[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF STANFORD UNIVERSITY]

The Cleavage of Phenyl Tetraacetyl-β-D-thioglucoside with Bromine. A Mechanistic Interpretation[1]

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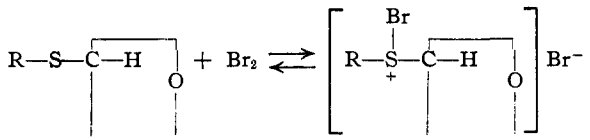
Recently it was found[2] that aryl or alkyl tetraacetyl-β-D-thioglucosides produce good yields of α-D-glucose pentaacetate when treated with a large excess of bromine in acetic acid. This reaction, which involves cleavage of the thio-aglycon and replacement with acetoxy, contrasts sharply to that observed for phenyl tetraacylglycosides. In the latter case nuclear bromination is the only reaction observed.[3]

It has been shown[2] that bromine alone, and no other constituent of the reaction mixture, is capable of producing cleavage of thioglucosides in acetic acid. With this in mind it became desirable to determine by what mechanism bromine is capable of engendering such cleavage, and to study other factors affecting the reaction. Several of these considerations are treated in the present paper.

The mechanism of the cleavage of acetylated thioglucosides with bromine proved to be unexpectedly complex, apparently proceeding by three distinct steps. Each of these steps is experimentally demonstrable, but it is not implied that these steps are unique. The cleavage is undoubtedly accompanied by side reactions of a complex nature at present not understood.

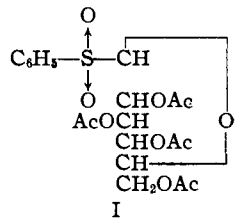
The initial step in the reaction seems to be an equilibrium addition of bromine to the sulfur atom of the thioglucoside to form a bromosulfonium bromide, as illustrated in Equation (1).



(1)

This postulate is logical in view of the known addition of bromine to organic sulfides, and is supported by several experimental facts.

In phenyl tetraacetyl-β-D-glucosyl sulfone, I, the sulfur atom of the original thioglucoside is bound to two oxygen atoms by semipolar linkages. The sulfur atom in I, having no available unshared electrons, is thus protected, and should be incapable of entering into an equilibrium such as Equation (1). Experimentally bromine in acetic acid is completely without action on the sulfone I. Only starting material was recovered when I was subjected to reaction conditions ordinarily resulting in cleavage.



I

A second consequence of Equation (1) is that the rate of the over-all reaction should increase with an increase in the relative bromine concentration. A study of the mutarotation displayed by the reaction as a function of bromine concentration proved this to be the case. Increasing the concentration of bromine speeded up the rate of mutarotation until it finally became unmeasurable. The effect of bromine concentration on mutarotation is seen in Fig. 1.

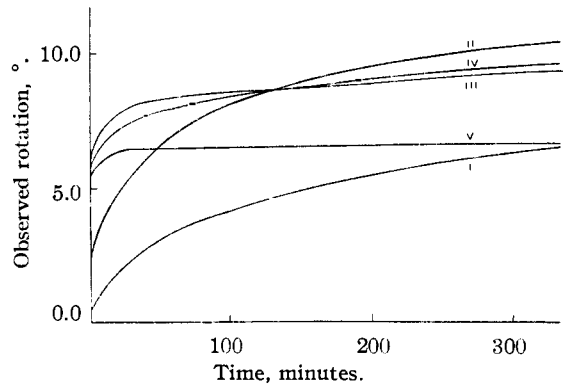


Fig. 1.—Mutarotations of phenyl tetraacetyl-β-D-thioglucoside with varying quantities of bromine: bromine quantities; equivalent: I, 0.6; II, 1.0; III, 2.5; IV, 5.0; V, 12.8.

Finally, an equilibrium such as (1) should be repressed in the presence of excess bromide, and this should be reflected in a diminished rate of mutarotation. When one equivalent of phenyl tetraacetyl-β-D-thioglucoside and one equivalent of bromine were allowed to react in the presence of three equivalents of lithium bromide, the mutarotation was strikingly repressed as shown in Fig. 2.

This repression of mutarotation is due to two factors, (a) the mass action effect of bromide causing Equation (1) to shift to the left, and (b) the removal of bromine from the reaction mixture by tribromide ion formation according to Equation (2).

$$Br_2 + Br^- \rightleftharpoons Br_3^- \qquad (2)$$

Nozaki and Ogg[4] have measured the equilibrium constant of Equation (2) at various temperatures. Extrapolating their data to room temperature, the

(1) Presented before the Division of Sugar Chemistry and Technology of the American Chemical Society, New York, N. Y., September, 1947.

(2) Bonner, THIS JOURNAL, 70, 770 (1948).

(3) Hurd and Bonner, *ibid.*, 67, 1764 (1945).

(4) Nozaki and Ogg, THIS JOURNAL, 64, 698 (1942).

