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THERMOLYSIS OF SUCROSE IN THE PRESENCE OF ALCOHOLS. A NOVEL METHOD FOR THE SYNTHESIS OF D-FRUCTOFURANOSIDES

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ABSTRACT

When sucrose is thermolyzed in the presence of alcohols, either neat or in dimethyl sulfoxide solution, the products are mainly D-glucose and the appropriate alkyl D-fructofuranosides. Conditions have been investigated for optimizing the yields of the latter products, with a view to utilization of the reaction as a synthetic method. Such sterically hindered alcohols as 2-methyl-2-propanol and three sterols did not readily take part in the reaction. Phenols appear to undergo the reaction, but the phenyl D-fructofuranosides are probably degraded subsequently, to give increased yields of 2,6-anhydro-D-fructofuranose.

INTRODUCTION

We have recently shown[1,2] that the thermolysis of sucrose (**1**) is facilitated in dimethyl sulfoxide solution, and that the reaction probably proceeds *via* a D-fructosyl carbocation (**2**) which may react with such alcohols as erythritol[1] or benzyl alcohol[2] to produce the appropriate D-fructofuranosides. This reaction has now been extended to a range of aliphatic alcohols and some phenols with a view to optimizing the synthetic utility of the reaction.

RESULTS AND DISCUSSION

In considering the effects of added alcohols on the thermolysis of sucrose (**1**) in dimethyl sulfoxide, we initially utilized the alcohols shown in Table I, and monitored the reaction by gas–liquid chromatography (g.l.c.). The products were mainly α- and β-D-glucopyranose, 2,6-anhydro-β-D-fructofuranose (**3**), D-fructose, and the appropriate α- and β-D-fructofuranosides (**4**). With some alcohols, the D-fructofuranosides were not completely resolved from D-fructose or D-glucose by g.l.c., but, in such cases, it was possible to degrade the latter products with alkali to reveal the D-fructofuranosides, which are very much less sensitive to alkaline degradation.

With methanol or benzyl alcohol, the D-fructofuranoside products were identified by comparison with authentic compounds in g.l.c. and thin-layer chromatography

TABLE I

THERMOLYSIS OF SUCROSE IN DIMETHYL SULFOXIDE IN THE PRESENCE OF ALCOHOLS

Alcohol	*Approximate maximum[a] yield (%) of D-fructofuranoside*	*Approximate maximum[a] yield (%) of anhydro-D-fructose*	R_t[b]
Methanol	57 (17)	0.3 (17)	5.79
Ethanol	54 (17)	0.4 (13)	5.43, 5.82
2-Propanol	23 (26)	1.2 (26)	5.71
2-Methyl-2-propanol	9 (20)	1.4 (25)	5.87
1-Butanol	20 (20)	0.8 (10)	8.06
Benzyl alcohol	55 (20)	0.4 (10)	15.33, 16.34

[a]As % of initial sucrose; the numbers in parentheses show the % of sucrose remaining at the time of maximum yield. [b]G.l.c. retention-times of D-fructofuranosides at 140° and 4°/min.

(t.l.c.). For 2-propanol, the products were new, and were isolated and characterized, and, for the remaining two alcohols mentioned in Table I, the identity of the products was assumed as indicated. The approximate yields shown in Table I are derived from g.l.c. peak-areas as the reaction progressed, and are based on several assumptions. First, it was assumed that D-glucose is produced in theoretical yield in the thermolysis of sucrose (as demonstrated in ref. 2). Thus, with the known, g.l.c. response-factors for sucrose and glucose, the amount of sucrose reacted could be calculated. The g.l.c. response-factors of the authentic methyl and benzyl D-fructofuranosides were known, and those of the remaining D-fructofuranosides were assumed to be similar. For the g.l.c. response of the anhydro-D-fructose, the response factor determined for 1,6-anhydro-D-glucopyranose was used. In all cases, as the reaction progressed, the yields of D-fructofuranosides and of anhydro-D-fructose rose to a maximum, and then

