EFFECT OF TRACES OF ACIDS ON REACTION OF SUCROSE IN DIMETHYL SULFOXIDE

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ABSTRACT

Attempts to apply the thermolysis of sucrose in dimethyl sulfoxide (Me₂SO) solution to the synthesis of D-fructofuranosides gave irreproducible results; this was found to be due to the presence of a trace, in variable proportions, of an acid impurity in the solvent. The thermolysis reaction has been shown to be catalyzed by traces of strong acids, and the kinetics of the acid-catalyzed reaction in Me₂SO, N,N-dimethyl-formamide, and water have been studied.

INTRODUCTION

Previous studies had demonstrated the thermolysis of sucrose in dimethyl sulfoxide (Me₂SO), and the potential uses of this reaction in preparing a variety of alkyl D-fructofuranosides[1,2]. However, in attempting to use the system to synthesize D-fructofuranosides by the addition of other nucleophiles designed to react with the intermediate D-fructosyl carbonium ion, we experienced apparently unpredictable variability in the extent and rate of the reaction. The primary suspect in causing this variability was the presence of water in the highly hygroscopic system, as water had been considered to be a major inhibitor of the initial formation of the D-fructosyl carbonium ion from sucrose[2]. Further experimentation indicated that this was not the cause, and the results implied that the agent leading to the variation in the rates was not water, but a minute amount of an impurity (in the Me₂SO) that acted as a catalyst for the reaction. The investigations described herein showed that the reaction is catalyzed by traces of acid; the kinetics of this acid-catalyzed reaction and the influence of added water have now been studied.

RESULTS AND DISCUSSION

In order to remove the variability observed in the rate of degradation of sucrose in Me₂SO, attempts were made to obtain the solvent as dry as possible by more intensive and careful use of distillation and of drying agents. These experiments gave Me₂SO in which sucrose at a concentration of 0.1M showed no signs of degradation,

TABLE I

THE EFFECT OF DIFFERENT ACIDS ON THE RATE OF DISAPPEARANCE OF SUCROSE (0.1M) IN Me_2SO AT 70°

Acid	k_{obs} (s^{-1})
Sulfuric[a]	3.5×10^{-4}
p-Toluenesulfonic[a]	2.5×10^{-4}
Acetic[a]	$>1 \times 10^{-7}$
None	$<1 \times 10^{-7}$

[a]Concentration, 1mM.

even after several days at 100°. It thus seemed possible that the more rigorous drying procedures used had not only removed water but some other reagent that catalyzed the degradation of sucrose. Because the reaction bears some similarities to the acid hydrolysis of sucrose, and as basic reagents (CaH_2, BaO) were used in the drying procedure, it seemed probable that the purification procedure had removed an impurity that caused an acid-catalyzed degradation of the sucrose. Consequently, a small proportion of sulfuric acid (1mM) was added to a solution of sucrose (0.1M) in the newly purified Me_2SO, and the sucrose was then found to have reacted almost completely after 1 h at 100°. The products of this reaction were the same as those found previously[2], α-D-glucopyranose being the major, primary product. Slow mutarotation throughout the reaction led to increasing proportions of β-D-gluco-pyranose, but none was initially detectable. D-Fructose was also produced, but in somewhat lower yields than found previously[2]. Small proportions of 2,6-anhydro-D-fructofuranose were also observed.

Table I shows the rate of disappearance of sucrose (k_{obs}) for three different acids in Me_2SO. The reaction is catalyzed by sulfuric and p-toluenesulfonic acids, both of which are strong acids (i.e., dissociated) in[3,4] Me_2SO, but not catalyzed by acetic acid, which is[3] a weak acid in Me_2SO.

The disappearance of sucrose in Me_2SO in the presence of acids must, therefore, involve specific acid catalysis by solvated hydrogen ions, and, by analogy with the acid hydrolysis of glycosides[5,6] (and acetals in general)[7], the most plausible mechanism for the reaction is as outlined in Scheme 1. Here, K represents the equilibrium con-
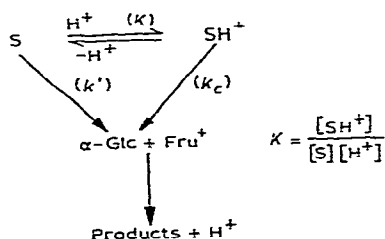
Scheme 1

stant between free sucrose and the sucrose protonated at the glycosidic oxygen atom, while k' and k_c are the rate constants for the rate-determining, glycosidic-bond-breaking step of the uncatalyzed and catalyzed reactions, respectively.

