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THE CATALYTIC *C*-DEUTERATION OF SOME CARBOHYDRATE DERIVATIVES*

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ABSTRACT

Carbohydrate derivatives are readily deuterated, at carbon atoms bound to free hydroxyl groups, by hot deuterium oxide containing Raney nickel. Configuration is maintained during the exchange; however, prolonged exposure to the catalyst leads to isomerizations.

INTRODUCTION

The use of Raney nickel as a hydrogen-transfer catalyst between alcohols and carbonyl compounds is well known[2,3]. A similar mechanism is involved in the nickel-catalyzed conversion of primary amines into secondary amines and ammonia[4]. The isomerization of substituted cyclohexanols[5] and 1-deoxyalditols[6] by Raney nickel has been explained by an analogous dehydrogenation–hydrogenation mechanism.

DISCUSSION

In a recent preliminary report[1], we outlined a simple method for the *C*-deuteration of alcohols, and particularly carbohydrate derivatives, by catalyzed exchange with deuterium oxide in the presence of deuterated Raney nickel.

$$R\text{–}CH_2OH \xrightarrow{^2H_2O} R\text{–}CH_2O^2H \xrightarrow{^2H_2O,\ Ni} R\text{–}C^2H_2O^2H$$

As the hydrogen adsorbed on Raney nickel exchanges rapidly with the deuterium of deuterium oxide, a property that Raney nickel shares with other hydrogenation catalysts[7,8], deuterated Raney nickel can be simply prepared by exchange of the protiated ("light") material with deuterium oxide[1,9]. Furthermore, deuterium oxide can act as a deuterium pool during exchange reactions. It appears that the exchange mechanism involves two main steps. (*a*) First, the alcohol is dehydrogenated by nickel; this step is analogous to the nickel-catalyzed dehydrogena-

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tion of alcohols reported by Chakravarti[3]. (*b*) Then, the carbonyl compound is reduced by the deuterium in deuterated Raney nickel (the large pool of deuterium in the form of deuterium oxide keeps the Raney nickel fully deuterated).

(*a*) $R_2CHO^2H + Ni \rightleftarrows R_2C{=}O + Ni(H^2H)$

(*b*) $R_2C{=}O + Ni(2^2H) \rightleftarrows R_2C^2HO^2H + Ni$

Simple alcohols exchange rapidly at the geminal position and slowly at the vicinal position. For example, the 1,2-cyclohexanediols exchange rapidly at C-1 and C-2, and slowly at C-3 and C-6; similarly, the 1,3-cyclohexanediols exchange rapidly at C-1 and C-3, and slowly at C-2, C-4, and C-6. The 1,4-cyclohexanediols eventually exchange at all carbon atoms. In all cases, loss of configuration is rapid. Such acyclic polyhydric alcohols as the alditols exchange rapidly, but the loss of configuration is considerable.

However, for such cyclic compounds as the methyl hexopyranosides or *myo*-inositol, the rate of deuteration is much higher than the rate of isomerization, making possible the deuteration of the compound with retention of configuration. Also, only those carbon atoms bearing free hydroxyl groups undergo exchange; the deuterium exchange at other oxygen-bonded carbon atoms, such as C-1 and C-5 of the methyl hexopyranosides, is extremely small[1]. An explanation of the retention of configuration is that the molecule is adsorbed so strongly to the catalytic surface that it does not alter its position relative to the surface during the dehydrogenation–deuterium-reduction steps, as desorption and readsorption should lead to isomerization. Especially at room temperature, the concentration of methyl glycosides in aqueous solution is greatly lessened on introduction of Raney nickel into the solution[10]. Alditols may isomerize more rapidly because they have less restricted conformations than cyclic polyhydric alcohols.

The slow deuterium-exchange at the vicinal positions of simple alcohols is probably due to enolization of the aldehyde or ketone formed by dehydrogenation of the alcohol, and may not require the presence of nickel. However, a mechanism suggested by Wright and Hartmann[11] for the isomerization of alditols by a nickel catalyst under hydrogenation conditions at high temperature, involving dehydrogenation of the alcohol to an enol followed by rehydrogenation, may also operate. However, the exchange at C-6 of methyl hexopyranosides without exchange at C-5 is not explained by this mechanism.

As stated previously[1], ^{13}C-n.m.r. spectroscopy is useful for the identification of the sites of deuteration in carbohydrate molecules, as the signals of carbon atoms bonded to deuterium are greatly attenuated[12], whereas the other carbon resonances are not affected, except for a small, β-deuterium-isotope displacement[13,14].