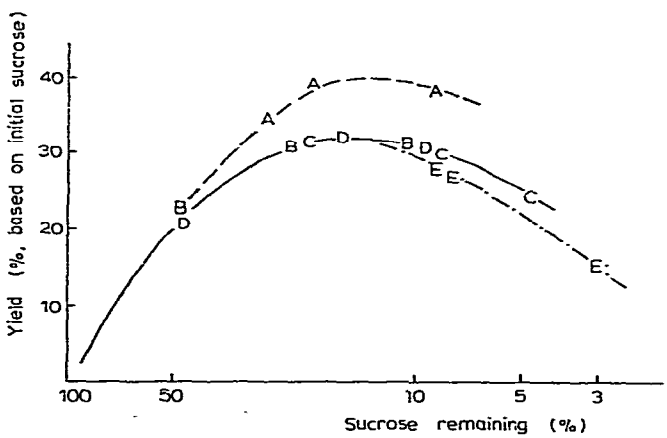
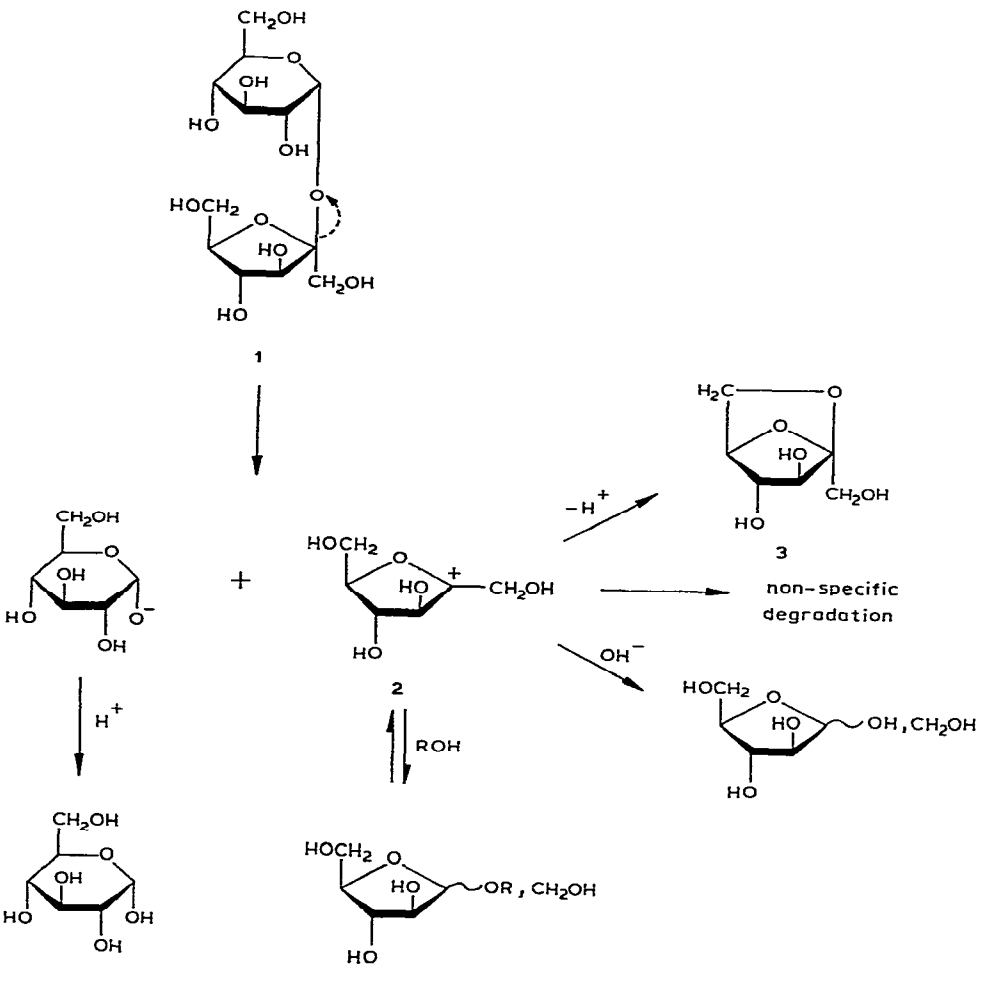


Fig. 1. Yield of benzyl D-fructofuranosides from sucrose and benzyl alcohol in dimethyl sulfoxide. [A, at 50°; B, at 70°; C, at 90°; D, at 110°; and E, at 130°.]

decreased; a typical curve is shown in Fig. 1, for benzyl alcohol. This disappearance of the original products of the reaction is apparently due to nonspecific, thermal degradation, which would yield a large number of products, each in very small yield.