From Scheme 1,

$$d[G]/dt = k'[S] + k_c[SH^+]$$
$$= (k' + k_c K[H^+])[S],$$

and, as the initial concentration of sucrose ($[S]_0$) is much greater than the initial concentration of acid ($[H^+]_0$), it may be assumed for most of the reaction that $[S] \gg [SH^+]$, and hence,

$$[G] = [S]_0 - [S]$$

$$\therefore \frac{d}{dt}([S]_0 - [S]) = \frac{-d[S]}{dt} = (k' + k_c K[H^+])[S],$$

and $\quad \ln \dfrac{[S]}{[S]_0} = -(k' + k_c K[H^+])t \qquad (1)$

$$= -k_{obs} t. \qquad (2)$$

The function $[S]/[S]_0$ was measured by gas–liquid chromatography (g.l.c.) of reaction samples after (trimethylsilyl)ation. As D-glucose has been shown to be produced in >95% yield, and to be stable under the reaction conditions[2], it is possible to assume the validity of the equation

$$\frac{[S]}{[S]_0} = \frac{[S]}{[S] + [G]}.$$

TABLE II

THE EFFECT OF $[S]_0$ AND $[H^-]_0$ ON k_{obs} IN Me_2SO AT $70°$

$[S]_0$ (mM)	$[H^-]_0$ (mM)	$k_{obs} \times 10^4$ (s^{-1})
10.4	1.79	4.4
20.2	1.73	3.8
30.3	1.71	4.3
40.4	1.74	4.1
46.5	1.69	4.0
101.0	0.87	2.0
101.0	1.60	3.6
101.0	2.50	5.4
101.0	4.17	10.3
182.7	1.68	2.7
275.7	1.68	3.2
453.7	1.65	3.0

After calibration of the relative, g.l.c. response-factors for sucrose and D-glucose, it was, therefore, possible to determine $[S]/[S]_0$ from g.l.c. peak-area ratios for sucrose and D-glucose and, by plotting the values according to Eq. 2, values of k_{obs} were obtained. These plots were found to be linear for more than 90% of the reaction at any of the initial concentrations of sucrose and acid examined. Thus, in accordance with Scheme 1 and Eq. 2, the reaction is pseudo-first order in sucrose. Table II shows the values obtained for k_{obs} under these different conditions.

The data in Table II refer to $[H^+]_0$, but because some of the acid exists in the form $[SH^+]$, it is necessary to find some relationship between $[H^+]$ and $[H]_0$ in order to solve Eq. 1. Because

$$[H^+]_0 = [H^+] + [SH^+]$$
$$= [H^+](1 + K[S]),$$

and, at the beginning of the reaction,

$$[H^+]_i = \frac{[H^+]_0}{1 + K[S]_i},$$

we may assume that

$$[H^+] = \frac{[H^+]_0}{1 + K[S]_0}, \tag{3}$$

as $[H^+]$ is constant and $[S]_i \simeq [S]_0$.

Thus, from Eqs. 1, 2, and 3,

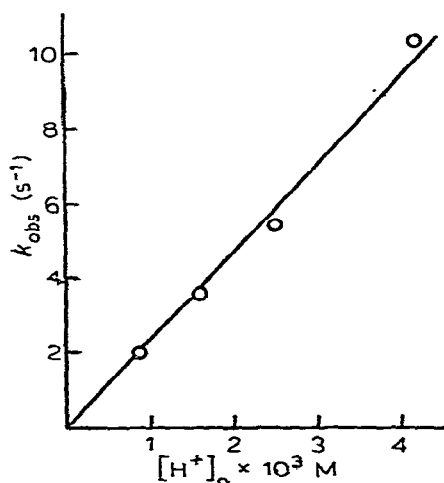$$k_{obs} = k' + \frac{k_c K[H^+]_0}{1 + K[S]_0}. \tag{4}$$

Fig. 1. Effect of sulfuric acid on rate for 0.1M sucrose in Me₂SO at 70°.

