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SELECTIVE DEUTERATION OVER RANEY NICKEL IN DEUTERIUM OXIDE: 1,6-ANHYDROHEXOSES*†

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ABSTRACT

The relative rates of protium–deuterium exchange, catalysed by deuterated Raney nickel in deuterium oxide, in various positions of 1,6-anhydrohexopyranoses and -furanoses have been studied. Conditions have been found under which 1,6-anhydro-β-D-galactopyranose may be labelled on C-3 and 1,6-anhydro-α-D-galactofuranose on C-2.

INTRODUCTION

In the first two papers of this Series[1,2] it was shown that regioselective deuteration of polyols may sometimes be achieved by the Koch–Stuart procedure[3]. In this method, a sugar, or a similar compound, is treated with Raney nickel in deuterium oxide, causing replacement by deuterium of hydrogen atoms that are bound to carbon atoms carrying free hydroxyl groups. In some cases, the rate of replacement within a molecule may vary considerably[1,2,4–6]; in a few instances, the variation is so great that it allows nearly complete deuteration in one position while hardly affecting the others. It was shown[1] that the methyl glycosides are not particularly good subjects for such selective deuteration: their flexibility counteracts steric hindrances (which are the main cause of selectivity) and their sidechains are too readily deuterated. In this paper we describe the investigation of 1,6-anhydrohexoses, which are rigid and have no sidechains. Many 1,6-anhydrohexoses are readily prepared by recently introduced methods[7,8].

Previously, it was found that equatorial hydrogen atoms exchange faster than axial ones, and a hydrogen atom *syn*-axial with an oxygen atom in a six-membered ring exchanges particularly slowly. A methoxyl group *cis* to a hydrogen atom

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hinders the exchange, particularly in a five-membered ring. A hydrogen atom geminal to an isolated hydroxyl group (that is, one having no other hydroxyl group on a neighbouring carbon atom) exchanges very slowly; if the geminal hydroxyl group is not free (*e.g.*, methylated), there is no exchange.

As in the previous papers[1,2], our aim was to find compounds and conditions under which at least 90% of one hydrogen atom was exchanged while no more than 10% exchanged in any other position. Material thus "labelled" would be suitable for the study of reaction mechanisms, n.m.r. spectra, or biosynthesis.

1,6-Anhydrohexopyranoses

The 1,6-anhydrohexopyranoses were treated with deuterated Raney nickel in deuterium oxide as described before[2,3] and the extent of deuteration was evaluated by integration of the ^{1}H- or ^{13}C-n.m.r. spectra. The results are shown in Table I.

The rate of exchange varies as would be expected from the behaviour of the cyclitols[2] and the methyl glycosides[1]. When H-3 is *endo* (axial), it is hindered by the anhydro bridge and exchange is very slow; when it is *exo* (equatorial), it exchanges rapidly. The equatorial H-4 in the *allo* and the *altro* isomers exchanges rapidly, but very slowly in the *gluco* and *manno* isomers where the geminal and the vicinal hydroxyl groups are both axial; this arrangement does not provide a favourable site for adsorption on the catalyst[2]. The axial H-4 exchanges rapidly in the *ido* isomer but slowly in the *gulo* isomer in which it is *syn*-axial with O-2; this exchange is even slower in the *galacto* isomer where H-4 is *syn*-axial with O-2 and also lacks an equatorial neighbouring hydroxyl group. An equatorial hydrogen atom on C-2 exchanges slowly because it is *cis* to O-1 (*allo, gulo*), and it exchanges very slowly in the *gluco* and *galacto* isomers where, in addition, it lacks the required equatorial neighbouring hydroxyl group. The axial H-2 in the *ido* isomer exchanges

TABLE I

HYDROGEN (EQUIVS.) FOUND IN VARIOUS POSITIONS OF 1,6-ANHYDROHEXOPYRANOSES AFTER EXCHANGE[a]

Anhydride	T (°)	t *(min)*	*H-2*	*H-3*	*H-4*	*H-5*	*Anal. method*[b]
β-D-allo-	100	60	0.48	0.95	0.03	1.00	^{1}H (Ac) in C_6D_6
β-D-altro-	100	180	0.84	1.00	0.18	0.91	^{1}H (Ac) in $CDCl_3$
β-D-galacto-	85	5	0.93	0.07	0.94	1.00	^{1}H in D_2O
β-D-gluco-	100	240	0.92	0.52	~0.90	~1.00	^{13}C in D_2O
		480	0.81	0	~0.55	~1.00	
β-D-gulo-	100	120	~0.35	~1.00	~0.45	0.94	^{13}C in D_2O
β-D-manno-	100	180	0.96	0.55	0.97	1.00	^{1}H (Ac) in $CDCl_3$
		360	0.93	0.18	0.90	1.00	
β-D-ido-	100	10	0.44	1.00	0.50	1.00	^{1}H (Ac) in $CDCl_3$