The results in Table I suggest that the more sterically hindered alcohols give lower yields of D-fructofuranosides; this is not surprising, as the approach of the O-nucleophile to the tertiary fructosyl carbocation (**2**) is likely to be very sensitive to steric factors. Furthermore, an increased yield of 2,6-anhydro-β-D-fructofuranose (**3**) appears to accompany a decreased yield of D-fructofuranosides (**4**), and this is interpreted as due to an increase in the relative effectiveness of intramolecular attack on the carbocation by O-nucleophile at C-6 as the intermolecular attack by the alcohol becomes more hindered (see Scheme 1). It should be noted, however, that, even when intermolecular attack by O-nucleophile is heavily inhibited, as with 2-methyl-2-



Scheme 1

propanol, the reaction leading to anhydro-D-fructose is very inefficient, and, in this case, the major proportion of the D-fructosyl carbocation must be degraded non-specifically.

We have not attempted to draw any conclusion from relative rates of reaction between sucrose and the alcohols. The rate of thermolysis of sucrose in dimethyl sulfoxide is extremely sensitive to traces of water (*cf.* ref. 2), and any study of rates of the reaction in the presence of alcohols would require extremely rigorous, experimental conditions that are beyond the scope of the present study.

The thermolysis of sucrose in the presence of alcohols has obvious potential as a method for the synthesis of D-fructofuranosides, and we have investigated the effect of varying temperature and concentration on the yields. This work was conducted with benzyl alcohol, and the effect of temperature is shown in Fig. 1. Evidently, maximal yields of the D-fructofuranosides are obtained by slow reaction at low temperatures, and, presumably, this is associated with increasing thermal degradation of these products at higher temperatures. The yield of the minor product (anhydro-D-fructose) increases at higher temperatures. It is possible that these opposing trends in yield may be associated with major differences in activation entropy in the relevant reaction, but there is also a possibility that some of the D-fructofuranosides may be converted into anhydro-D-fructose. This reaction almost certainly occurs with the phenyl D-fructofuranosides (see later). The formation of anhydro-D-fructose from the benzyl D-fructofuranosides does not appear to occur by anchimeric displacement of the benzyl group by the oxygen atom on C-6. Were this the case, the α, not the β, anomer would react, and, hence, the ratio of α to β anomer would decrease with time as the amount of anhydro-D-fructose increased. In fact, the ratio of α to β anomer increases (*e.g.*, from 1.7 to 1.9 between 400 and 1200 s at 110°, and from 1.9 to 2.5 between 350 and 850 s at 130°). We therefore conclude that the β is less

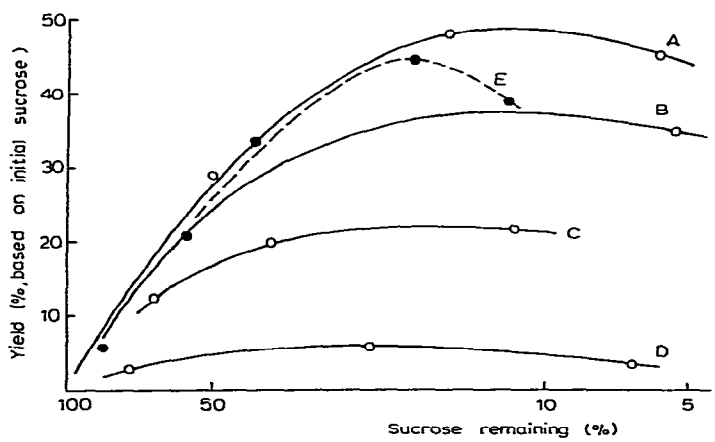


Fig. 2. Yield of benzyl D-fructofuranosides from sucrose and benzyl alcohol in dimethyl sulfoxide at 90°. [Molar ratio of benzyl alcohol to sucrose: A, 35.8; B, 22.1; C, 11.2; D, 2.4; E, neat benzyl alcohol.]

