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Hydrogen fluoride-mediated synthesis of 1-thiotrehaloses involving reaction of D-glucose with hydrogen sulfide*

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ABSTRACT

Hydrogen sulfide reacted with D-glucose in hydrogen fluoride solution to yield preponderantly α,α-1-thiotrehalose, β,β-1-thiotrehalose, and the α,β anomer. Conditions were found under which the thiotrehaloses were obtained in the respective proportions of 8:5:5.

INTRODUCTION

Dissolution of D-glucose in anhydrous hydrogen fluoride is known to result in a concentration-dependent mixture of products. In dilute solution, the main component is α-D-glucopyranosyl fluoride (**3**) in equilibrium with a mixture of reversion oligosaccharides. In concentrated solution, the equilibrium is shifted towards the reversion products. The interconversion between these entities is assumed[3] to take place *via* an oxocarbenium ion **2**.

Alcohols react readily with either D-glucose or D-glucan solutions in hydrogen fluoride, presumably *via* the ion **2**, to form alkyl D-glucopyranosides and such technologically important derivatives can be prepared in good yields through this reaction[4]. This requires the use of suitable conditions which include appropriate proportions of hydrogen fluoride, taking into account that an excess of it will protonate the alcohol and, thus, prevent the reaction.

Thioalcohols are better nucleophiles than alcohols and they are not readily protonated. Therefore they may be expected to react readily with a glucosyl cation in hydrogen fluoride solution to yield alkyl 1-thioglucopyranosides, provided that the reaction is carried out with stoichiometric amounts of reactants in order to avoid the possible formation of di(thioacetals) or poly(thioacetals) from dithiols[5]. The need for an easier access to 1-thio-α,α-trehalose[6], a potent inhibitor of the enzyme α,α-trehalase[7] (EC

* Carbohydrate Reactivity in Hydrogen Fluoride, Part 10. For Part 9, see ref. 1; for Part 8, ref. 2.

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3.2.1.28) primarily involved in the energetics of insects[8], led us to try to prepare this compound by reaction of D-glucose with hydrogen sulfide in anhydrous hydrogen fluoride.

RESULTS AND DISCUSSION

Bubbling of hydrogen sulfide into a solution of D-glucose in hydrogen fluoride at 0° for 1 h resulted in a rather complex mixture of products containing, as seen from the ^{13}C-n.m.r. spectrum of the crude reaction mixture resulting from *in situ* precipitation with diethyl ether, the three anomeric 1-thiotrehaloses **7**, **9**, and **11** with signals for C-1 at δ 82.9 for **7**, 83.7 for **9**, and 85.9–86.0 for **11**. Besides, the anomeric α- and β-1-thio-D-glucopyranoses **4** and **5** were detected by their signals at δ 81.0 and 80.8, together with a possible cyclic poly(thioacetal) derivative **6** having a high-field signal at δ 57.9. Reversion products, *i.e.*, D-glucooligosaccharides resulting from D-glucose intermolecular glycosidation, having a group of signals for C-1 at δ 97[3], may also be present, as well as the fluoride **3** (C-1 as a doublet of 221 Hz at δ 108.2).

Since the amounts of **7**, **9**, and **11**, as seen from the integration of the peak heights, were rather low (Table I, Experiment 1), a series of experiments, in which the temperature and the amount of hydrogen sulfide was varied, were carried out in order to find optimal conditions for the formation of the thiotrehaloses (Table I).

Initially, the experiments were performed by bubbling hydrogen sulfide through solutions in hydrogen fluoride during the full time of the experiment, *i.e.*, using an excess of hydrogen sulfide (Table I, Experiments 1–4). At −10°, the main product was a mixture of 1-thio-α- and -β-D-glucopyranose (**4** and **5**). When treated with hydrogen sulfide for 4 h at 0°, the main product was the dithioacetal derivative **6**; and at 20°, the thiotrehaloses **7**, **9**, and **11** were preponderant.