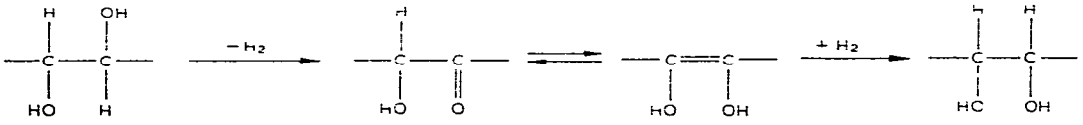
Aldoses are rapidly reduced to alditols by an excess of Raney nickel[15], even in the absence of ethanol as a hydrogen donor. Methyl glycosides and isopropylidene derivatives are usually stable in the presence of Raney nickel. Benzylidene groups are rapidly reduced to toluene by Raney nickel, even at room temperature, as illustrated

by the conversion of methyl 4,6-*O*-benzylidene-α-D-glucopyranoside into methyl α-D-glucopyranoside and toluene. Such nonreducing carbohydrates as sucrose may be *C*-deuterated directly[1]. A combination of derivatives has been used for the conversion of D-glucose-*1*-^2H into fully *C*-deuterated D-glucose[9].

The methyl pyranosides of D-glucose, D-galactose, and D-mannose are readily *C*-deuterated at C-2, C-3, C-4, and C-6 by this exchange reaction. For further identification, the *C*-deuterated products were also converted into their tetraacetates.

The 1,2-*O*-isopropylidene derivatives of α-D-gluco- and α-D-xylo-furanose are interesting, as *C*-deuteration at C-3 could not be observed, whereas exchange at C-5 and C-6 of the *gluco* derivative and C-5 of the *xylo* derivative proceeded normally. Neither 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose nor 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose showed any exchange with deuterium oxide in the presence of deuterated Raney nickel. 2,3:4,5-Di-*O*-isopropylidene-β-D-fructopyranose shows no significant exchange with tritiated water and Raney nickel[16]. Apparently, the proximity of the isopropylidene group prevents any effective interaction with the catalyst.

The exchange reaction is much faster than the isomerizations; however, with extended periods of exchange (2.5 d), the isomerizations can be considerable. The isomerizations were monitored by ^{13}C-n.m.r. spectroscopy and gas–liquid chromatography (g.l.c.) of the per(trimethylsilyl) ethers. Both methyl α-D-glucopyranoside and methyl α-D mannopyranoside give a mixture consisting mainly of the methyl pyranosides of α-D-glucose-*2,3,4,6,6*-$^2H_5$, α-D-mannose-*2,3,4,6,6*-$^2H_5$, a small proportion of methyl α-D-galactoside-*2,3,4,6,6*-$^2H_5$, and one further compound of comparable retention time in g.l.c., presumably methyl α-D-altropyranoside-*2,3,4,6,6*-$^2H_5$. It is noteworthy that the formation of an axial hydroxyl group is not disfavored. A similar case is the isomerization of cyclohexanediols: their equilibrium mixture in the presence of Raney nickel contains approximately equal amounts of the *cis* and *trans* isomers[10], Hence, the isomerization may also involve an enolization step following *cis*-hydrogenation by the catalyst[11].



Methyl α-D-galactopyranoside-*2,3,4,6,6*-$^2H_5$ is slowly converted into methyl α-D-glucopyranoside-*2,3,4,6,6*-$^2H_5$ and, eventually, also into methyl α-D-mannopyranoside-*2,3,4,6,6*-$^2H_5$.

The loss of configuration at C-5 is rapid during the exchange of 1,2-*O*-isopropylidene-α-D-glucofuranose. However, 1,2-*O*-isopropylidene-α-D-glucofuranose-*5,6,6*-$^2H_3$ preponderates in the equilibrium mixture, and only a relatively small (~30%) proportion of 1,2-*O*-isopropylidene-β-L-idofuranose-*5,6,6*-$^2H_3$ is formed.

myo-Inositol exchanges readily at all positions; although no attempt was made

to identify any isomerization products, the isolation, in good yield, of fully *C*-deuterated *myo*-inositol indicated that isomerizations are minor.

The isomerizations described that occur during *C*-deuteration may, of course, also be achieved in a non-deuterated medium, and may prove useful for the isomerization of di- and tri-saccharides.

It was originally considered that this exchange reaction, without isomerization, might be useful not only for the preparation of *C*-deuterated carbohydrates but also for the assignment of proton-decoupled, ^{13}C-n.m.r. spectra. However, for the latter purpose, the recently reported[17] effect of *O*-deuteration upon proton-decoupled, ^{13}C-n.m.r. spectra may be more useful.