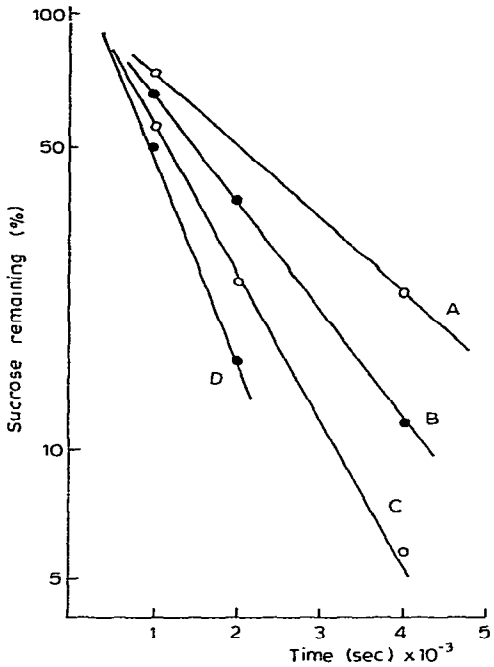


Fig. 3. Rate of loss of sucrose from 0.2M solution in dimethyl sulfoxide with various contents of benzyl alcohol; molar ratios as in Fig. 2.

stable than the α anomer, and that the degradation of both anomers proceeds *via* an intermediate such as the carbocation **2**, which may react partly to yield the anhydro-D-fructose. The lower thermal stability of the β anomer may be associated with facilitation of thermolysis by hydrogen bonding of the glycosidic oxygen atom with the hydrogen atom of either OH-1 or OH-3, or both (*cf.* ref. 2), whereas similar bonding in the α anomer could only occur with OH-1.

Increase in the concentration of benzyl alcohol resulted in an increased yield of the D-fructofuranosides (see Fig. 2), as the probability of reaction of the carbocation with the alcohol is increased in relation to its nonspecific degradation. The disappearance of sucrose still followed first-order kinetics, but the rate decreased as the proportion of benzyl alcohol was increased (see Fig. 3).

In order to optimize the method for synthesis of D-fructofuranosides, it therefore appears necessary to maximize the alcohol concentration and to minimize the temperature (within practical limits). The presence of even a small proportion of dimethyl sulfoxide has a very favorable effect on the reaction, and this may be associated with formation of some particular, solvated form (conformation ?) of the sucrose molecule in dimethyl sulfoxide solution. In the experiments described in Figs. 2 and 3, the sucrose was first dissolved in dimethyl sulfoxide, and then the benzyl alcohol was added. If sucrose was dissolved in the premixed solvents, the reaction was many times slower, and gave poorer yields. As a practical matter, however, the presence

of dimethyl sulfoxide often causes difficulty with separation and purification of products, because it is very difficult to remove it completely by distillation, and the traces left can adversely affect the chromatographic behavior.

Because of this circumstance, the reaction was examined by using neat alcohol as the reaction medium. The absence of "activation" by dimethyl sulfoxide, and the limited solubility of sucrose in the alcohols, usually restricted this approach to the high-boiling alcohols and to temperatures near to the melting point of sucrose. However, the solvolysis did occur, and D-fructofuranosides were formed. For sucrose in benzyl alcohol at 180°, the yield of D-fructofuranosides was ~70%, a value comparable to that found for the reaction performed in dimethyl sulfoxide at 90° with a large excess of benzyl alcohol (see Fig. 2). Slightly higher yields of anhydro-D-fructose were also produced, probably due to increased thermal breakdown of the D-fructosides. These reactions are the same as those observed earlier[3] in attempts to hydrogenolyze sucrose in ethanol solution at high temperatures, resulting in formation of the ethyl D-fructofuranosides and the anhydro-D-fructose.

When the benzyl alcohol was replaced by phenol, the reaction still occurred, to produce phenyl D-fructofuranosides, although in lower yield (~10%). G.l.c. analysis of this system was complicated by the development of a secondary set of peaks overlapping those of the phenyl D-fructofuranosides. These peaks, which began to appear about midway through the reaction, are attributed to the formation of phenyl D-glucosides, as peaks having similar g.l.c. retention-times and profile were produced when phenol was heated with D-glucose. A like situation was reported for the sucrose–benzyl alcohol reaction[2]. The most outstanding feature of the reaction in phenol was, however, the marked increase in the yield of the anhydro-D-fructose, the extra amount probably originating from the thermal degradation of the phenyl D-fructofuranosides; this would be in keeping with earlier studies on the thermal behavior of D-glucosides that showed that phenyl D-glucosides are less thermally stable than benzyl D-glucosides[4].