In order to control the amount of hydrogen sulfide used in the reactions, a series of experiments (Table I, Experiments 5–9) were carried out in closed bottles, adding measured amounts of liquid hydrogen sulfide at low temperature before closing the bottles. Experiments 5 and 6 were both performed at −10° for 1 h and showed, as might be expected from stoichiometric considerations, that when the amount of hydrogen sulfide was decreased, the proportion of reversion products increased, whereas less of the thioacetals **4**–**6** were formed. Similar results were obtained for Experiments 8 and 9 carried out at 20°. These preliminary experiments led us to the conclusion that the formation of 1-thiotrehaloses follows the pathway illustrated in Scheme 1 and that the formation of the thiotrehaloses is thermodynamically favored relative to that of α- and β-1-thio-D-glucose, and of the thioacetal. This was in fact supported when, in a separate experiment, 1-thio-α,α-trehalose was found not to be significantly modified in hydrogen fluoride solution for 1 h at 20° (^{13}C-n.m.r.).

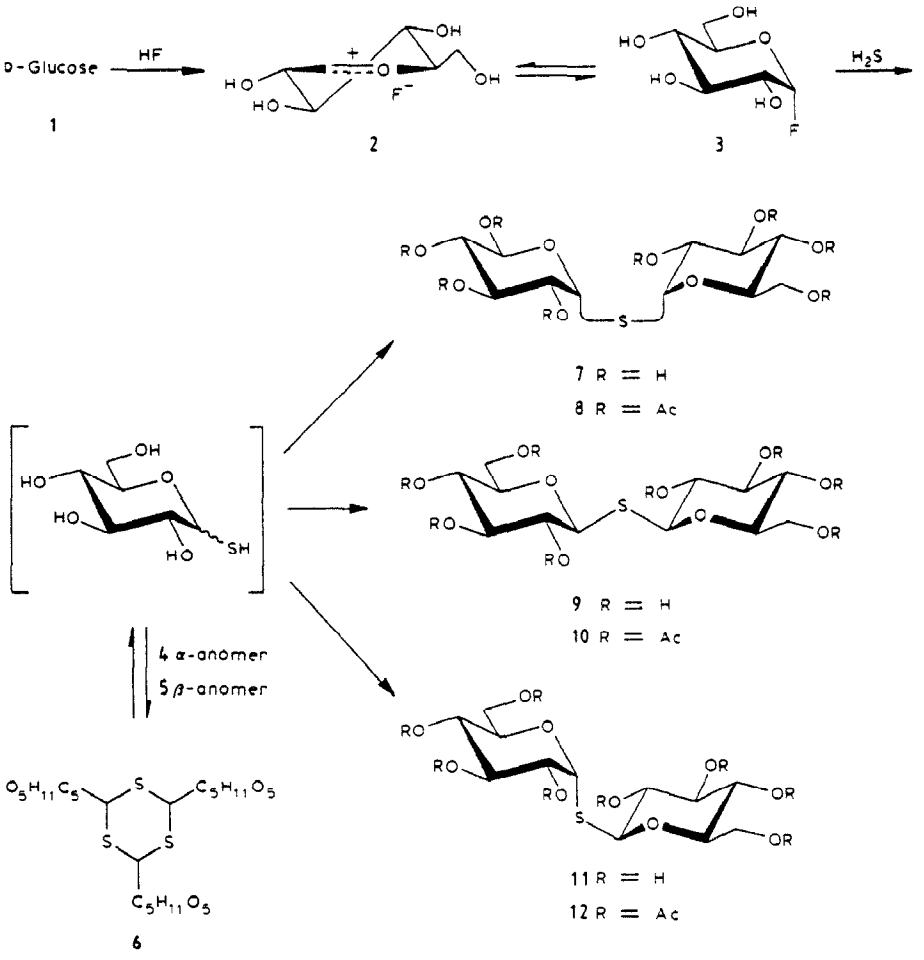
From these observations, it was concluded that optimal conditions for the formation of 1-thiotrehaloses could be attained by treatment of D-glucose in hydrogen fluoride with a slight stoichiometric excess of hydrogen sulfide at room temperature, in a closed vessel, followed by uninterrupted reaction of the same mixture with the vessel