[a]In all cases, H-1, H-6 and H-6' were assumed, and found, to be 1.00. [b]^{1}H (Ac) means ^{1}H-n.m.r. spectrum of the acetate.

rapidly, but in the *manno* and *altro* isomers it is *syn*-axial with O-4 and hence exchange is very slow.

As a consequence of this variation in the exchange rates, 1,6-anhydro-β-D-galactopyranose (**1**) is specifically deuterated on C-3. As this anhydride is readily prepared[8] and can be quantitatively hydrolysed to D-galactose by aqueous acids, this reaction constitutes a good method for labelling D-galactose with deuterium on C-3. The selectivity of the exchange of 1,6-anhydro-β-D-mannopyranose does not reach the standard we set ourselves, but would be sufficient for most purposes; this compound is readily prepared[9] and would provide D-mannose labelled on C-3.

The other anhydrides do not exchange specifically. According to the foregoing conclusions, in 1,6-anhydro-β-D-talopyranose, which we did not test, H-3 would exchange rapidly but H-2 and H-4 would also react and there would not be sufficient specificity.

1,6-Anhydro-β-D-galactopyranose isomerises readily under the conditions of the Koch–Stuart exchange. Even after 10 min at 80°, small signals of isomers are visible in the n.m.r. spectrum; after 1 h, epimerisation is extensive. The epimers could be recognized in the ^{13}C-n.m.r. spectrum (since the spectra of all of the diastereomers are known[10]) as 29% of the *gulo* (inversion on C-3), 14% of the *talo* (inversion on C-2), and 15% of the *ido* isomer (inversion on C-2 and C-3). Balza and Perlin[6] found that 1,6-anhydro-β-D-glucopyranose isomerizes, after 24 h, to give the *allo* (14%), the *gulo* (10%), and the *ido* isomers (26%). Isomerisation therefore occurs most readily in those positions where deuterium exchange is the most rapid, and yields the thermodynamically most stable diastereomers.

1,6-Anhydrohexofuranoses

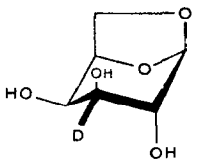
The 1,6-anhydrohexofuranoses used to be derivatives prepared with considerable difficulty in very small yields; a recent method[7], however, allows the preparation of four diastereomers by a one-flask procedure in a short time and in reasonable yields. Only these four diastereomers were submitted to the Koch–Stuart procedure; the results are shown in Table II.

TABLE II

HYDROGEN (EQUIVS.) FOUND IN VARIOUS POSITIONS OF 1,6-ANHYDROHEXOFURANOSES AFTER EXCHANGE[a]

Anhydride	T (°)	t *(min)*	*H-2*	*H-3*	*H-4*	*H-5*	*Anal. method*[b]
β-D-*allo*-	100	240	0.81	0.52	0.85	0.53	^1H (Ac) in C_6D_6
α-D-*galacto*-	100	15	0	0.84	1.00	>0.97	^1H (Ac) in $CDCl_3$
β-D-*manno*-	95	50	<0.20	<0.20	1.00	0.40	^{13}C in D_2O
α-D-*talo*-	100	300	0.93	0.86	0.86	1.00	^{13}C in D_2O

[a]In all cases, H-1, H-6 and H-6′ were assumed, and found, to be 1.00. [b]^1H (Ac) means ^1H-n.m.r. spectrum of the acetate.



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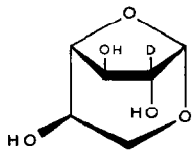

2

It may be seen that when H-2 and H-3 are both *exo* (*manno* isomer), they both exchange rapidly. When they are both *endo* (*allo, talo*), both exchange slowly; H-2, which is also hindered by the anomeric oxygen atom, exchanges particularly slowly. In 1,6-anhydro-α-D-galactofuranose (**2**), where H-2 is *exo* but H-3 is *endo*, — and also hindered by O-5 — only the former exchanges rapidly, providing thereby another example of specific deuterium exchange. This was the only case amongst our compounds of an anhydrofuranose having O-2 and O-3 *trans*.

