Carbohydrate Research, 111 (1982) 23–29
Elsevier Scientific Publishing Company, Amsterdam – Printed in The Netherlands

EFFECTS OF SUBSTITUENTS ON THE ACID-CATALYZED THERMOLYSIS OF SUCROSE IN DIMETHYL SULFOXIDE

WAYNE MOODY AND GEOFFREY N. RICHARDS
Department of Chemistry and Biochemistry, James Cook University of North Queensland, Townsville, Q4811 (Australia)

(Received June 1st, 1982; accepted for publication, July 7th, 1982)

ABSTRACT

The rates of acid-catalyzed degradation of a number of acetyl-substituted sucrose derivatives in dimethyl sulfoxide have been determined. The results indicate that the rate is markedly diminished by acetylation at O-1 or -3 of the D-fructosyl group. This increased stability of the substituted sucrose derivatives is also reflected in an increased stability of the D-fructose derivatives that are formed in the reaction.

INTRODUCTION

Previous investigations[1] of sucrose in hot dimethyl sulfoxide (Me_2SO) revealed that, in the presence of small proportions of strong acids, the D-fructosyl–glycosidic bond is broken to produce α-D-glucopyranose and a D-fructofuranosyl carbonium ion as primary products. The reaction involves protonation of the glycosidic oxygen atom prior to bond cleavage, and is favorable for sucrose (and ketoses in general), because of the stable, tertiary carbonium ion ultimately produced. In order to investigate some of the other factors that may influence the reaction, several sucrose derivatives have been examined, and their rates of degradation determined.

TABLE I

RATES OF DEGRADATION OF VARIOUS SUCROSE DERIVATIVES (0.1M SOLUTIONS IN Me_2SO CONTAINING mM H_2SO_4 AT 100°)

Compound	*Rate (s^{-1})*	*Positions of substitution*
Sucrose	2×10^{-3}	—
Octa-*O*-methylsucrose	7×10^{-5}	2,3,4,6,1′,3′,4′,6′
Tetra-*O*-acetylsucrose[a]	1×10^{-5}	3,3′,4′,6′
Penta-*O*-acetylsucrose	1×10^{-5}	2,3,6,3′,4′
Hexa-*O*-acetylsucrose[a]	$<1 \times 10^{-7}$	2,3,1′,3′,4′,6′
Octa-*O*-acetylsucrose	$<1 \times 10^{-7}$	2,3,4,6,1′,3′,4′,6′

[a]Derived from *in situ* hydrolysis of the *O*-isopropylidene derivatives (see Experimental section).

Of prime importance in the study of the acid-catalyzed decomposition of sucrose in Me_2SO is the potentially useful application of the reaction to the production of a variety of D-fructofuranosides[1,2]. Such appreciable losses can occur by nonspecific degradation of the D-fructose intermediates into such products as 5-(hydroxymethyl)-2-furaldehyde[3] that an insight into the factors that stabilize the D-fructose products would also be potentially useful from the synthetic point of view.

The purpose of this study is thus threefold: (*a*) the further investigation of the mechanism involved, and examination of some factors which render (*b*) the sucrose derivatives more stable to the reaction conditions, and (*c*) the intermediate, D-fructose products more stable.

RESULTS AND DISCUSSION

The rates of acid-catalyzed thermolysis of sucrose and of several derivatives in Me_2SO are shown in Table I. The method by which these rates were determined has been described[1,2]; however, two new assumptions are now involved. Firstly, the D-glucose derivative produced is assumed to be (*a*) stable and (*b*) the sole, D-glucose product of the reaction (a condition demonstrated as acceptable in the case of sucrose degradation[1,3]); and secondly, the constant relating the response factors in gas–liquid chromatography (g.l.c.) of the substituted sucrose and the substituted D-glucose produced is assumed to be, in all instances, the same as that relating sucrose and D-glucose. Both assumptions will no doubt cause some inaccuracy in the rate constants, but these inaccuracies will be much smaller than the major differences (of several orders of magnitude) with which we are concerned in interpreting these results.