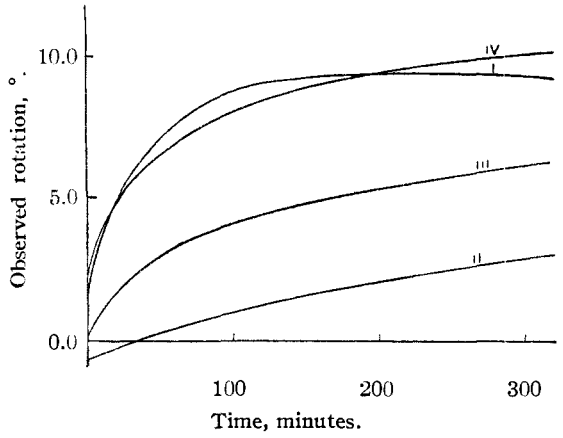
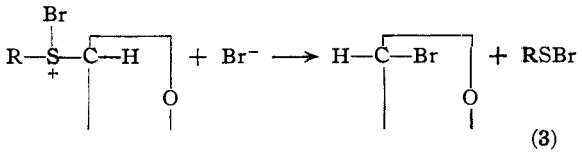


Fig. 2.—Repression of mutarotation in the presence of excess bromide ion: I, one equivalent bromine; II, one equiv. bromine and three equiv. lithium bromide; III, 0.6 equiv. bromine, slightly less than the quantity permitted by the bromine–tribromide equilibrium; IV, one equiv. bromine and three equiv. lithium perchlorate.

maximum concentration of bromine permitted by the equilibrium constant of Equation (2) was calculated, and a reaction was conducted employing slightly *less* than this quantity of bromine. The mutarotation curve was significantly higher than that obtained in the presence of lithium bromide, as seen by comparing Curves II and III of Fig. 2. This indicates that the removal of bromine by Equation (2) can not alone explain the repressed mutarotation in the presence of lithium bromide, and that the excess bromide ion must have indeed operated to repress the equilibrium in Equation (1). That the repression of mutarotation by lithium bromide was not a salt effect is seen by comparison of Curves I and IV of Fig. 2. Curve IV, obtained with one equivalent of bromine and three equivalents of lithium perchlorate, is practically identical with Curve I.

It is interesting to note that the mutarotation curves in Figs. 1 and 2 do not attain identical equilibrium values. This suggests that the composition of the product depends upon the concentration of bromine in the reaction mixture, a fact borne out by further evidence described below.

The second step in the mechanism of the cleavage seems to be an attack by a bromide ion or bromine molecule on the face of carbon atom one opposite the sulfur linkage in the bromosulfonium bromide. This step, involving Walden inversion, produces acetobromoglucose as the second intermediate as illustrated in Equation (3). The sulfur moiety is irreversibly cleaved, presumably as an unstable sulfenyl bromide.



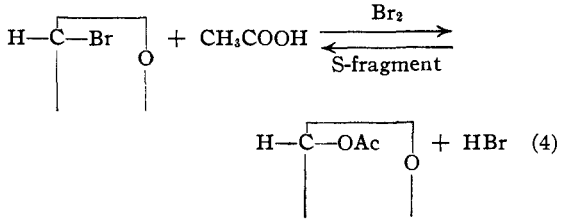
(3)

Such an hypothesis is logical in that the positively charged sulfur atom of the bromosulfonium bromide would attract the binding electrons between the sulfur and number one carbon atoms. The resulting electron deficiency at C-1 would render this center quite susceptible to attack by a nucleophilic agent such as bromide or bromine. The logic is supported by several experimental data.

In the first place, when phenyl tetraacetyl-β-D-thioglucoside was treated with excess bromine in carbon tetrachloride solution, acetobromoglucose was isolated in 84% yield. In this reaction acetic acid is absent and the mechanism is arrested at the second step. Only in the presence of acetic acid is the third step of the reaction possible, namely, the conversion of acetobromoglucose into glucose pentaacetate under the influence of bromine. It is interesting to note that phenyl tetraacetyl-β-D-glucoside, by contrast, gave ordinary para-bromination in carbon tetrachloride medium.

Secondly, even in the *presence* of acetic acid it is possible to demonstrate the existence of acetobromoglucose in the reaction mixture. The products isolated from the previous mutarotations, for example, all gave positive halogen analyses indicating the presence of a bromine-containing substance. More convincing is the fact that the product obtained from reaction of phenyl tetracetyl-β-D-thioglucoside with five equivalents of bromine in acetic acid produced a fair yield of tetraacetyl-β-D-glucosylbenzene when its ether solution was treated with an excess of phenylmagnesium bromide. Here is strong evidence for the presence of acetobromoglucose in the crude cleavage product, since it has been shown[5] that acetobromoglucose and phenylmagnesium bromide produce crystalline tetraacetyl-β-D-glucosylbenzene, whereas the glucose pentaacetates give only sirups. Equation (3) is apparently irreversible, since the presence of starting material in the products was never observed.

The third step in the cleavage is apparently the conversion of the intermediate acetobromoglucose into α-D-glucose pentaacetate under the influence of bromine molecules. In the presence of the sulfur fragment produced in the second step of the cleavage, the third step seems to involve an equilibrium. In the absence of such a sulfur fragment the reaction goes only to the right. These observations are summarized in Equation (4)



(4)

Bromide ions, present either as lithium bromide or

(5) Hurd and Bonner, THIS JOURNAL, 67, 1972 (1945).

hydrogen bromide, either in the presence or absence of a sulfur compound, are incapable of inducing this step, and it seems due solely to bromine molecules. The electronic interpretation of this unexpected reaction is at present obscure, but its occurrence is demonstrated by a number of experimental facts.