Being geminal to an isolated hydroxyl group, H-5 generally exchanges slowly. However, when it is *endo* (as it is in the *allo* and *manno* isomers) it exchanges readily; adsorption on the catalyst surface is then probably assisted by OH-3. In 1,6-anhydro-α-D-talofuranose, all of the hydrogen atoms exchange slowly.

Two instances require special comment: in 1,6-anhydro-β-D-allofuranose and in 1,6-anhydro-α-D-talofuranose, H-4 exchanges, albeit slowly. This is in accordance with other instances amongst furanoses, as observed by Wu *et al.*[11], and it has the required steric arrangement, namely, O-2 is *cis* and O-1 is *trans* to H-4.

When the exchange with 1,6-anhydro-α-D-galactofuranose is conducted for a prolonged period (6 h), the ^1H spectrum of the acetylated product shows the presence of a diastereomer (~20%). Inspection of the n.m.r. data — which are known for every diastereomer[12–18] — shows that this is the *altro* isomer, formed by inversion at C-5. Only the signals of H-1, H-4, H-6, and H-6′ were visible; the hydrogen atoms on C-2, C-3, and C-5 had been completely replaced by deuterium. Inversion is therefore accompanied by deuteration, as expected. The reaction was then repeated in ordinary water and, as a result, the signals of H-3 and H-5 were also detected. The ^{13}C-n.m.r. spectrum[19] showed five signals of 1,6-anhydro-β-L-altrofuranose (that of C-2 coincides with the C-2 signal of the *galacto* isomer). No other signals were present: it is remarkable, and not easily explained, that inversion occurs only on C-5. In this case, the centre where inversion occurs is the one where deuteration is the slowest.

To obtain some more information on the epimerisations that accompany deuteration, several exploratory experiments were conducted with small amounts of anhydrides and a very large excess of Raney nickel (to accelerate the epimerisation). G.l.c. of the acetates was used to detect the isomers obtained; unfortunately this method did not separate all of the isomers. After a reaction of 2 h, 1,6-anhydro-α-D-galactofuranose (**2**) showed the presence, in addition to substantial proportions of the *altro* isomer, of small proportions of the *allo* and traces of the *manno* isomer

(epimers of *altro*) and another peak which could be the *talo* isomer (epimer of *galacto*) or the *ido, gulo,* or *gluco* isomer. After 4 h, the *allo* and the other peak had increased but that of *manno* remained very small.

Treatment of 1,6-anhydro-β-D-mannofuranose under these conditions for 2 h resulted in its almost complete disappearance: the main product is the *altro* isomer (an epimer of *manno*), with smaller proportions of *galacto* and *allo* isomers (epimers of *altro*) and another product, may be *gluco*.

Under the same conditions, 1,6-anhydro-α-D-talofuranose epimerises slowly: after 10 h, the *galacto* and the *allo* isomers were found (epimers of *talo*) and also *altro* (from *galacto* or *allo*) and small proportions of the *gluco* and *ido* isomers.

Epimerisation may thus occur on C-2, C-3, or C-5. It appears that the *manno* isomer, in which both O-2 and O-3 are *endo,* has low thermodynamic stability (as would the *gulo* isomer), and that the *altro* isomer is the most stable.

To summarise: work described in this and in the preceding paper[1] has shown that D-galactose may be labelled by deuterium on C-2 (*via* the 1,6-anhydrofuranose), on C-3 (*via* the 1,6-anhydropyranose), and on C-3 and C-4 (*via* the methyl β-pyranoside); D-fructose on C-3 (*via* the methyl β-furanoside) and on C-5 (*via* the methyl β-pyranoside); and D-mannose on C-3 (*via* the 1,6-anhydropyranose). We have found no derivative that allows the selective deuteration of D-glucose (in which all the hydroxyl groups are equatorial).

It is not possible to achieve complete selectivity of labelling by this method (unless the compound has only one exchangeable hydrogen atom). In most cases this will not matter. Labelling by deuterium is used extensively[20] for the assignment of n.m.r. spectra, for the study of reaction mechanism and pathways, biosynthesis, and metabolism. For most of these uses, the essential feature is the ability to recognise a particular hydrogen or carbon atom; for this, it is not imperative that the labelling by deuterium be complete, nor does it matter if there are small amounts of deuterium in other positions. Partial deuteration may even be an advantage. For example, in D-glucose labelled *via* the 1,6-anhydropyranose (Table I), H-3 is completely and H-4 partially replaced by deuterium; both would be readily recognised in the n.m.r. spectra.