By choosing data from Table II where $[S]_0$ is constant, and by plotting k_{obs} vs. $[H^+]_0$ as shown in Fig. 1, it may be seen that $k' = {\sim}0$ and may be disregarded in the rate equation. Thus, it would seem that all of the reaction proceeds via the protonated sucrose, and

$$k_{obs} = \frac{k_c\,K[H^+]_0}{1 + K[S]_0},$$

or

$$\frac{[H^+]_0}{k_{obs}[S]_0} = \frac{1}{k_c\,K[S]_0} + \frac{1}{k_c}. \qquad (5)$$

When the experimental data in Table II were plotted as $[H^+]_0/k_{obs}[S]_0$ vs. $1/[S]_0$, a straight line resulted (see Fig. 2), and, from the slope and intercept, the values of $k_c = 0.22 \pm 0.06$ s^{-1} and $K = 1.1 \pm 0.3$M^{-1} were obtained. Calculations based on this value for K show that $[SH^+] = {\sim}0.1$mM for $[H^+]_0 = 1$mM and $[S]_0 = 0.1$M; i.e., in this system, ${\sim}10\%$ of the potentially available hydrogen ions are held by the reactive form of the protonated sucrose (SH^+). It had previously been shown by ^{1}H-n.m.r.-spectral methods that the anomeric hydroxyl group of various mono-
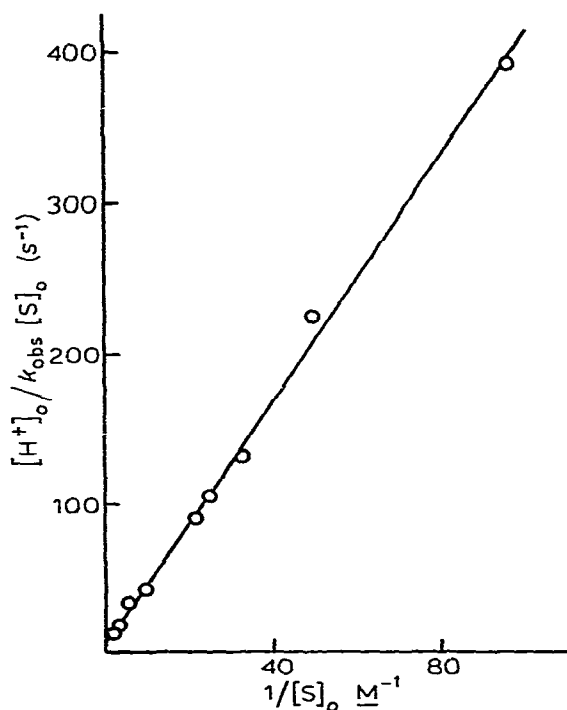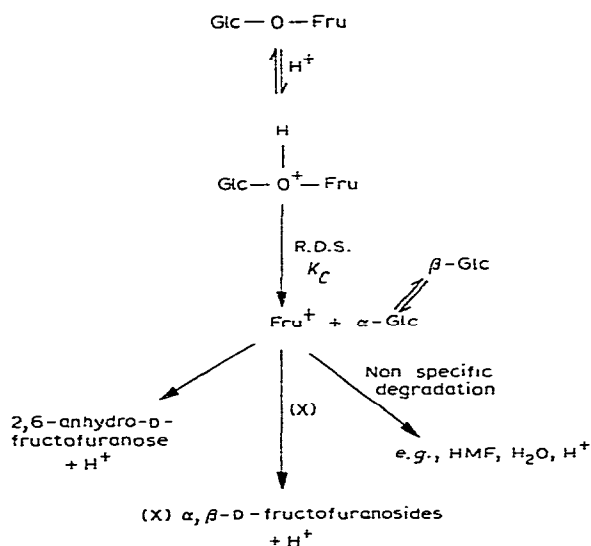

Fig. 2. Sucrose in Me$_2$SO at 70°.

