Carbohydrate Research
Elsevier Publishing Company, Amsterdam
Printed in Belgium

Note

Chemical modification of trehalose
Part IV[1]. The synthesis and conformation of 3,6: 3′,6′-dianhydro-α,α-trehalose

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(Received April 29th, 1970)

Previous ^{1}H-n.m.r. studies[1–3] have shown that symmetrical derivatives of the disaccharide trehalose (α-D-glucopyranosyl α-D-glucopyranoside) normally adopt chair conformations in which each ring is in the same C_1^4 form (*e.g.* **1**). It was therefore of interest to examine a derivative of the disaccharide in which the pyranoid rings were constrained into the alternative C_4^1 conformation; namely the 3,6:3′,6′-dianhydride (3,6-anhydro-α-D-glucopyranosyl 3,6-anhydro-α-D-glucopyranoside) **3**, and some of its *O*-substituted derivatives.

The dianhydride has been briefly described[4] but was not fully characterised. It may be conveniently prepared in 65% yield by the action of sodium methoxide on 6,6′-di-*O*-tosyltrehalose hexa-acetate[2] (**1**), or, less conveniently, *via* the corresponding 6,6′-di-iodo derivative **2**.

The resonances in the ^{1}H-n.m.r. spectrum of **3** overlapped to such an extent that an unequivocal interpretation was not possible. Consequently, the tetra-acetate **4** and tetrabenzoate **5** were prepared and their spectra determined at 100 MHz in both deuterochloroform and deuteropyridine (Table I). In the latter solvent, second-order effects complicated the spectra. In deuterochloroform, the tetra-esters gave similar spectra, but only the spectrum of the tetrabenzoate **5** was amenable to a complete, first-order analysis (Fig. 1).

The resonance due to H-1 and H-1′ occurred as a doublet (J 3.2 Hz) to low field (τ 4.20) of the signals for all other ring hydrogen atoms. It is of note that the chemical shift of these hydrogen atoms is about 0.2–0.3 p.p.m. downfield from its normal position in related trehalose derivatives existing in the C_1^4 conformation (*e.g.* **1**)[1–3]. This effect is attributed to the C_4^1 conformation **5** in which the axial O-3 would provide an added deshielding influence. In α-D-glucopyranosides with the normal C_1^4 conformation, this effect is reversed, since the axial O-1 deshields the H-3[3,5]. The resonance at next lowest field was a broad-limbed triplet at τ 4.64, which was assigned to either H-2,H-2′ or to H-4,H-4′ because of the known deshielding-effect of a benzoate group on an adjacent ring-proton[1,2,5,6]. Irradiation at this frequency collapsed the H-1,H-1′ doublet into a singlet, and a triplet at τ 5.18, which was partly overlapped, collapsed to a doublet. Consequently, the triplet at τ 4.64 was assigned to H-2,H-2′, and the triplet at τ 5.18 to H-3,H-3′. A further result of this decoupling experiment was to

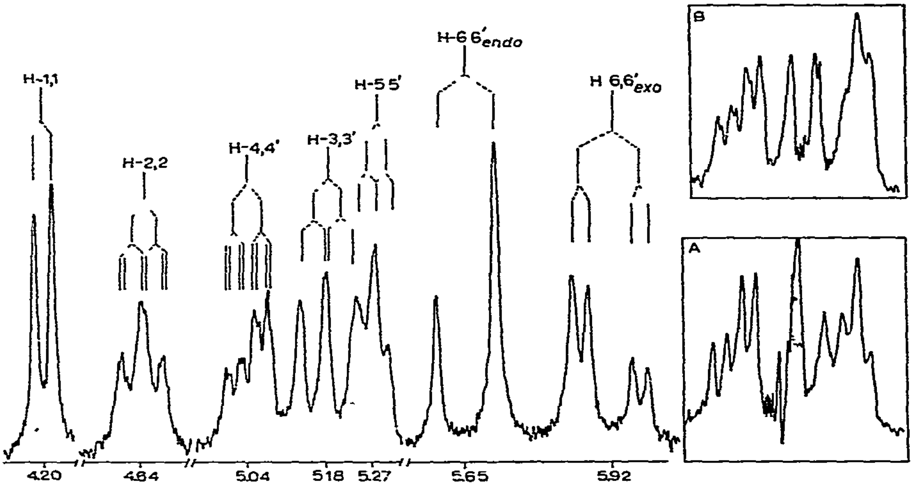

Fig. 1. The ^{1}H-n.m.r. spectrum of the tetrabenzoate 5 at 100 MHz. Inset is the portion of the spectrum τ 4.9–5.3 after decoupling of (*A*) H-2,H-2′ and (*B*) H-6$_{ex}$, H-6′$_{ex}$.

TABLE I

FIRST-ORDER CHEMICAL SHIFTS (τ VALUES) AND COUPLING CONSTANTS AT 100 MHz[a]

Compound:	*Benzoate* 5		*Acetate* 4	
Solvent:	*Chloroform-d*	*Pyridine-d$_5$*	*Chloroform-d*	*Pyridine-d$_5$*
H-1,H-1′	4.20d	3.82d	4.43d	4.16d
H-2,H-2′	4.64t	4.35cm	4.87t	4.70cm
H-3,H-3′	5.18t	4.8–5.25cm	5.3–5.5cm	5.2–5.4cm
H-4,H-4′	5.04q			
H-5,H-5′	5.27t			
H-6$_{en}$,H-6′$_{en}$	5.65d	5.58d	5.81d	5.83d
H-6$_{ex}$,H-6′$_{ex}$	5.92q	5.96q	6.06q	6.14q
$J_{1,2}$	3.2	3.2	3.0	3.2
$J_{2,3}$	4.4	—	4.0	—
$J_{2,4}$	0.9	—	<1	—
$J_{3,4}$	5.0	—	—	—
$J_{3,5}$	<0.7	—	—	—
$J_{4,5}$	2.4	—	—	—
$J_{5,6en}$	0	0	0	0
$J_{5,6ex}$	2.9	~2.5	2.3	2.9
$J_{6en,6ex}$	10.8	10.8	10.7	10.5

