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Note

Analysis of the hexaacetate of 3,6-anhydro-α,α-trehalose by ^{1}H-n.m.r.-spectroscopy

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The title disaccharide derivative **3** has the anhydro ring in a distorted $^1C_4$(D) conformation, and the other ring in a classic $^4C_1$(D) conformation. The detailed analysis provides a basis of reference for analyzing spectra of related, more-complex systems.

Asymmetrically substituted derivatives of α,α-trehalose are of considerable interest, as detailed in a recent paper[1], for enzymological investigations and in metabolic studies on insects and higher animals. Their chemical synthesis is difficult, as most classical reactions favor symmetrical disubstitution of the disaccharide, although a kinetic acetonation method[2] provides a promising preparative route for monosubstituted derivatives of α,α-trehalose[1]. In earlier work[3] directed toward synthesis of 6-deoxy-α,α-trehalose[4], monotosylation of α,α-trehalose, followed by treatment with lithium aluminum hydride and subsequent acetylation, gave[3] a mixture from which the title compound, 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl 2,4-di-*O*-acetyl-3,6-anhydro-α-D-glucopyranoside (3,6-anhydro-α,α-trehalose hexaacetate, **3**) was isolated crystalline in 10.7% yield by chromatographic separation from the peracetates of the parent disaccharide and of the corresponding 3,6:3′,6′-dianhydro derivative. The ^{1}H-n.m.r. spectrum of **3** was examined in the acetyl-group region[3], and that of the dianhydro derivative was subsequently investigated in more detail[5].

In view of the importance of 3,6-anhydroaldohexopyranose residues in such natural products as marine algal polysaccharides[6] and also in synthetically modified polysaccharides having potentially varied properties[7], and considering the noteworthy changes brought about in aldohexose ring-systems by the ring-inversion resulting from formation of 3,6-anhydro[3,5,7,8] or 1,6-anhydro[9] bridges, we undertook a detailed ^{1}H-n.m.r. spectral analysis of the title compound **3** in comparison with two reference compounds, methyl α-D-glucopyranoside tetraacetate (**2**) and methyl 2,4-di-*O*-acetyl-3,6-anhydro-α-D-glucopyranoside[3] (**1**) as models for the two parts of **3**. The

study provided data of value in monitoring the formation of 3,6-anhydro bridges in related di-, oligo-, and poly-saccharides, and in determining the extent to which the spectrum observed for **3** may be regarded as an additive summation of the spectra of the two models **1** and **2**, and how the linkage between the component residues influences the spectral properties. These studies also furnish reference data for observing the conversion of aldohexopyranose residues into their 3,6-anhydrides in carbohydrate antibiotics that have been chemically modified.

All spectra were recorded in chloroform-*d* and were amenable to complete analysis; Table I records chemical-shift and spin-coupling data for compounds **1** and **3** recorded at 220 MHz, and the data for **2** are taken from a detailed analysis[10] in which the individual acetoxyl groups were also specifically attributed. Fig. 1 provides a schematic display, to scale, that depicts the chemical-shift correlations between individual proton-resonances of the three compounds.