Inspection of Table I shows that all of the multi-substituted derivatives studied have much lower rates of reaction compared with that of sucrose under the same conditions. The extreme decrease in reactivity observed for octa-*O*-acetylsucrose is probably due, at least partly, to the electron-withdrawing nature of the acetyl group, which must result in a lower extent of protonation of the glycosidic oxygen atom. Competition for the proton catalyst by the carbonyl oxygen atom will have a similar effect. This, in turn, must lessen the rate of scission of the glycosidic linkage. Comparison with the reactivity of octa-*O*-methylsucrose, however, shows that this inductive effect is not the sole factor operating, as, if it were, the order of reactivity should be octa-*O*-methylsucrose > sucrose > octa-*O*-acetylsucrose.

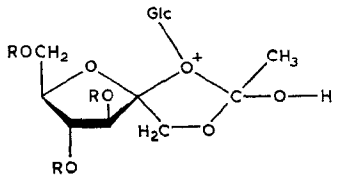
The fact that methylation slows, rather than accelerates, the reaction is not surprising, in view of the similar effects found for the acid hydrolysis of glycosides which, in a sense, is a special case of the present reaction[4]. For example, all isomeric monomethyl ethers of methyl β-D-glucopyranoside, and all derivatives of gentiobiose mono-*O*-methylated in the nonreducing group, were shown to have lower rates of hydrolysis than the parent compounds[5]. The substituents are presumed to introduce a further energy-barrier to the attainment of the transition-state conformation necessary to accommodate the formation of the carbonium ion[6,7]. For a pyranoid ring, the accommodation of a carbonium ion requires conversion from a chair into

a half-chair conformation, a process disfavored by substituents, at least in the case of D-glucose. However, a furanoid ring has a conformation that is much closer to the planar structure required, and hence, the generation of a carbonium ion on it should be much less susceptible to the nonbonded interactions of substituents[8]. Obviously, this should hold for sucrose, where scission of the D-fructosyl–O glycosidic bond should be relatively little influenced by the presence of substituents.

It would thus seem that a third type of effect may be responsible for the stability of octa-*O*-acetylsucrose to acid-catalyzed degradation, and examination of the reaction rates for partially acetylated sucrose derivatives (see Table I) gives some indication as to the positions of substitution that have the most effect in this regard.