When acetobromoglucose was treated with large excesses of bromine in acetic acid, α-D-glucose pentaacetate resulted in good yield. In the presence of small amounts of bromine this conversion was incomplete. The conversion was not observed when acetobromoglucose in acetic acid was permitted to stand alone, or treated with either hydrogen bromide or lithium bromide. The replacement of bromine with acetoxy in Equation (4) seems to occur substantially without inversion, since α-D-glucose pentaacetate is the chief product. Nevertheless, other substances such as β-D-glucose pentaacetate are presumably present in the crude products, since the specific rotations of the crude products are usually lower than that of α-D-glucose pentaacetate. The effect of bromine concentration on rotation of the crude products is illustrated in Fig. 3. Possibly the replacement of bromine with acetoxy proceeds by a mechanism which would inherently lead to complete racemization at the first carbon atom were it not for an asymmetric bias toward the α-anomer produced by the remaining asymmetric centers.

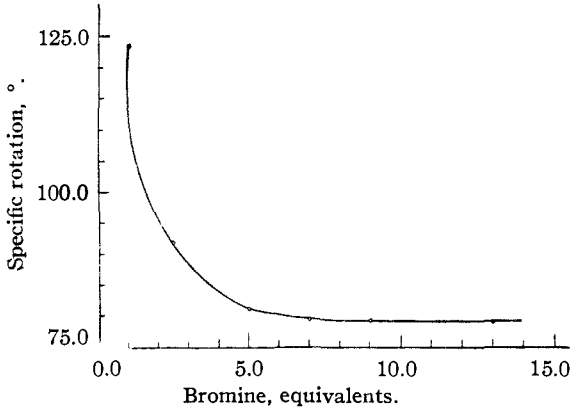


Fig. 3.—Rotations of crude products obtained on treating acetobromoglucose in acetic acid with varying quantities of bromine.

The ultimate fate of the sulfur fragment obtained on cleavage has not been determined in every case. It is significant that when one equivalent of bromine acted on phenyl tetraacetyl-β-D-thioglucoside, diphenyl disulfide was isolable in good yield from the crude product. When 2.5 equivalents of bromine were used, the crude product tested qualitatively for sulfur, but diphenyl disulfide was not isolable. When five or more equivalents of bromine acted on the thioglucoside, the crude product was void of sulfur. Apparently the bromine concentration determines the ultimate fate of the cleaved thiophenyl moiety. Possibly the sulfenyl bromide postulated in Equation (3) undergoes addition in the presence of excess bromine giving a fragment such as $RSBr_2^+$, Br^- which, on subsequent processing with water, hydrolyzes to a water-soluble sulfinic or sulfonic acid, while a deficiency of bromine permits conversion of the sulfenyl bromide to the disulfide.

Whatever the actual structure of the intermediate sulfur fragment, its labile nature seems to promote an equilibrium between products and intermediates of the cleavage reaction. The products recovered when varying quantities of bromine were allowed to act on phenyl tetraacetyl-β-D-thioglucoside were not homogeneous, but showed properties dependent upon the bromine concentration. With low bromine concentrations sulfur-containing solids or sirups were obtained, while higher bromine concentrations led to sulfur-free solids or sirups. The specific rotation of these products depended upon bromine concentration as shown in Curve I of Fig. 4.

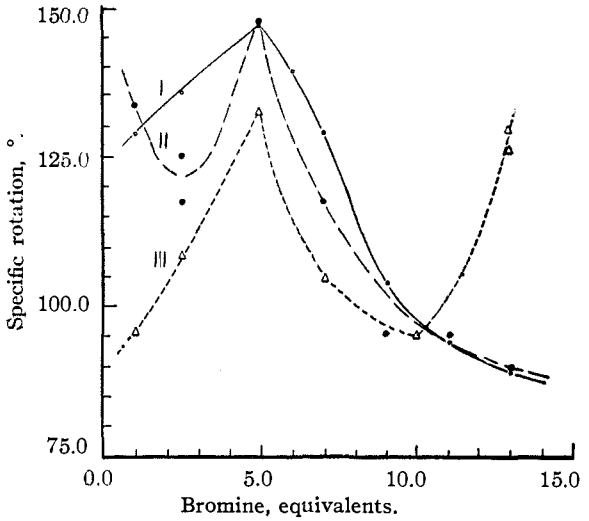


Fig. 4.—Rotations of crude products obtained on treating various substances with varying quantities of bromine in acetic acid: I, —○—, phenyl tetraacetyl-β-D-thioglucoside; II, — —●— —, acetobromoglucose and diphenyl disulfide; III, -----△-----, α-D-glucose pentaacetate and diphenyl disulfide.

The equilibrium nature of the last step of the cleavage is indicated by certain similarities of Curves I, II and III of Fig. 4. These curves were obtained by permitting varying quantities of bromine in acetic acid to act, respectively, on phenyl tetraacetyl-β-D-thioglucoside (the starting material), on acetobromoglucose (the postulated intermediate) and diphenyl disulfide, and on α-D-glucose pentaacetate (the chief product) and diphenyl disulfide. The crude products from each of these reactions were strikingly similar, at least above five equivalents of bromine. Below 2.5 equivalents of bromine the products from each reaction contained sulfur, and appeared not to be

identical. Each curve in Fig. 4 reaches a maximum at about five equivalents of bromine, due presumably to a maximum quantity of acetobromoglucose in each crude product obtained with this quantity of bromine. In this connection it is significant that each crude product showing a maximum gave an approximately equal yield of tetraacetyl-β-D-glucosylbenzene on treatment with phenylmagnesium bromide. The anomalous rise at the tail of Curve III is at present unexplainable.