Similar behavior was also exhibited by two other phenols, as shown in Table II.

TABLE II

THERMOLYSIS OF SUCROSE IN BENZYL ALCOHOL AND IN PHENOLS

Compound	*Approximate maximum yield (%) of D-fructofuranosides*	*Approximate maximum yield (%) of anhydro-D-fructose*	*Approximate maximum yield (%) of D-fructose*
Benzyl alcohol[a]	70	5	1
Phenol[b]	<20[c]	15	0.4
p-Cresol[a]	<20[c]	10	0.4
p-Methoxyphenol[a]	<20[c]	8	0.6
o,o-Di-*tert*-butyl-*p*-cresol[d]	not detected	5	20.0

[a]At 180°. [b]At 170°. [c]Overlaps in g.l.c. with D-glucosides. [d]At 150°.

As with phenol itself, we concluded that reaction occurs to produce the D-fructofuranosides, and that these are less thermally stable than those of benzyl alcohol. Probably, the phenyl aglycon is lost from the D-fructofuranosides (**4**), to produce the D-fructosyl carbocation (**2**), which subsequently yields an increased amount of anhydro-D-fructose (**3**) as shown in Scheme 1. For such a reaction (**4** → **2**), the electron-withdrawing effects of the phenyl aglycons relating to Table II would be in the order phenyl > *p*-hydroxyphenyl > *p*-methoxyphenyl, and this is compatible with the relative yields of anhydro-D-fructose. By contrast, when the severely hindered 2,6-di-*tert*-butyl-4-methylphenol was used, no evidence could be found for D-fructofuranoside formation. In this case, the yields of anhydro-D-fructose and D-fructose were similar to those expected for a thermolysis of sucrose without involvement of a phenol.

The experiments described herein demonstrate a novel method for the synthesis of D-fructofuranosides. The major limitations of the method lie in the very limited application to sterically hindered alcohols, especially tertiary alcohols. It is unfortunate that many physiologically active alcohols whose D-fructofuranosides would be of potential, pharmacological interest are sterically hindered. Thus, we have attempted to prepare the D-fructofuranosides of cholesterol, testosterol, and testosterone by reaction with sucrose in dimethyl sulfoxide, and in melts, without finding any indication of formation of such products.

EXPERIMENTAL

General methods. — Unless otherwise indicated, t.l.c. plates (silica gel) were developed with 12:1:1 2-butanone–ethanol–water, sprayed with 5% sulfuric acid in ethanol, and heated at 120°. Gas–liquid chromatography of samples per(trimethylsilyl)ated with Tri-Sil (Pierce) was performed on an SE-30 column, as described earlier[1]. Electron-impact, mass spectra were obtained by direct insertion, or g.l.c. (SE-30 column) techniques. The thermolysis of sucrose in the presence of the various alcohols was performed by two separate, general procedures; an example of each of these is given.

Isopropyl D-fructofuranosides by reaction in dimethyl sulfoxide. — Dry 2-propanol (100 mL) was added by syringe to a solution of sucrose (15 g) in dry dimethyl sulfoxide (100 mL) in a sealed flask. The solution was then boiled under reflux for 5.5 h, at which time, a sample showed (g.l.c.) maximal yield of the D-fructofuranoside products. The 2-propanol and most of the dimethyl sulfoxide were then removed by vacuum distillation at 50°, giving an amber-colored syrup which was extracted with 1-butanol until no D-fructoside remained in the syrup (t.l.c.). The combined extracts were washed with water, and evaporated to a syrup which was purified by passage through a column (35 × 140 mm) of Amberlite C.G.-400 resin (borate form) eluted with water. The β anomer was eluted in the first 150 mL, whereas the α anomer, which forms a complex with the column-bound borate, was eluted more slowly (800–1500 mL). After evaporation of the appropriate fractions to dryness,