EXPERIMENTAL

General methods. — Melting points are uncorrected, solutions were evaporated under vacuum, n.m.r. spectra were recorded with Varian EM 360 and CFT 20 spectrometers, and deuterated Raney nickel was measured as the settled volume in deuterium oxide. Mixture melting points are for a mixture with the corresponding "light" material: the constants reported are those of the "light" compounds. The ^{13}C-n.m.r. chemical-shifts are given in p.p.m. from tetramethylsilane, with 1,4-dioxane (67.22 p.p.m.) as the internal reference standard. For the assignment of ^{13}C-n.m.r. signals, see ref. 17. Gas–liquid chromatography (g.l.c.) was performed with an F and M 700 instrument, using a thermal conductivity detector, helium as the carrier gas (12 mL/min), and a detector current of 150 mA. The column (183 cm × 3.17 mm) contained Chromosorb W as the support and 10% of SE-30 as the liquid phase: temperatures: inlet, 215°; detector, 250°: oven, 185° (unless otherwise stated). The per(trimethylsilyl) ethers were prepared by dissolving the sample (2 mg) in dry pyridine (0.3 mL), and adding chlorotrimethylsilane (0.2 mL) and dry ethyl ether (0.3 mL). A 10-μL portion of the supernatant solution was injected.

Deuterated Raney nickel. — The preparation of deuterated Raney nickel from commercial, light Raney nickel (W. R. Grace and Co., No. 28) has been described[1,9].

Methyl α-D-glucopyranoside-2,3,4,6,6-^{2}H$_5$ (**1**). — A solution of methyl α-D-glucopyranoside (3 g) in deuterium oxide (30 mL) was evaporated to dryness. The residue was dissolved in deuterium oxide (80 mL), and deuterated Raney nickel (20 mL, settled volume) was added. This mixture was boiled under reflux for 10 h, and cooled, and the nickel was filtered off (through five layers of filter paper) and washed with a small volume of hot deuterium oxide; the solid on the filter paper should not be allowed to become dry, as Raney nickel is pyrophoric. The filtrate was evaporated to dryness, and the residue was recrystallized twice from anhydrous ethanol; yield 2.3 g (75%), m.p. 165–166°, $[\alpha]_D^{23}$ +152° (*c* 2, water), mixture m.p. 165–167°; lit.[18] m.p. 167–168°, $[\alpha]_D$ +157° (*c* 2, water). The retention time (g.l.c.) was the same (15 min) as that of the "light" material. For ^{13}C-n.m.r. data, see Table I.

Methyl 2,3,4,6-tetra-O-acetyl-α-D-glucopyranoside-2,3,4,6,6-^{2}H$_5$ (**2**). — Compound **1** was acetylated with acetic anhydride and pyridine in the usual way[19]. The

TABLE I

PROTON-DECOUPLED ^{13}C-N.M.R. SPECTRA[a] OF COMPOUNDS **1**, **3**, **5**, **7**, **9**, AND **11** (a) AND THEIR "LIGHT" ANALOGS (b)

Compound	*C-1*	*C-2*	*C-3*	*C-4*	*C-5*	*C-6*	*Me*
1 a	99.9				72.2[b]		55.7
b	99.9	72.1[c]	74.0	70.4	72.3[c]	61.5	55.7
3 a	99.8				71.1[b]		55.6
b	99.8	69.9	70.2	68.9	71.2	61.8	55.6
5 a	101.5				73.1[b]		55.4
b	101.5	70.7[c]	71.4[c]	67.5	73.2	61.7	55.4
7 a	103.9				76.4[b]		57.8
b	103.9	73.8	76.6	70.5	76.5	61.6	57.8
9 a	104.5				75.6[b]		57.8
b	104.5	71.5	73.6	69.4	75.7	61.7	57.8
11[d] α a	92.8				71.9[b]		
b	92.8	72.2	73.6	70.4	72.0	61.6	
11[d] β a	96.6				76.3[b]		
b	96.6	74.9	76.5	70.4	76.4	61.6	

[a]Measured in deuterium oxide solution. Chemical shifts are in p.p.m. from Me_4Si, using 1,4-dioxane (67.22 p.p.m.) as the internal reference standard. [b]For β-deuterium isotope-effect, see refs. 14 and 17. [c]For corrected assignment, see ref. 17. [d]Values obtained from the anomeric mixture.

tetraacetate was recrystallized from ethanol; m.p. 100–102°, $[\alpha]_D^{22}$ +128° (*c* 4, chloroform), mixture m.p. 100–101°; lit.[18] m.p. 101–103°, $[\alpha]_D^{25}$ +130° (*c* 2, chloroform).