TABLE I

Products formed by the action of hydrogen sulfide on D-glucose in hydrogen fluoride solution[a]

Experiment No.	*H_2S (mL)*	*Reaction temp. (degrees)*	*Reaction time (h)*	*Products (%)*					
				4 + 5	**6**	**7**	**9**	**11**	*Reversion products*
Experiments carried out in open bottle bubbling H_2S through the HF solution									
1	excess	−10	1	67	0	8	3	6	17
2	excess	0	1.5	28	26	26	7	10	3
3	excess	0	4	6	59	14	13	8	0
4	excess	20	1.5	11	13	53	9	14	0
Experiments carried out in closed bottle with measured amount of hydrogen sulfide									
5	0.3 (0.8 mol. equiv.)	−10	1	30	10	27	5	16	11
6	0.2 (0.53 mol. equiv.)	−10	1	15	0	31	6	22	26
7	0.2	0	2.5	11	31	25	6	16	12
8	0.3	20	0.5	8	19	33	17	23	0
9	0.2	20	1	2	14	39	18	25	1
Experiments carried out, first in closed bottle, then in open bottle									
10	0.2	1.5 h at 0°, and then 4 h at 20°		0	9	32	37	21	1
11	0.2	20	0.7–1	0	4	30	23	42	1
12	0.2	20	0.75–0.5	0	10	31	22	37	0
13	0.2	20	0.5–1.5	0	2	36	13	37	13
14	0.2	20	1–1.5	0	5	41	27	25	2

[a] In all experiments, solutions of D-glucose (2 g, 11 mmol) in HF (4 mL) were used. The crude products (see Experimental section) were analyzed by 125-MHz ^{13}C-n.m.r. spectroscopy by measuring peak-heights of nonoverlapping signals. In addition to the products shown, the crude mixtures contained a number of other products, each in small amounts. Hence, the percentages shown are relative; true yields were 40–60% of those shown.



opened in order to let any excess of hydrogen sulfide escape and, thus, shift the equilibrium towards the formation of thiotrehaloses. Experiments 10–14 (Table I) showed the composition of the products obtained through this method. It is seen that the products are primarily the 1-thiotrehaloses with small amounts of unidentified products. The yield in 1-thio-α,α-trehalose **7** was optimal for a reaction time of 1 h at 20°, and the separation of **7** from the anomeric disaccharide mixture was achieved by column chromatography of the octa-*O*-acetyl derivative **8**.

In order to support the reaction proposed in Scheme 1 for the formation of 1-thiotrehaloses, 1-thio-α- (**4**) and -β-D-glucopyranose (**5**) were treated separately with one molar equivalent of D-glucose in hydrogen fluoride for 1.5 h at 20°. This gave a mixture of the 1-thiotrehaloses **7**, **9**, and **11**, however in proportions that indicated a slow anomerization process during the reaction for both sequences involving either of the 1-thio-D-glucopyranose anomers.

Although a mutarotation process has already been reported for 1-thio-β-D-glucopyranose in water, solution properties and equilibrium composition for 1-thiogly-

TABLE II

^{13}C-N.m.r. data for compounds **4**–**6**, **7**, **9** and **11**

Compound	*^{13}C-Chemical shifts*		
	C-1	*C*-2–5	*C*-6
4	81.02	77.73, 73.98,72.66,70.40	61.64
5	80.80	76.62, 73.80, 72.34, 70.31	61.38
6	57.91	75.36, 71.94, (2C), 70.58	63.67
7	82.89	74.62, 73.60, 71.4, 70.4	61.4
9	83.74	80.77, 78.02, 73.10, 70.48	61.75
11	85.95	80.88, 77.95, 74.65, 73.94	61.70
	86.02	73.58, 71.78, 70.33, 70.21	61.38

coses are not known. In order to obtain some insight on the mutarotation of 1-thio-α- and -β-D-glucopyranose and, furthermore, to confirm the ^{13}C-n.m.r. identification of **4** and **5**, the spectra were recorded for both compounds. Solutions in deuterium oxide were prepared from the corresponding sodium salts by acidification with hydrochloric acid. The spectra, recorded for freshly prepared solutions, showed pure **4** and **5** (Table II). Both solutions underwent a slow mutarotation and reached equilibrium after several days at 20°, at which time both contained ~ 28% of the α-D anomer **4** and ~ 72% of the β-D anomer **5**, accompanied by some decomposition products. The mutarotation of **5** has been studied previously through optical rotations; however, the equilibrium composition was not determined[9].