Glc — O — Fru

$\updownarrow$ H$^+$

H
|
Glc — O$^+$— Fru

R.D.S.
K_C β-Glc

Fru$^+$ + α-Glc

Non specific
degradation

2,6-anhydro-D-
fructofuranose
+ H$^+$

(X)

e.g., HMF, H$_2$O, H$^+$

(X) α,β-D-fructofuranosides
+ H$^+$

Scheme 2

saccharides undergoes rapid protonation in acidic Me$_2$SO, and that there is significant competition for the proton by the other hydroxyl groups present[8].

Thus, the kinetics of the acid catalyzed degradation of sucrose in Me$_2$SO are well explained by the mechanism outlined in Scheme 2. The initial products of the reaction are α-D-glucopyranose and the D-fructosyl carbonium ion. The α-D-gluco-pyranose mutarotates relatively slowly, to produce an equilibrium mixture of the anomers, and the D-fructosyl carbonium ion has only a transitory existence, reacting by several different pathways depending on the conditions. By undergoing an intra-molecular reaction with the 6-hydroxyl group, it can produce 2,6-anhydro-D-fructo-furanose. The D-fructosyl carbonium ion can also react with water either initially
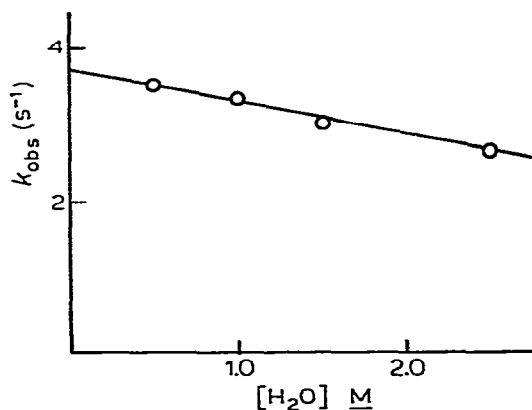

Fig. 3. Effect of water on rate for 0.1M sucrose in Me$_2$SO–water mixtures containing 1.6mM sulfuric acid at 70°.
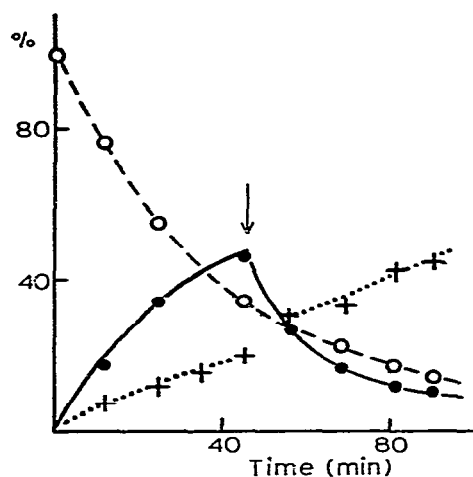
Fig. 4. Effect of adding water (1%) to an ongoing reaction of 0.1M sucrose in Me₂SO containing 1.6mM sulfuric acid at 70°. (Key- ○, sucrose; +, D-fructose; ●, 2,6-anhydro-D-fructose × 10; arrow, water added.)

present or produced during the reaction, with formation of α,β-D-fructofuranose, which subsequently changes, to afford some of the pyranose anomers. A third type of pathway involving elimination of water leads to the formation of small unsaturated molecules, notably 5-(hydroxymethyl)-2-furaldehyde. In the absence of any available nucleophiles, this nonspecific degradation of the D-fructosyl carbonium ion pre-dominates. However, if a suitable nucleophile (such as an alcohol) is added to the reaction mixture, the D-fructosyl carbonium ion can react with it to produce the α- and β-D-fructofuranosides. If water is added, there is a marked increase in the pro-portion of D-fructose produced. Addition of water also causes a decrease in the rate of reaction (see Fig. 3), although the effect is much less significant than was previously thought. When a small proportion (1 %) of water is added to an ongoing reaction in dry Me₂SO, only minor changes are observed (see Fig. 4). The rate of reaction decreases slightly, and, as expected, the yield of D-fructose increases, while the yield of the anhydro-D-fructose decreases. Possibly, in an earlier experiment[2] in which water appeared to inhibit the reaction completely, the reaction solvent containing