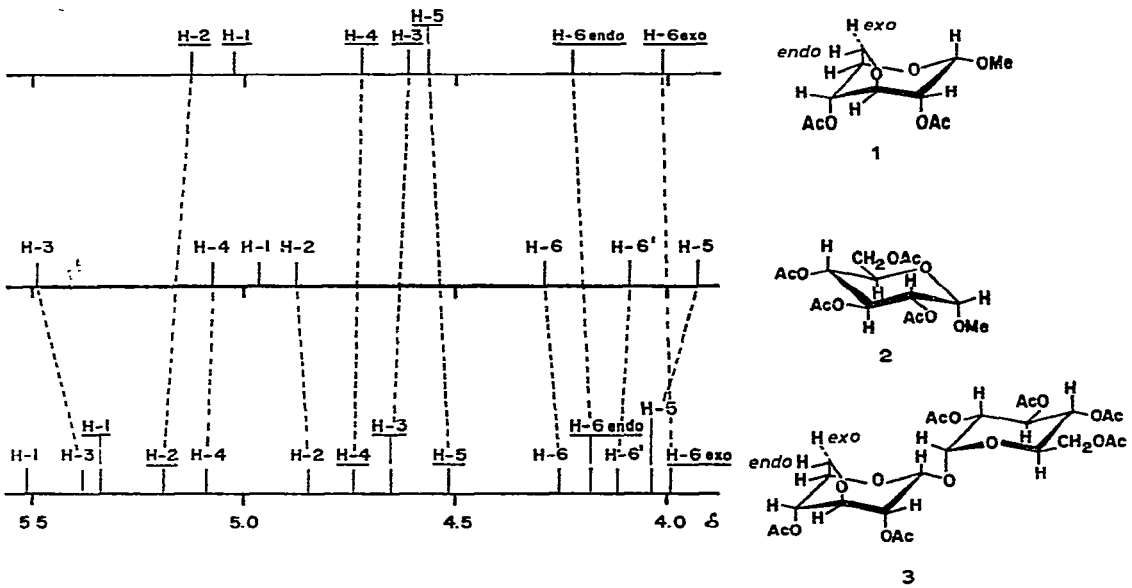

Fig. 1. Schematic comparison of chemical shifts of protons in compounds **1**, **2**, and **3**. [Protons indicated by an underscore correspond to protons of the 3,6-anhydroglucopyranosyl ring-system.The dotted lines trace the relationship of corresponding proton-signals for the three compounds. The rotameric attribution about the anomeric linkage in **3** is arbitrary.]

The ring-inversion wrought by formation of the 3,6-anhydride is manifested by gross changes in the appearance of the spectra, as may be seen by comparing shifts of corresponding protons in **1** and **2** (see Fig. 1 and Table I) and by examining the major changes in spin couplings. However, as is evident from the signal-positions for compound **3** in Fig. 1, the effects of the two components in the molecule largely reflect a simple additivity of the signals of **1** and **2**. For the anhydrohexose ring, the signal-positions of H-3, H-4, H-5, H-6*endo*, and H-6*exo* scarcely differ between compounds **1**

TABLE I

^{1}H-N.M.R. SPECTRAL DATA FOR METHYL 2,4-DI-*O*-ACETYL-3,6-ANHYDRO-α-D-GLUCOPYRANOSIDE (**1**), METHYL 2,3,4,6-TETRA-*O*-ACETYL-α-D-GLUCOPYRANOSIDE (**2**), AND 2,3,4,6-TETRA-*O*-ACETYL-α-D-GLUCOPYRANOSYL 2,4-DI-*O*-ACETYL-3,6-ANHYDRO-α-D-GLUCOPYRANOSIDE (**3**) IN CHLOROFORM-*d*

Compound	*Chemical shifts* (*δ*)									*Coupling constants* (*Hz*)						
	H-1	*H-2*	*H-3*	*H-4*	*H-5*	*H-6*	*H-6'*	*OAc*	*OMe*	$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$	$J_{5,6}$	$J_{5,6'}$	$J_{6,6'}$
1[a]	5.02	5.12	4.61	4.72	4.57	4.22[b]	4.01[c]	2.05, 2.17	3.53	3.4	4.5	5.2	2.1	0	2.8	10.8
2[d]	4.96	4.88	5.49	5.07	3.92	4.29	4.09	2.07, 2.00, 2.03, 2.09[e]	3.42	3.5	9.5	9.5	10.0	4.6	2.5	12.2
3[f,g]	5.34	5.19	4.65	4.74	4.51	4.18[b]	3.99[c]	2.18, 2.21		3.2	4.4	5.1	2.3	0	2.8	10.7
3[h]	5.51	4.84	5.38	5.09	4.03	4.25	4.11	2.03, 2.06, 2.08, 2.11		3.7	10.2	9.4	10.0	4.1	2.0	12.4

[a]Long-range couplings $J_{3,4}$ 0.7, $J_{3,5}$ 0.4 Hz. [b]The *endo* proton. [c]The *exo* proton. [d]Data from ref. 10. [e]Definite assignments for the 2-, 3-, 4-, and 6-acetoxyl groups, respectively. [f]Resonances for the 3,6-anhydro-α-D-glucopyranosyl portion. [g]Long-range couplings $J_{2,4}$ 0.6, $J_{3,5}$ 0.4, $J_{4,6exo}$ 0.4 Hz. [h]Resonances for the α-D-glucopyranosyl portion.