The key role of the intermediate sulfur fragment in promoting the equilibrium apparent in the third step of the cleavage is emphasized by contrasting Curve II of Fig. 4 with Fig. 3. The latter, obtained in comparable experiments where diphenyl disulfide was absent, passes through no maximum and a substantially homogeneous product is obtained above 2.5 equivalents of bromine. Similarly, although the products obtained by action of bromine on α-D-glucose pentaacetate in the *presence* of diphenyl disulfide are frequently similar to those from the other sources, bromine *alone* in acetic acid is completely without action on α-D-glucose pentaacetate. No reaction was observed on treatment of a D-glucose pentaacetate in acetic acid either with one equivalent or eleven equivalents of bromine.

The complexity of the proposed mechanism for the cleavage of thioglucosides with bromine makes it probable that even the present proposal represents a considerable oversimplification. The apparent labilizing action of bromine on acetyl groups[2] suggests the possibility of ring shifts and acetyl migrations as side reactions. The sulfur moiety, whose fate is at present obscure, may enter the mechanism in a fashion even more complicated than that suggested. The precise stereochemical course of the reaction is not clear, nor have its kinetics as yet been understandable. Definitive answers on these points must await future research, and the present work is intended merely as the broad outline of a more exact mechanism.

Experimental Part

Phenyl Tetraacetyl-β-D-glucosyl Sulfone and Bromine.—Phenyl tetraacetyl-β-D-glucosyl sulfone (0.50 g.; prepared by oxidation of phenyl tetraacetyl-β-D-thioglucoside with hydrogen peroxide[6]) was dissolved in glacial acetic acid (20 ml.) with warming, cooled, and bromine (0.80 ml.) added. The mixture stood at room temperature for four hours, was poured into water, and the solid extracted twice with ether. The extract was washed with water, sodium bisulfite solution, again with water, and then with sodium bicarbonate solution. During the last washing a white solid precipitated. This was filtered and dried, yield 0.40 g., m.p. 188–190°. The ether filtrate was dried over anhydrous sodium sulfate, decanted, and the solvent distilled to yield an additional 0.10 g. of solid. The combined products were recrystallized from 2-propanol to give 0.40 g. (80%) of pure starting material, m.p. 188–188.5°, mixed m.p. 188–188.5°, $[\alpha]^{25}D$ −25.0° (chloroform, *c*, 2.120). It is interesting to note that the negative sulfone group prevents nuclear bromination in this reaction.

Phenyl Tetraacetyl-β-D-thioglucoside and Bromine. One Equivalent Bromine.—Phenyl tetraacetyl-β-D-thioglucoside (1.00 g.) was dissolved in acetic acid (10 ml.) and a solution of bromine (0.115 ml., one equivalent) in acetic acid (5 ml.) was added. After standing for twenty-one hours the solution was poured into water, extracted with ether, and processed in the usual fashion.[2] On distillation of the ether from the purified extract there resulted 0.67 g. of a slightly cloudy, amber sirup. On scratching, this crystallized; it was recrystallized from 2-propanol, giving 0.19 g. (77%) of diphenyl disulfide. This was again recrystallized from 2-propanol to give pure material, m.p. 59–60°. The sample was void of optical activity.

TABLE I

MUTAROTATIONS OF PHENYL TETRAACETYL-β-D-THIOGLUCOSIDE IN THE PRESENCE OF VARYING QUANTITIES OF BROMINE

Run	Bromine, equivalents	Time, minutes	Observed rotation, °
A	0.6	2	0.24
		10	1.29
		60	3.22
		230	5.68
		410	6.79
		∞	12.31
B	1.0	3	2.34
		15	4.38
		30	5.52
		69	7.28
		218	9.56
		561	10.95
		∞	11.74
C	2.5	2	6.18
		10	7.19
		20	7.77
		42	8.23
		156	8 66
		400	9.43
		∞	10.17
D	5.0	6	6.01
		15	6.94
		35	7.59
		155	8.73
		473	9.86
		∞	10.86
E	12.8	11	5.69
		20	5.89
		110	6.35
		480	6.68
		∞	7.36
F	1.0 plus 3.0 equiv. LiBr	2	−0.51
		10	−0.41
		60	0.46
		205	2.13
		495	4.07
		1469	6.48
		∞	9.38
G	1.0 plus 3.0 equiv. $LiClO_4$	2	1.76
		15	4.09
		30	5.85
		60	7.63
		205	9.34
		∞	6.70

(6) Bonner and Drisko, THIS JOURNAL, 70, 2435 (1948).

In a second experiment the above conditions were duplicated exactly, except that the reaction mixture was permitted to stand at room temperature for one week. Processing in the usual fashion gave 0.60 g. of crude, sirupy product which crystallized spontaneously. The material was recrystallized twice from 2-propanol to give 0.12 g. (49%) of diphenyl disulfide, m.p. 58.5–59.5°. A mixed melting point of this sample, the above sample, and an authentic sample of diphenyl disulfide (m.p. 59–60°) showed no depression, 59.5–60.2°.

Mutarotations with Varying Quantities of Bromine.—The following mutarotations were shown by phenyl tetraacetyl-β-D-thioglucoside in acetic acid in the presence of varying quantities of bromine. The thioglucoside (1.000 g.) was dissolved in acetic acid (9 ml.) and the requisite quantity of bromine added from a capillary pipet. The stop-watch was started at this point, the solution diluted to 10.00 ml., placed in a 1-dcm. polarimeter tube, and the mutarotation followed. Results are given in Table I.