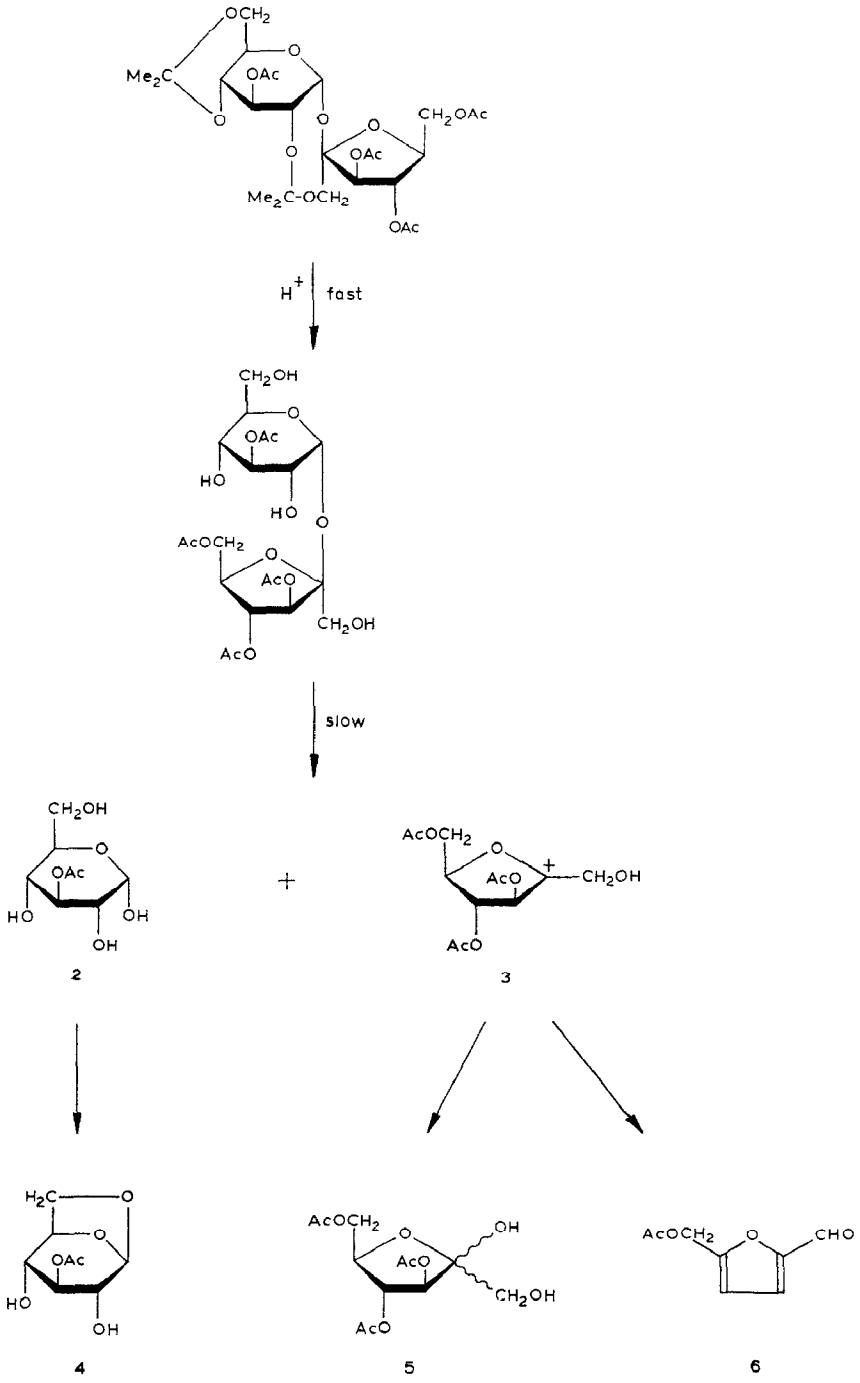
Beginning with the postulate that some acetyl groups stabilize the glycosidic bond in sucrose towards this reaction, it may be noted that the 2,3,1′,3′,4′,6′-hexaacetate has a stability similar to that of the octaacetate; therefore, the 4- and 6-*O*-acetyl groups are probably not involved in the stabilization. The 3,3′,4′,6′-tetraacetate is relatively labile, and it is concluded that the 1′- or the 2-*O*-acetyl group, or both, is involved in the stabilization, but, as the 2,3,6,3′,4′-pentaacetate is similarly labile, it seems that the 1′-*O*-acetyl group must be most responsible for the stabilization.

The sterically determined effects of the acetyl groups, just discussed, are evidently more important than their general inductive effect on protonation of the glycosidic oxygen atom, because the 1′- and the 2-*O*-acetyl group should be similarly effective in the latter regard. The peculiar effectiveness of the 1′-*O*-acetyl group in stabilizing the glycosidic linkage may be associated with formation of a five-membered-ring complex, such as **1**, which would presumably be more stable than the form in which the glycosidic oxygen atom is protonated. Inspection of molecular models indicated that the 2-*O*-acetyl group is less likely to form a cyclic complex analogous to **1**.



1

The introduction of acetyl groups onto the D-fructosyl group of sucrose evidently stabilizes not only the sucrose derivative but also the D-fructose products formed. This is obviously of synthetic importance, as it extends the range of conditions under which the reaction may be performed, or the products isolated. An example is seen in the case of 2,1′:4,6-di-*O*-isopropylidenesucrose tetraacetate, which was heated in Me_2SO containing mM sulfuric acid at 150°. The isopropylidene protecting-groups were removed very rapidly under these conditions (see Experimental section), leaving 3,3′,4′,6′-tetra-*O*-acetylsucrose, which is degraded very slowly. After 5 h at 150°, the starting material had been consumed, and the major products


OCH2
Me2C
OAc
CH2OAc
Me2C-OCH2
H+
fast
CH2OH
AcOCH2
AcO
slow
2
3
4
5
6
CHO

Scheme 1

of the reaction were found to be those indicated in Scheme 1, *viz.*, 3-*O*-acetyl-D-glucose (**2**) and 3,4,6-tri-*O*-acetyl-D-fructofuranose (**5**). Under the conditions of the reaction, **2** is dehydrated to 3-*O*-acetylevoglucosan (**4**), while some of the intermediate, D-fructosyl carbonium ion (**3**) is lost as 5-(acetoxymethyl)-2-furaldehyde (**6**).