The structure of the poly(thioacetal) **6** has not been unequivocally proved and a pure product was not obtained. The proposed structure is based solely on the ^{13}C-n.m.r. spectrum which is very similar to that of D-glucose diethyl dithioacetal[10]. The signal at δ 57.8 could only be explained by a structure having two sulfur atoms attached to the anomeric carbon and, with hydrogen sulfide, this would likely lead to a cyclic compound as in **6**, in which the three D-glucose units are bound as in a dithioacetal.

The present method allows access, in a one-step procedure, to 1-thio-α,α-trehalose **7** from inexpensive and readily available precursors. Although this synthesis is still not stereospecific and the yield is low, it is more convenient than the previously described procedures[6] for a large-scale preparation of this 1-thiodisaccharide.

EXPERIMENTAL

General methods. — Melting points are uncorrected. Optical rotations were measured with a Perkin–Elmer 241 instrument. N.m.r. spectra were obtained on a Bruker AM 500 instrument. Spectra of unacylated products were recorded for solutions in D_2O (internal 1,4-dioxane, δ 67.4; or acetone, δ 31.07). For acetylated compounds, solutions in $CDCl_3$ were used with the central peak of the triplet (δ 76.91) as internal reference. F.a.b.-mass spectra were measured in the positive and negative modes (Xe, glycerol matrix) with a double-focusing Kratos-AEI MS-50 apparatus (Manchester),

fitted with an f.a.b. 11NF Ion Tech atom-gun and a 1.2-T magnet, operating at the full accelerating potential (6 kV), and a MAT SS 200 Finnigan (DEC-PDP 11-34) computer.

Anhydrous HF was a commercial product obtained in steel cylinders. Prior to use, it was kept in polyethylene bottles at $-20°$. All reactions with HF were conducted in polyethylene bottles. H_2S was a commercial product obtained in cylinders. Separation of *O*-acetylated 1-thiodisaccharides was performed by flash chromatography on a Silica Gel 60 column (230–400 mesh, Merck) with diethyl ether as eluent. The purity of all compounds was ascertained by t.l.c. on Silica Gel plates (Merck 60 F_{254}, Darmstadt) with diethyl ether as eluent for acylated derivatives and with methanol for free unacylated sugars.

Reaction of D-*glucose with* H_2S *in HF.* — For conditions of all experiments, refer to Table I. In Experiments 1–4, D-glucose was dissolved in HF at 0° and a stream of H_2S was bubbled (1 bubble/s) through the solution under the conditions of temperature and time shown in Table I. When the reactions were performed in a cooled container (Experiments 5–9), the solution of D-glucose in HF was cooled in Dry Ice, and liquid H_2S, obtained by condensing the gas in a tube cooled in Dry Ice, was added. The bottle was then cooled and kept under the conditions shown in Table I. Precautions should be taken because of the elevated pressure in the flask). In Experiments 10–14, the bottle was finally opened and kept for the time shown.

The products were, in all cases, isolated by cooling the reaction mixture in Dry Ice, followed by addition of diethyl ether. This precipitated the products as sticky gums which, on repeated washing and stirring with ether, formed amorphous powders that could be filtered off.