The bromine–bromide–tribromide equilibrium applying at 23° and the molar concentrations obtaining in Run F of Table I permit a bromine concentration of 0.7 equivalent in this run as calculated from the extrapolated data of Nozaki and Ogg.[4] Run A, using 0.6 equivalent of bromine, represents the case where *less* than this permitted quantity of bromine was employed.

Run G, employing lithium perchlorate in place of lithium bromide, was conducted as follows. Lithium carbonate (0.25 g., 3 equivalents) was treated with 60% perchloric acid (1.135 g., 3 equivalents) and acetic acid (4 ml.). The resulting clear solution was treated with acetic anhydride (2.96 ml., 10% excess), resulting in vigorous heating. On cooling the anhydrous lithium perchlorate solution was diluted to 10 ml. with acetic acid. To this was added phenyl tetraacetyl-β-D-thioglucoside (1.00 g.) and bromine (0.116 ml., 1 equivalent), and the mutarotation was followed.

The data presented in Table I were obtained at room temperature, with no special provision for temperature control. Small deviations from the anticipated behavior to be found in Table I and the corresponding Fig. 1 are probably to be explained by temperature variations in the successive runs, since room temperature was relatively variable at the time of the year these measurements were made. Polychromatic light was employed in these mutarotations, since the free bromine in the solutions absorbed enough of the sodium D-line to make measurements with this wave length impossible. Similarly, as the bromine concentration in the successive runs was increased, errors in the polarimetric readings were found to increase due to the greater optical density of the more concentrated solutions.

Properties of Products as a Function of Bromine Concentration.—Each of the mutarotated mixtures above (with exception of Runs A, F and G), plus several other similar reactions which were not followed polarimetrically, were processed for isolation of the product. In Runs 4, 5, 6 and 7 below, which were not followed polarimetrically, the reaction mixture (1.00 g. thioglucoside and the requisite quantity of bromine in 10 ml. acetic acid) was permitted to stand for twenty-eight hours before processing. Processing in each experiment was as follows. The reaction mixture was poured into water (50 ml.) and extracted twice with 25-ml. portions of ether. The extract was washed with water (25 ml.), sodium bisulfite solution (25 ml.) to remove free bromine, twice with water (25-ml. portions), saturated sodium bicarbonate solution (25 ml.) and finally with water (25 ml.). It was then dried over anhydrous sodium sulfate, decanted (rinsing the drying agent once with ether), and the solvent distilled. The properties of the products obtained are given in Table II.

The products from Runs 1, 2 and 3 of Table II were found to be convertible into a product very similar to that obtained in Run 8 by further action of excess bromine. The products from Runs 1, 2 and 3 were each dissolved in 10 ml. of acetic acid and 1.2 ml. of bromine added. After standing overnight the reaction mixture was thrown into water and processed in the manner described above. The crude, solid product was recrystallized by dissolving in *ca.* 3 ml. of 2-propanol, adding water until slightly turbid, and placing the mixture at 0° for several hours. In each case α-D-glucose pentaacetate, showing no mixed melting point depression with an authentic sample, was obtained. These data are summarized in Table III.

TABLE II

PRODUCTS OBTAINED BY ACTION OF VARYING QUANTITIES OF BROMINE ON PHENYL TETRAACETYL-β-D-THIOGLUCOSIDE IN ACETIC ACID

Run	Bromine, equivalents	Crude product: Yield. g.	Form	$[\alpha]^{25}D$	*c*, g./100 ml.
1[a]	1.0	0.85	Solid	128.1[c]	2.200
2[a]	2.5	.80	Sirup[b]	136.2	1.842
3	5.0	.75	Sirup[b]	145.0	1.434
4	6.0	.67	Sirup[b]	139.0	5.187
5	7.0	.70	Sirup	128.1	3.926
6	9.0	.74	Sirup[b]	104.6	2.620
7	11.0	.69	Solid[d]	94.4	2.653
8	12.8	.72	Solid[e]	88.5	2.535

[a] The crude samples from these runs gave positive qualitative sulfur analyses, while the remainder were negative. All samples gave more or less positive analyses for halogen, although some results were rather inconclusive. [b] These sirups showed a greater or lesser tendency to crystallize on standing several days. [c] All rotations were measured in chloroform in a 1-dcm. tube. [d] This material was recrystallized from dilute 2-propanol to yield 0.35 g. of impure α-D-glucose pentaacetate, m. p. 106–108.5°, showing no m. p. depression with a pure sample. [e] This material was recrystallized from 2-propanol in the manner described in the text to yield 0.29 g. of α-D-glucose pentaacetate, m. p. 109–110°.

TABLE III

PRODUCTS OBTAINED ON TREATING CERTAIN CRUDE PRODUCTS IN TABLE II WITH AN EXCESS OF BROMINE IN ACETIC ACID

Run	Crude product: Yield. g.	$[\alpha]^{25}D$	*c*. g./100 ml.[a]	α-D-Glucose pentaacetate: Yield. g.	M. p., °C.
1	0.33	82.1	1.317	0.14	108.5–109.5
2	.31	77.8	1.570	.15	110–111
3	.31	70.8	1.713	.07	109–110

[a] All rotations taken in chloroform in a 1-dcm. tube.