The mass spectrum of the per-*O*-(trimethylsilyl) derivative of compound **4** showed a parent ion at *m/z* 348 and smaller peaks at *m/z* 289 and 279, indicating loss of $CH_3COO^{\cdot}$ and $Me_3SiO^{\cdot}$, respectively. The molecular weight of the parent ion indicated the presence of only one acetate group in the molecule, and, based on the structure of the starting material, this is assigned to C-3. The mass spectrum of per(trimethylsilyl)ated compound **5** did not show a parent ion, but, as is typical for fructofuranose derivatives[9,10], it indicated cleavage at C-1–C-2 and C-5–C-6, followed by elimination of neutral substituents from the furanoid ring. Thus, for example, cleavage at C-1 (*i.e.*, loss of $\cdot CH_2OMe_3Si$), followed by elimination of acetic acid, produces a peak at *m/z* 287. Several processes of this type could be readily assigned. Owing to complexity arising from an anomeric mixture, the ^{1}H-n.m.r. spectrum was not straightforward, but was consistent with the presence of fructose and three acetate groups. This compound is, therefore, tentatively identified as 3,4,6-tri-*O*-acetyl-α,β-D-fructofuranose (**5**).

It should be noted that the experimental conditions used favor the formation of **4** and **6**, rather than **2** or **5**. It would thus seem that strategic acetylation of the sucrose starting-material may result in the formation of D-fructosides of improved stability; this may prove to be of synthetic significance, especially in the formation of D-fructosides from less reactive nucleophiles.

EXPERIMENTAL

Reagents. — 4,6-*O*-Isopropylidenesucrose hexaacetate, 1,2:4,6-di-*O*-isopropylidenesucrose tetraacetate[11], 2,3,6,3′,4′-penta-*O*-acetylsucrose[12,13], and octa-*O*-methylsucrose were prepared as previously described. Sucrose and octa-*O*-acetylsucrose were obtained commercially. All compounds were pure according to t.l.c. and g.l.c., and they were dried *in vacuo* before use. Pure, dry Me_2SO was prepared as previously reported[1]. Ethyl acetate (A.R.) and petroleum ether (b.p. 40–60°) were distilled prior to use.

Instrumentation. — G.l.c. was performed with a Shimadzu Model GC-6AM instrument, using a column of 3% of SE-30 on Chromosorb W-HP (80–100 mesh). Peak areas were determined by using a Hewlett–Packard 3380 electronic integrator. Liquid chromatography (l.c.) was conducted in a Varian-5000 Liquid Chromatograph, using an analytical NH_2-10 column and a Waters Associates Differential Refractometer R401. ^{1}H-Nuclear magnetic resonance (^{1}H-n.m.r.) spectra were recorded at 100 MHz with a Jeol JMN-MH-100 Spectrometer. Mass spectra were recorded with a Jeol JMSD-100 Mass Spectrometer interfaced with a gas chromatograph (Jeol-JGC-20KFP) for g.l.c.–m.s.

Kinetics. — Solutions (0.1M) of the aforementioned compounds in Me_2SO

were heated in the presence of mM sulfuric acid, as previously described[1]. The progress of their decomposition was monitored by g.l.c. of per(trimethylsilyl)ated samples taken at appropriate intervals[1]. The rates of disappearance of the various substituted sucroses were calculated from the ratio of their g.l.c. peak-areas to those of the substituted D-glucose products, subject to the assumptions already outlined.

In the case of 2,1′:4,6-di-*O*-isopropylidenesucrose tetraacetate, the identities of the products were verified by isolation and identification as follows. A solution of 2,1′:4,6-di-*O*-isopropylidenesucrose tetraacetate (400 mg) in pure, dry Me_2SO (5 mL) containing mM sulfuric acid was heated to 150°. After 10 min under these conditions, the starting material was almost completely converted into 3,3′,4′,6′-tetra-*O*-acetylsucrose, and t.l.c. on silica gel with 5:1 ether–acetone showed the disappearance of the starting material (R_F 0.61) and the appearance of a major product (R_F 0.06). A transitory, minor spot (R_F 0.20) was assigned to the intermediate 3,3′,4′,6′-tetra-*O*-acetyl-2,1′-*O*-isopropylidenesucrose[11,14]. Throughout this time, samples examined by g.l.c. showed only a large, single peak in the disaccharide region, with only very small changes in the retention time (from 11.45 to 11.36 min; 140° + 10°/min). The temperature was then held for 5 h at 150° after which time, g.l.c. and t.l.c. indicated that the material having R_F 0.06 had been almost completely consumed, and that three new, faster-running products had been formed. The solution was then cooled to 80°, the acid neutralized with barium carbonate, and the bulk of the Me_2SO removed by vacuum distillation at 80°. The residue was extracted with the minimum amount of 3:1 ethyl acetate–petroleum ether, and the extract applied to a column of silica gel and eluted with the same solvent by[15] "flash chromatography". By this means, the crude material was separated into three fractions (1, 2, and 3).