Methyl α-D-*galactopyranoside*-2,3,4,6,6-$^2H_5$ (**3**). — Methyl α-D-galactopyranoside (3 g) was deuterium-exchanged as described for **1**; yield 2.0 g (66%), m.p. 114°, $[\alpha]_D^{23}$ +190° (*c* 2, water), mixture m.p. undepressed; lit.[20] m.p. 114–116°, $[\alpha]_D$ +192.7° (water). The retention time (g.l.c.) was the same (11 min) as that of the "light" material. For ^{13}C-n.m.r. data, see Table I.

Methyl 2,3,4,6-tetra-O-*acetyl*-α-D-*galactopyranoside*-2,3,4,6,6-$^2H_5$ (**4**). — Compound **4** was prepared as for compound **2**; m.p. 86°, $[\alpha]_D^{22}$ +133° (*c* 3, chloroform), mixture m.p. undepressed; lit.[20] m.p. 86–87°, $[\alpha]_D$ +132.5° (chloroform).

Methyl α-D-*mannopyranoside*-2,3,4,6,6-$^2H_5$ (**5**). — Methyl α-D-mannopyranoside (3 g) was deuterium-exchanged as described for compound **1**; yield 2 g (66%); m.p. 193°, $[\alpha]_D^{23}$ +80° (*c* 1, water), mixture m.p. undepressed; lit.[21] m.p. 193–194°, $[\alpha]_D$ +79.2° (water). The retention time (g.l.c.) was the same (10 min) as that of the "light" material. For ^{13}C-n.m.r. data, see Table I.

Methyl 2,3,4,6-tetra-O-*acetyl*-α-D-*mannopyranoside*-2,3,4,6,6-$^2H_5$ (**6**). — Compound **6** was prepared as for compound **2**; m.p. 65°, $[\alpha]_D^{23}$ +50° (*c* 1, chloroform); mixture m.p. undepressed; lit.[22] m.p. 65°, $[\alpha]_D$ +49.1° (chloroform).

Methyl β-D-*glucopyranoside*-2,3,4,6,6-$^2H_5$ (**7**). — Methyl β-D glucopyranoside (3 g) was deuterium exchanged as described for **1**: yield 2.1 g (68%); m.p. 108°, $[\alpha]_D^{23}$ −32° (*c* 3, water), mixture m.p. 108°; lit.[23] m.p. 108–110°, $[\alpha]_D$ −34.2° (water).

The retention time (g.l.c.) was the same (116 min) as that of the "light" material. For ^{13}C n.m.r. data, see Table I.

Methyl 2,3,4,6-tetra-O-*acetyl-β*-D-*glucopyranoside*-2,3,4,6,6-$^{2}H_5$ (**8**). — Compound **8** was prepared as for compound **2**; m.p. 105°, $[\alpha]_D^{23}$ −19° (*c* 3, chloroform), mixture m.p. undepressed; lit.[24] m.p. 104°, $[\alpha]_D$ −18.7° (chloroform).

Methyl β-D-*galactopyranoside* 2,3,4,6,6-$^{2}H_5$ (**9**). — Methyl β-D-galactopyranoside (3 g) was deuterium-exchanged as described for **1**; yield 2.0 g (65%); m.p. 177°, $[\alpha]_D^{23}$ 0° (*c* 3, water), mixture m.p. undepressed; lit.[25] m.p. 178–180°, $[\alpha]_D$ +0.7° (water). The retention time (g.l.c.) was the same (13 min) as that of the "light" material. For ^{13}C n.m.r. data, see Table I.

Methyl 2,3,4,6-tetra-O-*acetyl-β*-D-*galactopyranoside*-2,3,4,6,6-$^{2}H_5$ (**10**). — Compound **10** was prepared as for compound **2**; m.p. 92–93°, $[\alpha]^{23}$ −14° (*c* 3, chloroform), mixture m.p. undepressed; lit.[25] m.p. 94°, $[\alpha]_D$ −14.05° (chloroform).

The isomerization of methyl α-D-*glucopyranoside*-2,3,4,6,6-$^{2}H_5$ (**1**). — A solution of methyl α-D-glucopyranoside (3 g) in deuterium oxide (30 mL) was evaporated to dryness; the residue was dissolved in deuterium oxide (80 mL), and deuterated Raney nickel (20 mL, settled volume) was added. The mixture was boiled under reflux for 2.5 d, and cooled, the catalyst was removed by filtration, and the filtrate was evaporated to a colorless syrup. The proton-decoupled, ^{13}C-n.m.r. spectrum of this syrup showed the presence of **1** [δ 99.9 (C-1), 72.2 (C-5), and 57.0 (Me)], **5** [δ 101.5 (C-2), 73.1 (C-5), and 55.4 (Me)], and **3** [δ 99.8 (C-1), 71.1 (C-5), and 55.6 (Me)]. G.l.c. showed the major components to be **1** (14 min, area 7.2), **5** (10 min, area 7.5), **3** (11 min, area 2.4), and a further, unidentified compound (8 min, area 1.0). By repeated, fractional recrystallization from ethanol, compound **5** (m.p. 193°, $[\alpha]_D^{23}$ +77° in water) was isolated as the first fraction, and compound **1** (m.p. 165°, $[\alpha]_D^{23}$ +155° in water) as the other fraction.