Phenyl Tetraacetyl-β-D-thioglucoside and Bromine in Carbon Tetrachloride.—Phenyl tetraacetyl-β-D-thioglucoside (0.97 g.) was dissolved in carbon tetrachloride (20 ml.) and bromine (1.5 ml.) added. The mixture stood at room temperature for two hours, after which it was decolorized by shaking with sodium bisulfite solution. After washing with sodium bicarbonate solution and with water, then drying over sodium sulfate, the solvent was distilled *in vacuo*. There was obtained 0.76 g. (84%) of crude sirup which crystallized spontaneously, m.p. 79–80°. On recrystallization from 2-propanol the melting point was raised to 88–88.5° and the sample showed $[\alpha]^{25}D$ 201° (chloroform, *c*, 3.675). This substance showed no mixed melting point depression (86–88°) with a sample of acetobromoglucose (of m.p. 86–88°).

In a repetition of this experiment, a crude yield of 0.95 g. (102%) was obtained. The crude product contained considerable foreign material as indicated by its low melting point, 72–74°, its low specific rotation, $[\alpha]^{25}D$ 166.0° ($CHCl_3$, *c*, 3.070), and the fact that it analyzed qualitatively for sulfur as well as halogen. Since the crude product obtained on comparable runs in acetic acid was void of sulfur, it is obvious that the nature of the solvent plays a decisive role in the ultimate fate of the sulfur fragment obtained on cleavage.

Bromination of Phenyl Tetraacetyl-β-D-glucoside in Carbon Tetrachloride.—Phenyl tetraacetyl-β-D-glucoside (1.00 g.) was dissolved with warming in carbon tetrachloride (25 ml.) and the solution cooled to room temperature. Bromine (1.5 ml.) was added, and the mixture became murky. An additional quantity (25 ml.) of carbon tetrachloride was therefore added, and the mixture allowed to stand for an hour. After washing and drying in the usual fashion the solvent was distilled *in vacuo* to yield 1.36 g. (114%) of thick sirup which crystallized rapidly. This was recrystallized from 2-propanol giving 0.76 g. (64%) of pure *p*-bromophenyl tetraacetyl-β-D-glucoside, m.p. 131.5–132°, mixed m.p. with an authentic sample 131.5–132.5°.

Acetobromoglucose and Bromine in Acetic Acid.—Acetobromoglucose (0.93 g.) was dissolved in acetic acid (10 ml.) and varying quantities of bromine, as indicated in Table IV, were added. The reaction mixtures were permitted to stand for twenty-nine hours, and the crude products were isolated in the manner described for the corresponding experiments with phenyl tetraacetyl-β-D-thioglucoside. Each crude product was recrystallized from 2 ml. of 2-propanol to give α-D-glucose pentaacetate in varying yield and state of purity. The results of these experiments are summarized in Table IV.

TABLE IV

PRODUCTS OBTAINED BY ACTION OF VARYING QUANTITIES OF BROMINE ON ACETOBROMOGLUCOSE IN ACETIC ACID

Run	Bromine, equivalents	Crude product[a] Yield, g.	Form	$[\alpha]^{25}D$	c, g./100 ml.[c]	α-D-glucose pentaacetate Yield, g.	M. p., °C.[d]
1	1.0	0.60	Sirup[b]	123.4	2.675	0.05	108–109
2	2.5	.57	Solid	92.4	1.830	.21	107.5–109
3	5.0	.52	Solid	81.3	2.153	.20	109.5–110.5
4	7	.56	Solid	79.3	3.253	.21	109.5–110.5
5	9	.58	Solid	79.2	2.578	.26	110–111
6	13	.61	Solid	77.8	3.076	.24	110–112

[a] All crude products gave a faint positive analysis for bromine. [b] This material crystallized on standing overnight. [c] All rotations were taken in chloroform in a 1-dcm. tube. [d] A mixed melting point of all these samples with α-D-glucose pentaacetate showed no depression, 108–111°.

Acetobromoglucose, Diphenyl Disulfide, and Bromine in Acetic Acid.—Samples of acetobromoglucose (0.93 g.) and diphenyl disulfide (0.25 g., 0.5 equivalent) were dissolved in acetic acid (10 ml.) with warming. The solutions were cooled to room temperature and treated with the requisite quantity of bromine. After standing for twenty-seven hours each mixture was poured into water and the crude product isolated as described in the previous section. The properties and yields of each crude product are given in Table V.

Acetobromoglucose in Acetic Acid.—Acetic acid alone was found to be without action on acetobromoglucose. Acetobromoglucose (1.50 g.) was dissolved in acetic acid (15 ml.) and allowed to stand overnight. The mixture was poured into water, extracted with ether, and processed in the usual way. There resulted 1.40 g. (93%) of clear sirup which rapidly crystallized. The specific rotation was practically that of pure starting material, $[\alpha]^{25}D$ 194.2° (chloroform; *c*, 1.767). On recrystallization from 2-propanol there resulted 1.14 g. of pure starting material, m.p. 89–90°.

Acetobromoglucose and Hydrogen Bromide in Acetic Acid.—Acetobromoglucose (1.50 g.) was dissolved in acetic acid (15 ml.) and 1.6 ml. of 32% hydrogen bromide in acetic acid was added. After standing overnight the product was isolated as usual. There was obtained 1.36 g. of sirup which quickly crystallized, $[\alpha]^{25}D$ 189.1° (chloroform; *c*, 3.117). On recrystallization there resulted 0.96 g. of starting material, m.p. 87.5–88.5°.