and **3**, and the same correspondence exists between H-4, H-6, and H-6′ of compound **2** as compared with corresponding signals for **3**. The interglycosidic linkage evidently forces certain protons in compound **3** into magnetic environments influenced by the spatial proximity of the residues, and leads to some moderate shift-differences; thus, H-2 of the anhydro ring in **3** resonates at lower field than it does in the model anhydride **1**, and upfield shifts are observed for resonances of the axial protons H-2 and H-3 in the other ring of **3** as compared with the model compound **2**, whereas the H-5 signal is shifted downfield.

The glycosidic methoxyl groups in **1** and **2** have a greater shielding effect than the glycosyl groups in **3**, so that the H-1 signals in **3** fall to lower field; the equatorial H-1 of the monocyclic moiety resonates at lower field than the axial H-1 of the bicyclic component.

The spin couplings observed for the two separate parts of the molecule **3** are essentially identical to those in the model compounds **1** and **2**, indicating that no significant distortion of either component is induced by the glycosidic linkage.

The acetyl-group resonances for compound **3** are manifested as a group of four signals to relatively high field that may with reasonable confidence be attributed to the four acetyl groups on the α-D-glucopyranosyl group, although it would be an unjustified presumption to assign each of these four individual signals by comparison with the specifically identified[10] signals for compound **2**. The two low-field, acetyl-group signals of **3** (δ 2.18 and 2.21) most probably arise from the two acetoxyl groups on the 3,6-anhydro-α-D-glucopyranosyl group, although attributions of acetoxyl-group resonances and the steric dispositions of these groups made solely on the basis of chemical shifts must always be approached with considerable skepticism in the absence of more-concrete evidence[11]. Indeed, as has already been pointed out[3], the model anhydride **1** displays one of its acetyl-group resonances at relatively high field, suggesting that compound **1** might possibly adopt a boat-like conformation having the 2-acetoxyl group equatorially disposed. However, the near-perfect identity of the proton–proton spin-coupling data for the 3,6-anhydro-α-D-glucopyranosyl ring-system in compounds **1** and **3** (see Table I) militates strongly against this supposition, and it may be safely concluded that the anhydrohexopyranosyl group in each compound has the same conformation. In each instance, the detailed spin-coupling data accord with an approximate $^1C_4$(D) conformation for the anhydro sugar ring-system and a classic $^4C_1$(D) conformation for the α-D-glucopyranosyl group. The anhydro-sugar rings are evidently distorted away from the idealized $^1C_4$(D) conformation, as manifested by the relatively large values of $J_{2,3}$ and $J_{3,4}$ and relatively small value of $J_{4,5}$ for a system in which H-2,3,4, and 5 are nominally equatorial and for which a non-distorted $^1C_4$(D) conformation would have given very small couplings[12]. Such distortions are well established for related anhydrohexopyranoses that have been studied in the solid state by X-ray crystallography[13]. Complete ^{1}H-n.m.r. data on the tetraacetate of the dianhydride analog of **3** are not available, but spin-coupling values for the corresponding tetrabenzoate[5] are close to those observed for **1** and the anhydro-sugar portion of **3**. For the anhydro-sugar systems in **1** and **3**, the long-range,

"W"-type couplings, zero couplings between H-5 and H-6*endo*, and relatively small (~10.7 Hz) geminal couplings between H-6*exo* and H-6*endo*, are all as expected[9,12,14] and need not be discussed further.

EXPERIMENTAL

The spectra of compounds **1** and **3** (~10% in chloroform-*d*) were recorded at 220 MHz at ~25°; chemical shifts, given as the mid-point of each multiplet on scans at 500-Hz sweep-width, are relative to tetramethylsilane as the internal reference. Spin couplings were measured from spectra recorded at 100-Hz sweep-width. All signals were clearly differentiated and free from second-order characteristics, other than the anticipated[15] ABX systems for H-6,6', and 5. Spectral data for **2**, taken from ref. 10, also refer to solutions in chloroform-*d*; the acetyl-group resonances for this compound are specifically identified[10] (see Table I).

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