Even if deuteration is not completely specific, the simplicity and rapidity of the Koch–Stuart method warrants its use: stereospecific deuteration by chemical reactions is usually a long multi-step procedure. Moreover, the method is economical because deuterium oxide is the cheapest source of deuterium.

EXPERIMENTAL

Materials and methods. — 1,6-Anhydro-β-D-glucopyranose was a commercial sample, the *manno* isomer was a gift of Dr. N. W. H. Cheetham, and all the other 1,6-anhydropyranoses were donated by Dr. N. K. Richtmyer. The anhydrofuranoses used in the exchange were synthesised according to ref. 7. Samples of 1,6-anhydro-α-L-gulo- and ido-furanoses were obtained from Professor P. Köll.

N.m.r. spectra were recorded with a Cameca 250 spectrometer in Grenoble

and with a Jeol JNM-FX-100 or a Bruker CXP-300 spectrometer in Sydney, using the solvents indicated in the Tables.

^{1}H-N.m.r. spectra. — The ^{1}H-n.m.r. spectra of the 1,6-anhydropyranoses[21] and of their acetates[22] have been described. In most cases, the spectra of the acetates proved to be the most useful; however, in the spectra of the *gluco* and *gulo* isomers recorded in chloroform-*d* there is an overlap of signals. In these cases we used the ^{13}C-n.m.r. spectra[10]. In the spectrum[22,23] of 2,3,4-tri-*O*-acetyl-1,6-anhydro-β-D-allopyranose in chloroform-*d* the signals of H-2 and H-4 overlap but they are well separated in the spectrum recorded in benzene-d_6: δ 5.47 (d, $J_{1,2}$ 2.4 Hz, H-1), 5.40 (t, $J_{2,3}$ 4.8, $J_{3,4}$ 4.8 Hz, H-3), 5.19 (ddd, $J_{2,4}$ ~0.5 Hz, H-2), 5.01 (ddd, $J_{4,5}$ 2.2 Hz, H-4), 4.05 (quintet, $J_{5,6exo}$ 5.3, $J_{5,6endo}$ 1.0 Hz, H-5), 3.26 (dd, $J_{6exo,6endo}$ −8.3 Hz, H-6*endo*), 3.21 (dd, H-6*exo*), 1.80, 1.74, and 1.70 (s, Ac).

In the ^{1}H-n.m.r. spectrum of 2,3,4-tri-*O*-acetyl-1,6-anhydro-β-D-mannopyranose small signals appear, after exchange, at δ 4.00–4.15; these are not the signals of a 1,6-anhydrohexopyranose and could not be identified.

The ^{1}H-n.m.r. spectra of the triacetates of 1,6-anhydro-β-D-allofuranose[12] and 1,6-anhydro-β-D-galactofuranose[14] have been described. In the former, the signals of H-2 and H-3 could not be assigned; deuterium labelling has now shown that the signal at δ 5.44 is that of H-2, and the one at δ 5.20 that of H-3.

^{13}C-N.m.r. spectra. — The ^{13}C-n.m.r. spectra of the 1,6-anhydropyranoses have been described[10,24]. Our spectra show that in the Tables collated by Bock and Pedersen[25], the value (70.5) given for C-3 of 1,6-anhydro-β-D-gulopyranose is wrong; it should be 69.6 p.p.m. The value listed is from ref. 24; the correct value is found in ref. 10. The ^{13}C-n.m.r. spectra of the 1,6-anhydrohexofuranoses will be published elsewhere[19].

Deuterium exchange was conducted as previously described[1,2,4].

Two columns (2000 × 3 mm) were used for gas-chromatographic analysis: (*i*) one packed with 3% stabilised (Analabs, SLP-026) polydiethylene glycol adipate on Chromosorb W.H.P., 100–120 mesh (Hewlett–Packard), operated at 190°; (*ii*) the other packed with 3% SP 2401 on Chromosorb W.H.P., 100–120 mesh, operated at 170°. Retention times of the anhydrofuranose acetates: (*i*) *allo* 14.6, *altro* 9.3, *galacto* 4.9, *gluco* 7.5, *gulo* 7.6, *ido* 7.3, *manno* 8.4, and *talo* 7.4 min; (*ii*) 8.9, 6.7, 3.6, 5.4, 7.2, 6.7, 6.7, and 5.8 min, respectively.

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