When 1.00 g. of acetobromoglucose and 0.25 g. of diphenyl disulfide were dissolved in 10 ml. of acetic acid and treated with 1.0 ml. of 32% hydrogen bromide in acetic acid, no mutarotation was observed. On processing as usual there resulted 0.86 g. of crude product, a sirup which crystallized spontaneously. Due to the diphenyl disulfide present this material had a low rotation, $[\alpha]^{25}D$ 144.0° (chloroform; *c*, 2.763). On recrystallization from 2-propanol pure acetobromoglucose resulted, m.p. 87.5–88°; mixed m.p. 88–89°.

TABLE V

PRODUCTS OBTAINED BY ACTION OF VARYING QUANTITIES OF BROMINE ON ACETOBROMOGLUCOSE AND DIPHENYL DISULFIDE IN ACETIC ACID

Run	Bromine, equivalents	Crude product[a] Yield, g.	Form	$[\alpha]^{25}D$	c, g./100 ml.[b]
1	1.0	0.83	Sirup[c]	134.2	2.330
2	2.5	.90	Sirup	117.4	6.693
2A	2.5	.92	Sirup	125.4	3.940
3	5.0	.76	Sirup[c]	147.1	6.670
4	7.0	.66	Sirup[c]	117.9	6.423
5	9.0	.70	Solid	95.9	6.026
6	11.0	.69	Solid	95.4	7.543
7[d]	13.0	1.15	Solid	88.9	1.217

[a] Crude products from Runs 1 and 2 gave positive tests for sulfur, and diphenyl disulfide could be isolated from Run 1. Other products were void of sulfur. All products except that from Run 7 gave faint analyses for halogen. [b] All rotations were taken in chloroform in a 1-dcm. tube. [c] These products underwent partial crystallization on standing overnight. [d] In Run 7 1.50 g. of acetobromoglucose and 0.40 g. of diphenyl disulfide in 15 ml. of acetic acid were used instead of the usual quantities. By recrystallization of the crude product from 2-propanol there was obtained 0.61 g. of α-D-glucose pentaacetate, m. p. 110–111°, mixed m.p. 110–112°. An additional 0.15 g. of lower purity (m. p. 103° up) was obtained from the mother liquors.

In a second experiment the above reaction was duplicated exactly except that 0.25 g. of diphenyl disulfide was included in the reaction mixture. In this case the observed rotation dropped from 17.04° (two minutes) to 8.19° (1685 minutes). The mutarotation curves in the two experiments were strictly of the same shape, the latter being uniformly about 0.60° below the former. Thus, although lithium bromide has an effect on acetobromoglucose in acetic acid solution, this effect is not modified in any way by the presence of diphenyl disulfide. This behavior contrasts sharply to the action of bromine on acetobromoglucose, where diphenyl disulfide has a marked effect on the reaction. The cause of the mutarotation of acetobromoglucose in the presence of lithium bromide is under investigation at the present time.

Acetobromoglucose and Lithium Bromide in Acetic Acid.—Acetobromoglucose (1.00 g.) was dissolved in acetic acid, and lithium bromide (1.00 g., 4.7 equivalents) was dissolved with warming in the same solvent, then cooled. The two solutions were mixed and diluted to 10 ml. with more acetic acid, and the mutarotation followed. The observed rotation dropped from a value of 17.60° (after two minutes) to 8.50° (after 1555 minutes), the downward trend being quite gradual.

α-D-Glucose Pentaacetate and Bromine in Acetic Acid.—Reference has already been made[2] to the lack of reaction of α-D-glucose pentaacetate with bromine in acetic acid. Thus starting material was recovered in 74% yield when α-D-glucose pentaacetate was treated with 11.3 equivalents of bromine in acetic acid. Further evidence of this lack of reaction has now been obtained in the presence of one equivalent of bromine. When α-D-glucose pentaacetate was treated with one equivalent of bromine in acetic acid, no mutarotation was observed during the course of 1765 minutes. An 82% yield of starting material, m.p. 111–112°, was obtained by treating the reaction mixture in the usual manner.

α-D-Glucose Pentaacetate, Diphenyl Disulfide and Bromine in Acetic Acid.—In contrast to the above lack of reactivity of α-D-glucose pentaacetate and bromine in acetic acid, these reagents showed a very marked reaction in the presence of diphenyl disulfide. Mixtures of α-D-glucose pentaacetate (0.89 g.) and diphenyl disulfide (0.25 g., 0.5 equivalent) were dissolved in acetic acid (10 ml.). The requisite amount of bromine was added from a capillary pipet, and the reaction mixtures were allowed to stand at room temperature for twenty-nine hours. They were then poured into water, extracted into ether, and the crude product isolated as described before. The results are given in Table VI. It will be seen that, with the exception of Run 6 (in duplicate), the crude products are quite similar to those obtained above 2.5 equivalents of bromine in Tables II and V.

TABLE VI

PRODUCTS OBTAINED BY ACTION OF VARYING QUANTITIES OF BROMINE ON α-D-GLUCOSE PENTAACETATE AND DIPHENYL DISULFIDE IN ACETIC ACID

Run	Bromine, equivalents	Crude product			
		Yield, g.	Form	$[\alpha]^{25}D$	c, g./100 ml.[b]
1	1.0	0.94	Solid	95.9	3.640
2	2.5	1.05	Sirup	108.7	5.440
3	5.0	0.79	Sirup[a]	132.5	4.499
4	7.0	.62	Sirup[a]	104.9	2.993
5	10.0	.73	Solid	95.8	3.662
6	13.0	.70	Solid	129.9	3.995
6A	13.0	.77	Solid	126.6	2.993

[a] These samples crystallized on standing overnight. [b] All rotations in chloroform in a 1-dcm. tube.