*(2,3,4,6-Tetra-*O*-acetyl-α-*D*-glucopyranosyl) 2,3,4,6-tetra-*O*-acetyl-1-thio-α-*D*-glucopyranoside (octa-*O*-acetyl-1-thio-α,α-trehalose)* (**8**), *(2,3,4,6-tetra-*O*-acetyl-β-*D*-glucopyranosyl) 2,3,4,6-tetra-*O*-acetyl-1-thio-β-*D*-glucopyranoside (octa-*O*-acetyl-1-thio-β,β-trehalose)* (**10**), *and (2,3,4,6-tetra-*O*-acetyl-α-*D*-glucopyranosyl) 2,3,4,6-tetra-*O*-acetyl-1-thio-β-*D*-glucopyranoside (octa-*O*-acetyl-1-thio-α,β-trehalose)* (**12**). — An experiment was carried out, as reported in Experiments 10–14 of Table I, using D-glucose (10 g, 55 mmol) in HF (20 mL) and liquid H_2S (1 mL). The mixture was kept for 1.5 h at 0° in a closed bottle (the pressure decreased after 0.5 h, indicating absorption of H_2S), and 1.5 h at 20° with the bottle opened. Precipitation and washing with diethyl ether gave a crude product (10 g) which contained **7**, **9**, and **11** in the relative molar proportions of 13:13:24, as shown by the ^{13}C-n.m.r. spectrum. Acetylation with acetic anhydride–pyridine gave a compound (18 g) which crystallized from diethyl ether to furnish a mixture (7.2 g, 37%) which contained mainly the octaacetates **8**, **10**, and **12** in the relative proportions of 16:10:23. Chromatography of the mother liquor material gave an additional amount (1.0 g) of the same product, bringing the total yield to 43%. This product (2.0 g) was flash-chromatographed on a column of silica gel with diethyl ether as the eluent. The first component to be eluted crystallized from diethyl ether to give octa-*O*-acetyl-1-thio-α,α-thiotrehalose (0.40 g, 8.8%, based on D-glucose) (**8**). The two isomeric products, **10** and **12**, were only partially separated, and the pure products were obtained after repeated chromatography.

Octa-O-acetyl-1-thio-α,α-trehalose (**8**). M.p. 186–188° (from dichloromethane–pentane), $[\alpha]_D^{20}$ +266° (*c* 2.4, chloroform); ^{1}H-N.m.r.: δ 5.88 ($J_{1,2}$ 6.0 Hz, H-1), 5.32 ($J_{3,4}$ 10 Hz, H-3), 5.10 ($J_{2,3}$ 10 Hz, H-2), 5.06 ($J_{4,5}$ 10 Hz, H-4), 4.28 ($J_{5,6a}$ 5.5 Hz, H-5), 4.28 (H-6a), and 4.10 ($J_{5,6'b}$ 4.0, $J_{6a,6b}$ 14 Hz, H-6b); ^{13}C-n.m.r.: δ 78.4 (C-1), 70.3, 70.1, 68.4, 68.3 (C-2–C-5), and 61.7 (C-6); lit.[11] m.p. 191–192°, $[\alpha]_D$ +259.2° (chloroform).

Octa-O-acetyl-1-thio-β,β-trehalose (**10**). M.p. 172–173° (after successive crystallizations from ethanol, and then from dichloromethane–diethyl ether), $[\alpha]_D^{20}$ −40.5° (*c* 0.7, chloroform); ^{1}H-n.m.r.: δ 5.24 ($J_{3,4}$ 9.5 Hz, H-3), 5.12 ($J_{4,5}$ 9.5 Hz, H-4), 5.07 ($J_{2,3}$ 9.2 Hz, H-2), 4.84 ($J_{1,2}$ 10.2 Hz, H-1), 4.28 ($J_{6a,6b}$ 12.5 Hz, H-6a), 4.18 ($J_{5,6b}$ 2.5 Hz, H-6b), and 3.70 ($J_{5,6a}$ 5.0 Hz, H-5); ^{13}C-n.m.r.: δ 80.5 (C-1), 76.1, 73.7, 70.1, 68.1, (C-2–5), and 62.0 (C-6); lit.[11] m.p. 175–176°, $[\alpha]_D$ −35.5°.