the α anomer was obtained as a colorless syrup which gave a single spot in t.l.c., and a single peak in g.l.c. It was acetylated with acetic anhydride in pyridine, and *isopropyl 1,3,4,6-tetra-*O*-acetyl-α-*D*-fructofuranoside* was isolated as a colorless syrup which was pure by g.l.c. and t.l.c.; $[\alpha]_D^{28}$ +63.6° (*c* 4.4, $CHCl_3$); ^{1}H-n.m.r. ($CDCl_3$): δ 5.34 (d, 1 H, $J_{3,4}$ 1.6 Hz, H-3), 4.95 (m, 1 H, CH_3-C*H*-CH_3), 4.0–4.5 (m, 6 H, H-1,4,5,6), 2.08 (m, 12 H, CO-CH_3), and 1.18 (2 d, 6 H, *J* 6 Hz, CH_3-CH-CH_3); ^{13}C-n.m.r. ($CDCl_3$): 170.4–168.3, (*C*O-CH_3), 107.2 (C-2), 80.6, 80.0, 78.0 (C-3,4,5), 64.9, 63.3 (C-1,6), 60.1 (CH_3-*C*H-CH_3), 24.1, 23.8 (*C*H_3-CH-*C*H_3), and 21.3 p.p.m. (CO-*C*H_3); m.s.: [P-OAc·]$^+$ *m/z* 331.132 ($C_{15}H_{23}O_8$ requires 331.139), [P-CH_2OAc·]$^+$ *m/z* 317.154 ($C_{14}H_{21}O_8$ requires 317.124), and [P-CH_3CH=CH_2]$^+$ *m/z* 275.

The β anomer, which was quickly eluted from the borate column, was contaminated by other products, including D-glucose, anhydro-D-fructose, and 5-(hydroxymethyl)-2-furaldehyde. Alkali-labile products were removed by treatment of the concentrated syrup with 0.1M sodium hydroxide for 45 min at 100°; the solution was made neutral (pH 7) with sulfuric acid, and evaporated to dryness, the residue extracted into 2-propanol, and the extracts evaporated to dryness. The resultant, brown syrup contained only the β anomer and anhydro-D-fructose; these were separated by means of a column of silica gel eluted with 1 : 19 methanol–ethyl acetate, to give pure isopropyl β-D-fructofuranoside as a colorless syrup. This was converted into the *tetraacetate*, obtained as a colorless syrup which was pure by g.l.c. and t.l.c., and had $[\alpha]_D^{28}$ −42.4° (*c* 2, $CHCl_3$); ^{1}H-n.m.r. ($CDCl_3$): δ 5.40 (m, 2 H, H-3, CH_3-C*H*-CH_3), 4–4.5 (m, 6 H, H-1,4,5,6), 2.12 (s, 12 H, CO-CH_3), and 1.15 (2 d, 6 H, *J* 6 Hz, CH_3-CH-CH_3); ^{13}C-n.m.r. ($CDCl_3$): 170.3–169.7 (-*C*O-CH_3), 103.6 (C-2), 77.3, 76.3, 75.5 (C-3,4,5), 66.4 (CH_3-*C*H-CH_3), 64.0, 63.8 (C-1,6), 24.4, 24.0 (*C*H_3-CH-*C*H_3), and 20.7–20.3 p.p.m. (-CO-*C*H_3); m.s.: [P-OAc·]$^+$ *m/z* 331.134 ($C_{15}H_{23}O_8$ requires 331.139), [P-CH_2OAc·]$^+$ *m/z* 317.133 ($C_{14}H_{21}O_8$ requires 317.124); the anomers gave virtually identical mass spectra.

Benzyl D-*fructofuranosides by reaction in neat alcohol.* — Dry, powdered sucrose (5 g) was added to dry benzyl alcohol (25 mL) contained in an open flask at 180°. The sucrose dissolved rapidly on stirring, and the reaction was monitored by taking periodic samples and analyzing by g.l.c. after per(trimethylsilyl)ation. After 2.5 h, the yield of benzyl D-fructosides was at the maximum, and the solution was cooled to room temperature, dissolved in chloroform (100 mL), and extracted with water (3 × 30 mL). The extracts were combined, and backwashed with chloroform (40 mL). The aqueous solution was then evaporated to dryness, and the resultant, pale-brown syrup fractionated on a column of silica gel with 2-butanone under pressure. This gave moderately pure samples of both the α and the β anomer. Repetition of the column chromatography gave pure samples of both benzyl α- and β-D-fructofuranoside, which had properties identical to those reported[2].

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