Phenylmagnesium Bromide and Certain Reaction Products.—Two runs were conducted simultaneously to see if the acetobromoglucose postulated as an intermediate in the cleavage reaction could be converted into tetraacetyl-β-D-glucosylbenzene by action of phenylmagnesium bromide. Those products which were found in previous experiments to have a maximum rotation were employed on the assumption that they contained a maximum quantity of acetobromoglucose.

In Run 1 tetraacetyl-β-D-thioglucoside (2.00 g.) was dissolved in acetic acid (20 ml.) and treated with bromine (1.16 ml., 5 equivalents). In Run 2 acetobromoglucose (1.86 g.) and diphenyl disulfide (0.50 g., 0.5 equivalent) in acetic acid (20 ml.) were treated with bromine (1.16 ml., 5 equivalents). These mixtures were permitted to stand at room temperature for twenty-three hours, and then processed in the usual way, doubling the volume of each wash. The crude products were kept in their dried ether solutions until used in the reaction below.

Phenylmagnesium bromide (0.27 mole, enough for more than 200% excess over the theoretical quantity required to take care of both above runs) was prepared from bromobenzene (28.4 ml.) and magnesium (6.6 g.) in dry ether (125 ml.). The Grignard solution was divided into two equal portions, placed in three-necked flasks equipped with dropping funnel and reflux condenser, and to each portion was added, dropwise and with vigorous stirring, the filtered ether solutions obtained in Runs 1 and 2 above. Each addition took about twenty minutes, and a yellowish precipitate resulted from both runs. Each mixture then stood overnight, and was worked up in the following manner. The mixture was poured into water (100 ml.) and the reaction vessel rinsed with water (10 ml.). The vessel was then rinsed with acetic acid (20 ml.) and these rinsings added very cautiously to the previous water-ether system. Vigorous reaction ensued at this point, and two clear layers separated. The ether layer was washed once with water, this being combined with the original water layer. The ether was then washed again with water, with sodium bicarbonate solution until neutral, and dried over anhydrous sodium sulfate. After decanting and rinsing the drying agent with ether, the solvent was distilled leaving crude diphenylmethylcarbinol. From Run 1 this crude product weighed 6.14 g., and from Run 2, 6.16 g.

The aqueous layer was rinsed with ether (20 ml.), and evaporated to dryness *in vacuo* on the steam-bath. Anhydrous sodium acetate (5 g.) was added to the residue, and the mixture treated with acetic anhydride (20 ml.). Heating produced vigorous reaction, and when this subsided additional acetic anhydride was added (two 20-ml. portions). The acetylation mixture was refluxed for forty minutes, cooled and poured into water (350 ml.). After stirring for one hundred minutes the aqueous mixture was extracted twice with ether. The ether extract was washed with water, bicarbonate solution, and water, and then dried over sodium sulfate. The dried extract was decolorized by filtration through a bed of Darco and Celite, and the solvent was distilled from the colorless filtrate. The weights of crude solid obtained in each case were 0.60 g. from Run 1 and 0.58 g. from Run 2. Each of these solids was recrystallized from 2-propanol (8 ml.) to yield fairly pure samples of tetraacetyl-β-D-glucosylbenzene. Run 1: yield 0.38 g., m.p. 152–153°, mixed m.p. with an authentic sample (m.p. 155–156°) 154–156°. Run 2: yield 0.37 g., m.p. 152–153°, mixed m.p. 154–156°.

In a third experiment α-D-gluclose pentaacetate (0.89 g.) was dissolved in acetic acid (10 ml.) containing diphenyl disulfide (0.25 g.) and bromine (0.58 ml., 5 equivalents) was added. On standing for twenty-four hours the product, an amber sirup, was isolated in the usual manner. This product showed $[\alpha]^{25}D$ 127.5° (chloroform, *c*, 3.027), in fair agreement with Run 3 of Table VI. A portion of this sirup (0.63 g.) was dissolved in dry ether (25 ml.) and added dropwise with stirring in the usual apparatus to a solution of phenylmagnesium bromide prepared from bromobenzene (14.2 ml.) and magnesium (3.3 g.) in dry ether (60 ml.). After addition the homogeneous mixture was stirred for an hour under reflux, then cooled, poured into water, and processed exactly as described above. The residue obtained on vacuum distillation of the water layer was acetylated using 10 g. of sodium acetate and 60 ml. of acetic anhydride as before. By the previous processing of the acetylation mixture there resulted 0.27 g. of crude tetraacetyl-β-D-glucosylbenzene. This was recrystallized from 2-propanol to give a white solid, m.p. 150.5–152.5°, mixed m.p. with tetraacetyl-β-D-glucosylbenzene 151–154°.

Summary

A study has been made of the mechanism whereby phenyl tetraacetyl-β-D-thioglucoside is converted into α-D-glucose pentaacetate by action of bromine in acetic acid.

Evidence is presented that this unusual reaction proceeds by three distinct steps, (1) equilibrium addition of bromine to the sulfur atom of the thioglucoside to form a bromosulfonium bromide, (2) Walden inversion attack of a bromide ion or bromine molecule on this bromosulfonium bromide to form acetobromoglucose, and (3) conversion of acetobromoglucose to α-D-glucose pentaacetate under the influence of bromine molecules.

The fate of the cleaved sulfur moiety from the thioglucoside is uncertain, but it has been shown to produce an equilibrium between the final products and certain of the intermediates in the cleavage reaction.

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