Octa-O-acetyl-1-thio-α,β-trehalose (**12**). M.p. 168–169° (from dichloromethane–diethyl ether), $[\alpha]_D^{20}$ +114° (*c* 1, chloroform); ^{1}H-n.m.r. (α-D-glucopyranosyl residue): δ 6.0 ($J_{1,2}$ 5.09 Hz, H-1), 5.34 ($J_{3,4}$ 9.5 Hz, H-3), 5.15 ($J_{4,5}$ 9.5 Hz, H-4), 5.01 ($J_{2,3}$ 10.2 Hz, H-2), 4.38 ($J_{5,6a}$ 2.3 Hz, H-5), 4.38 ($J_{6a,6b}$ 13.5 Hz, H-6), and 4.10 ($J_{5,6b}$ 3.3 Hz, H-6), (1-thio-β-D-glucopyranoside residue): δ 5.20 ($J_{3,4}$ 9.5 Hz, H-3), 5.09 ($J_{4,5}$ 9.5 Hz, H-4), 5.07 ($J_{2,3}$ 9.3 Hz, H-2), 4.56 ($J_{1,2}$ 10.2 Hz, H-1), 4.18 ($J_{6a,6b}$ 12.5 Hz, H-6a), 4.14 ($J_{5,6b}$ 4.6 Hz, H-6b), and 3.71 ($J_{5,6a}$ 2.2 Hz, H-5); ^{13}C-n.m.r.: δ 82.6, 82.0 (C-1), 76.2, 73.6, 70.9, 70.5, 70.2, 68.4, 67.8 (C-2–5), 61.9, and 61.1 (C-6); lit.[11] m.p. 170°, $[\alpha]_D$ +115°.

Reaction of 1-thio-α- and -β-D-glucopyranose with D-glucose in HF. — 1-Thio-β-D-glucopyranose sodium salt dihydrate[12] (1.0 g, 3.9 mmol) and D-glucose (0.83 g) were dissolved in HF (4 mL), and the solution was kept at 20° for 1.5 h. The mixture was then treated as described above to give a product (1.5 g) that was analyzed by ^{13}C-n.m.r. spectroscopy. This showed that the product contained 1-thio-α,α-trehalose (**7**, ~11%), 1-thio-β,β-trehalose (**9**, ~26%), 1-thio-α,β-trehalose (**11**, ~63%), and small amounts of other unidentified products.

A similar reaction, carried out with the sodium salt of 1-thio-α-D-glucopyranose[6], gave a mixture containing **7** (~37%), **9** (~21%), and **11** (~42%).

1-Thio-α,α-trehalose (**7**). — A suspension of the octaacetate **8** (1.2 g, 1.72 mmol) in methanol (50 mL) was treated with sodium methoxide for 4 h. The resulting solution was de-ionized with Amberlite IR-120 (H^+) cation-exchange resin, filtered through carbon, and evaporated to give pure **7** (^{13}C-n.m.r.) (600 mg). Recrystallization from methanol–ethanol gave a product having m.p. 244–246°, $[\alpha]_D^{20}$ +390° (*c* 0.7, water); ^{13}C-n.m.r.: δ 82.9 (C-1), 76.6, 73.6, 71.4, 70.4 (C-2–5), and 61.4 (C-6); m.s. f.a.b.$^{(+)}$: *m/z* 359 [24, $(M + H)^+$], 325 [10, $(MH - SH_2]^+$], and 163 (33, glycosyl cation); m.s. f.a.b.$^{(+)}$ (NaCl): *m/z* 381 [54, $(M + Na)^+$], and 325 (8, $MH\text{-}SH_2^+$); m.s. f.a.b.$^{(-)}$: *m/z* 357 (52, $[M-H]^-$) and 195 (40, $[GlcS]^-$); lit.[6] m.p. 138–148°, $[\alpha]_D^{20}$ +358° (*c* 0.53, water).

Anal. Calc. for $C_{12}H_{22}O_{10}S$: C, 40.21; H, 6.19; S, 8.95. Found: C, 40.08; H, 6.13; S, 8.80.

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