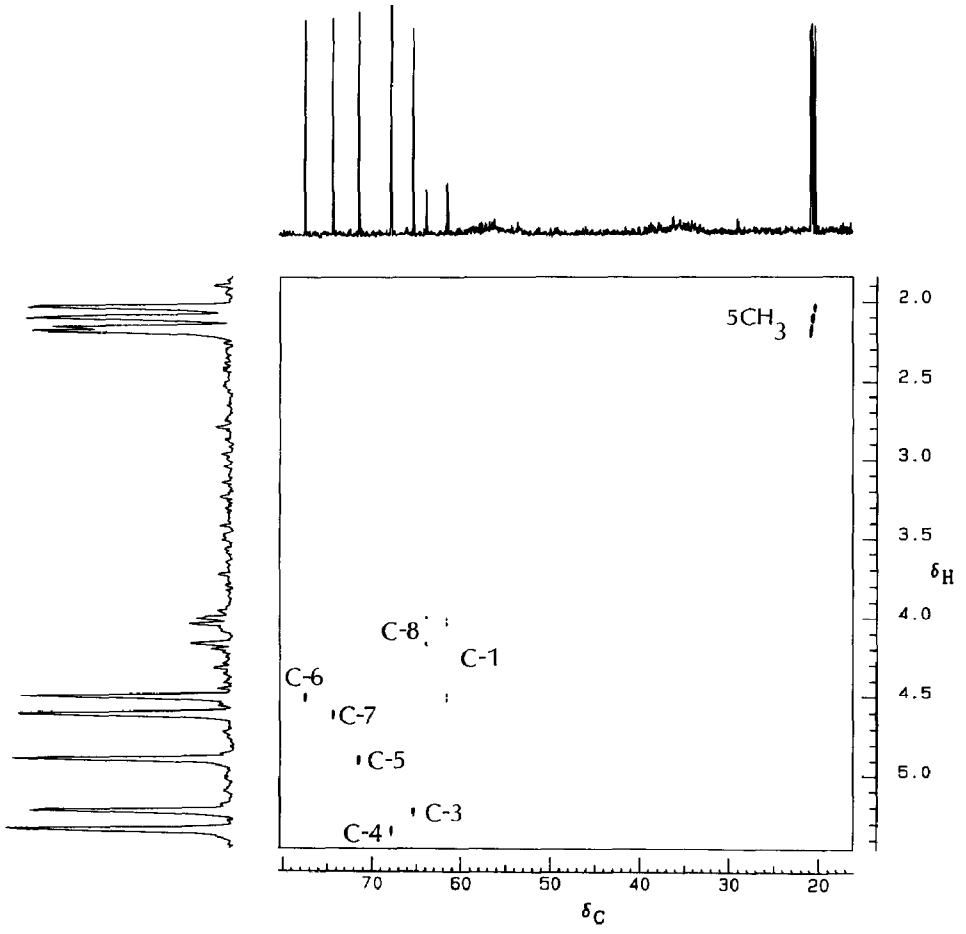


Fig. 2 Contour plot and F_1 and F_2 projections of 2D ^{13}C–^1H chemical-shift-correlated ^{13}C-n.m.r. spectrum of 1,3,4,5,8-penta-*O*-acetyl-2,7-anhydro-L-*glycero*-β-D-*manno*-octulopyranose (**4**) in $CDCl_3$ solution at 100.6 MHz, with ^1H decoupling in both dimensions.

atives **3** and **4** have been verified by 1D and 2D ^1H- and ^{13}C-n.m.r. spectroscopy. It may be noted that **3** and **4** are homologs of 1,6-anhydrohexopyranose derivatives.

EXPERIMENTAL*

General. — The anhydro-octulose penta-acetate **4** was prepared by treatment of **3** with acetic anhydride in pyridine at 0°. However, insufficient material was available for characterization of **4** by traditional methods. The structure of **4** was defined by its ^1H- and ^{13}C-n.m.r. spectra.

*Certain commercial equipment, instruments, and materials are identified in this paper in order to specify adequately the experimental procedure. Such identification does not imply recommendation by the National Institute of Standards and Technology, nor does it imply that the materials or equipment are necessarily the best available for the purpose.

N.m.r. spectroscopy. — N.m.r. spectra were acquired at 300 K, by use of a Bruker Instruments Model WM-400 spectrometer that was equipped with digital frequency generation, a process controller, and a 5-mm dual frequency, ^{13}C–^{1}H probe. 1D ^{1}H-N.m.r. spectra were measured at 400 MHz by using a 90° pulse (35 μs), a spectral width of 1.13 kHz (**3**) or 3.27 kHz (**4**), and either 8192 or 16 384 data points zero-filled to 16 384 or 32 768 points, respectively. Analysis of the 1D ^{1}H-n.m.r. spectrum of **3** was assisted by hydroxyl-proton decoupled spectra obtained by addition of a trace of trifluoroacetic acid to the solution of **3** in $(CD_3)_2SO$. 1D ^{13}C-N.m.r. spectra were obtained at 100.6 MHz by means of a 90° pulse (12 μs), a spectral width of 20 kHz, 16 384 data points zero-filled to 32 768 points, a pulse recycle time of 6.4 s, WALTZ-16 composite pulse ^{1}H decoupling[21], and a line-broadening of 1 Hz.

2D-COSY ^{1}H-n.m.r. spectra were acquired by use of 90° pulses (35 μs), 2048 (t_2) x 512 (t_1) point data sets zero-filled to 1024 points in the t_1 dimension, four scans per spectrum with two dummy scans, and a spectral width of 1.13 kHz in both dimensions. 2D Heteronuclear, carbon–proton chemical-shift-correlated ^{13}C-n.m.r. spectra were recorded by use of 4096 (t_2) x 256 (t_1) point data sets zero-filled to 512 points in the t_1 dimension, 64 scans with two dummy scans, spectral widths of 10.2 kHz in the F_2 dimension and either 1.13 kHz (**3**) or 1.63 kHz (**4**) in the F_1 dimension, and 90° ^{1}H and ^{13}C pulse widths of 29 and 12 μs, respectively. These spectra were obtained with WALTZ-16 ^{1}H decoupling[21] in the F_2 dimension and BIRD ^{1}H–^{1}H (vicinal) decoupling[18] in the F_1 dimension. The average delay periods $1/2J(CH) = 3.45$ and $1/4J(CH) = 1.72$ ms were used. All 2D-n.m.r. data sets were filtered with sine-bell window functions in both dimensions.

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