On evaporation, fraction 1 gave a pale-yellow syrup (12.5 mg) which was pure by g.l.c. and t.l.c. The ^{1}H-n.m.r. spectrum ($CDCl_3$) showed δ 9.67 (s, 1 H, CHO), 7.21 and 6.59 (both d, 2 H, J 4 Hz, CHR=CHR′), 5.13 (s, 2 H, =C-CH_2-O-), and 2.12 (s, 3 H, CH_3COO-), and the compound was assigned as 5-(acetoxymethyl)-2-furaldehyde (**6**).

Evaporation of fraction 2 produced a syrup (17.2 mg). Deacetylation of a sample of this material with sodium in methanol gave a compound that behaved identically to levoglucosan in t.l.c., g.l.c., and l.c. Examination of the per(trimethylsilyl) derivative by g.l.c.–m.s. (OV-1 column, 23 eV) showed peaks at m/z 348(M^+), 289, 279, 245, 200, 185, 149, 117, 75, and 73. This compound was assigned as 3-*O*-acetyllevoglucosan (**4**).

Evaporation of fraction 3 afforded a syrup (26.3 mg). Deacetylation of a sample of this material produced a compound having behavior identical to that of fructose by t.l.c., g.l.c., and l.c. Per(trimethylsilyl)ation of the syrup gave a derivative which, on examination by g.l.c.–m.s. (OV-1, 23 eV), showed peaks at m/z 383, 303, 287, 273, 260, 243, 217, 204, 191, 174, 147, 133, 117, 75, and 73. It was assigned as being 3,4,6-tri-*O*-acetyl-α,β-D-fructofuranose (**5**) (see Results and Discussion).

REFERENCES

1 W. Moody and G. N. Richards, *Carbohydr. Res.*, 108 (1982) 13–22.
2 W. Moody and G. N. Richards, *Carbohydr. Res.*, 97 (1981) 247–255.
3 L. Poncini and G. N. Richards, *Carbohydr. Res.*, 87 (1980) 209–217.
4 J. N. BeMiller, *Adv. Carbohydr. Chem.*, 22 (1967) 25–108.
5 K. K. De and T. E. Timell, *Carbohydr. Res.*, 4 (1967) 72–77.
6 J. T. Edward, *Chem. Ind. (London)*, (1955) 1102–1104.
7 A. F. Bochkov and G. E. Zeikov, *Chemistry of the* O-*Glycosidic Bond*, Pergamon, Oxford, 1979, pp. 181–184.
8 J. W. Green, *Adv. Carbohydr. Chem.*, 21 (1966) 95–142.
9 N. K. Kochetkov and O. S. Chizhov, *Adv. Carbohydr. Chem.*, 21 (1966) 39–93.
10 J. Lönngren and S. Svensson, *Adv. Carbohydr. Chem. Biochem.*, 29 (1974) 41–106.
11 R. Khan and K. S. Mufti, *Carbohydr. Res.*, 43 (1975) 247–253.
12 J. G. Buchanan, D. A. Cummerson, and D. M. Turner, *Carbohydr. Res.*, 21 (1972) 283–292.
13 G. G. McKeown, R. S. E. Serenius, and L. D. Hayward, *Can. J. Chem.*, 35 (1957) 28–36.
14 R. Khan and H. Lindeth, *Carbohydr. Res.*, 71 (1979) 327–330.
15 W. Still, M. Kahn, and A. Mitra, *J. Org. Chem.*, 43 (1978) 2923–2925.