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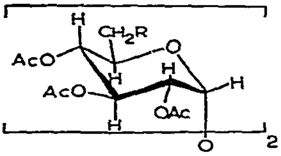
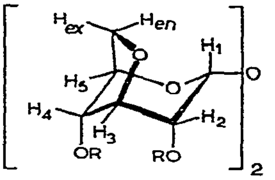
[a] The stated multiplicity (d, doublet; t, triplet; q, quartet; cm, complex multiplet) of the resonances ignores small, long-range couplings which often only result in a broadening of the limbs of the multiplet.



1 R = OTs
2 R = I



3 R = H
4 R = Ac
5 R = Bz

remove the smallest splitting from an octet at τ 5.04 (J 5.0, 2.4, and 0.9 Hz) which was therefore assigned to H-4,H-4′; the small splitting of 0.9 Hz was the long-range coupling $J_{2,4}$ which indicates the diequatorial "W" conformation of these hydrogen substituents[7]. Of the remaining resonances, a doublet at τ 5.65 (10.8 Hz) and a quartet at τ 5.92 (10.8, 2.9 Hz) were assigned to H-6,H-6′, of which only one was coupled to H-5,H-5′. Examination of molecular models of the fused-ring system **3**–**5** revealed that H-6_{endo} subtends a 90° dihedral angle with H-5, and hence a zero coupling would be predicted[8]. For this reason, the doublet at τ 5.65 was assigned to the *endo* hydrogen atoms, and the quartet to the *exo* hydrogen atoms. The relative chemical shifts agree with this conclusion, since the *endo* hydrogen atoms would suffer greater deshielding and give signals to low field of those for the *exo* hydrogen atoms.

The observed coupling constants (Table I) suggest that the pyranoside rings exist in a slightly distorted C_4^1 conformation, with H-2,2′, H-3,3′, H-4,4′, and H-5,5′ in equatorial positions. The large values of $J_{2,3}$ and $J_{3,4}$ (4.4 and 5.0 Hz, respectively) may be rationalised by a slight deformation of the ring at C-3 in order to accommodate the anhydro bridge; such a distortion would decrease the dihedral angles $\varphi_{2,3}$ and $\varphi_{3,4}$ from the theoretical value of 60° for the perfect chair and hence increase the value of the coupling constants[8]. The observed long-range couplings $J_{2,4}$ and $J_{3,5}$ confirm the diequatorial positions of these pairs of hydrogen atoms and hence the C_4^1 conformation of the dianhydride.

No ^{1}H-n.m.r. studies of 3,6-anhydropyranosides have been described previously, and our results are of interest in confirming the C_4^1 conformation of this fused-ring system. The closely related 1,6-anhydrohexopyranoses have been widely studied by p.m.r. spectroscopy and the C_4^1 conformation confirmed[9]. The pattern of H-6_{endo} and H-6_{exo} in these 1,6-anhydrides is similar to that observed for **4** and **5**.

EXPERIMENTAL

*3,6-Anhydro-α-*D*-glucopyranosyl 3,6-anhydro-α-*D*-glucopyranoside* (**3**). — 6,6′-Di-*O*-tosyltrehalose hexa-acetate[2] **1** (5 g) was dissolved in acetone (5 ml) and treated with 0.5M methanolic sodium methoxide (25 ml). The mixture was then heated under reflux for 2 h, after which time t.l.c. (butyl acetate–pyridine–water, 5:3:1) indicated that the reaction was complete. The reaction mixture was neutralised with Amberlite IR-120 (H$^+$) resin, filtered, and stored at 0° to give material (1.1 g, 65%), m.p. 170–

175°, which was recrystallised from ethanol to give **3** as needles, m.p. 199–206°, $[\alpha]_D$ +26° (*c* 0.24, water); the m.p. was not improved by further recrystallisations from ethanol (Found: C, 47.3; H, 5.7. $C_{12}H_{18}O_9$ calc.: C, 47.1; H, 5.9%).

Application of the same procedure to 6,6′-dideoxy-6,6′-di-iodotrehalose hexaacetate (**2**) afforded the diahydride **3** in 44% yield.

The tetra-acetate **4** was obtained in the usual way (68% yield) with acetic anhydride–pyridine. It had m.p. 232–234° (from ethanol), $[\alpha]_D$ +99° (*c* 0.38, chloroform) (Found: C, 50.75; H, 5.5. $C_{20}H_{26}O_{13}$ calc.: C, 50.65; H, 5.5%).

The tetrabenzoate **5** was prepared by the usual procedure with benzoyl chloride–pyridine (83% yield). It had m.p. 202–206° (from ethanol), $[\alpha]_D$ −78° (*c* 0.34, chloroform) (Found: C, 66.5; H, 4.7. $C_{40}H_{34}O_{13}$ calc.: C, 66.5; H, 4.75%).

ACKNOWLEDGMENTS

We are indebted to the Physico-Chemical Measurements Unit at Harwell for the 100-MHz ^{1}H-n.m.r. spectra, and one of us (C.K.L) thanks J. Sainsbury for a grant.

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