The isomerization of methyl α-D-*galactopyranoside*-2,3,4,6,6-$^{2}H_5$ (**3**). — Methyl α-D-galactopyranoside was subjected to the same, prolonged exchange-conditions as had been used for the *gluco* isomer **1**. The proton-decoupled, ^{13}C-n.m.r. spectrum showed the presence of mainly **1** and **3**. G.l.c. showed, as major components, **1** (14 min, area 16.8) and **3** (11 min, area 13.2), a trace of **5** (10 min), and an unidentified component (8 min, area 1.0).

The isomerization of methyl α-D-*mannopyranoside*-2,3,4,6,6-$^{2}H_5$ (**5**). — Methyl α-D-mannopyranoside was subjected to the same, prolonged exchange conditions as had been used for the *gluco* isomer **1**. The proton-decoupled, ^{13}C-n.m.r. spectrum showed the presence of mainly **5** and **1**. G.l.c. showed, as major components, **5** (10 min, area 16), **1** (14 min, area 10), and an unidentified component (8 min, area 1.0).

Attempted C-protium—C-deuterium exchange of 1,2:5,6-di-O-*isopropylidene-α*-D-*glucofuranose and 1,2:3,4-di*-O-*isopropylidene-α*-D-*galactose*. — The di-*O*-isopropylidene derivatives of D-glucose and D-galactose[26] were repeatedly subjected to the exchange conditions described for **1**. No *C*-deuteration was observable by ^{1}H- or ^{13}C-n.m.r. spectroscopy, and, in both cases, the starting material was recovered unchanged.

α-D-*Glucopyranose*-2,3,4,6,6-$^2H_5$ (**11**). — Compound **1** (10 g) was hydrolyzed with hydrochloric acid as described previously[9], to give α-D-glucopyranose-*2,3,4,6,6-*$^2H_5$; yield 6 g (64%): m.p. 142°, $[\alpha]_D^{23}$ +49° (*c* 1, water); lit.[27] m.p. 146°, $[\alpha]_D$ +52.7°. For ^{13}C-n.m.r. data, see Table I.

myo-*Inositol*-$^2H_6$ (**12**). — *myo*-Inositol (3 g) was deuterium-exchanged as described for **1**, and the product was recrystallized twice from water–2-propanol; yield 2 g (64%), m.p. 222–225°; lit.[28] m.p. 224–226°. The product had no p.m.r. and ^{13}C-n.m.r. spectra. It was found convenient to purify the crude compound *via* its hexaacetate, which crystallizes very readily in pure form.

Hexa-O-*acetyl*-myo-*inositol*-$^2H_6$ (**13**). — Impure *myo*-inositol-$^2H_6$ (500 mg) was acetylated in boiling acetic anhydride (10 mL) containing concentrated sulfuric acid (3 drops) for 5 min. The solution was cooled, and poured into water (100 mL), and the mixture was stirred until crystallization was complete (5 min). The solid was filtered off, washed with water, and dried. One recrystallization from methanol gave pure **13**: yield 1.0 g (84%), m.p. 213–215°, mixture m.p. 214–215°; lit.[28] m.p. 214–215°.

Hydrogenolysis of methyl 4,6-O-benzylidene-α-D-glucopyranoside with Raney nickel. — Methyl 4,6-*O*-benzylidene-α-D-glucopyranoside (6 g), Raney nickel (W. R. Grace and Co., No. 28; 50 mL, settled volume), and water (200 mL) were stirred for 1 h at room temperature, and the insoluble, upper liquid-layer was then identified as toluene by its p.m.r. spectrum and odor. The nickel was filtered off, and the filtrate evaporated to dryness. The residue (3.1 g) was recrystallized from ethanol, to give methyl α-D-glucopyranoside (2.5 g), m.p. 165°, $[\alpha]_D^{23}$ +157° (*c* 3, water). The p.m.r. spectrum and the proton-decoupled. ^{13}C-n.m.r. spectrum were identical to those of authentic material.

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