TABLE III

THE EFFECT ON k_{obs} WHEN SOLUTIONS OF 0.1M SUCROSE AND 0.01M H₂SO₄ ARE HEATED IN Me₂SO, DMF, AND WATER AT 40°

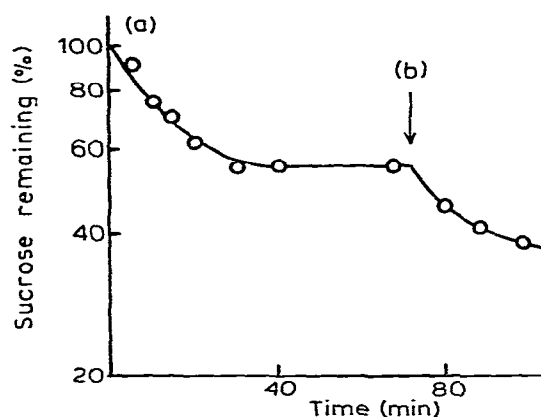| Solvent	k_{obs} (s^{-1})
Me₂SO	1.2×10^{-4}
DMF	1.6×10^{-4}
H₂O	0.2×10^{-4}

Fig. 5. Effect of adding acid to the reaction of 0.1M sucrose in DMF at 70°; (a) 1% (v/v) of 0.1M sulfuric acid in DMF added; (b) further addition of 1% (v/v) of acid.

water was fortuitiously free from the unknown, acid impurity. Alternatively, the impurity itself may have reacted with water and become inactive.

As may be seen from Table III, when water itself is the solvent, the reaction progresses at a lower rate. When N,N-dimethylformamide (DMF) is used as the solvent, instead of Me_2SO, the rate of reaction is slightly enhanced. The difference in rates for the three solvents may reflect a difference in their affinity for the proton relative to that of the glycosidic oxygen atom, with water having the greatest affinity. Thus, in Me_2SO and DMF, sucrose would be more extensively protonated, the concentration of the species SH^+ would be higher, and, consequently, the reaction would be faster, because this is the species involved in the rate-determining step.

A further difference in the three solvents is seen during the course of the reaction. Only in Me_2SO is the added acid truly catalytic, in that addition of small amounts of acid promote a high and constant rate throughout the reaction. In both water and DMF, addition of the acid causes a rapid reaction initially, but the rate gradually decreases, and becomes zero at some point during the reaction (dependent on the proportion of acid added). The behavior is illustrated in Fig. 5 for DMF; (a) after addition of the first aliquot of acid, the reaction progresses at a slowly decreasing rate, to become zero when ~55% of the sucrose remains; and (b) on addition of a second aliquot of acid, the reaction begins again. The same profile is found for water as the solvent, although, in this instance, the rate decreases even more rapidly (for the conditions described in Fig. 5) and becomes zero at ~80% of the sucrose remaining. Thus, it seems that, both in water and in DMF, there is a minor reaction-product that is a base which gradually consumes the acid and leads to a decreasing rate of reaction. The reaction rate is only linear in these solvents when much larger proportions of acid are used (e.g., as described in Table III).

Other solvents, such as alcohols, ethers, and "glymes", can also be shown to support the reaction; however, they are usually very poor solvents for sucrose, and

often necessitate the use of temperatures ($\sim 180°$) at which thermal decomposition of the products is substantial. Such basic solvents as pyridine are unsuitable, for obvious reasons. Thus, it would seem that, for this and similar synthetic reactions in which it is desired to add various nucleophiles to the D-fructosyl carbonium intermediate, Me_2SO is the solvent of choice.

In conclusion, it should be pointed out that the reaction system investigated here is a special case of the much-studied, acid hydrolysis of glycosides[5,6], but differs in two important respects. Firstly, the concentration of acid employed is much lower than that generally used, an important consideration in synthesis, as many carbohydrates and their derivatives are unstable under acidic conditions. Secondly, by using a non-aqueous solvent, it is possible to trap the intermediate carbonium ion with a variety of nucleophiles, to give useful products, rather than obtaining the free sugar, as would be the case in water. A further feature peculiar to the system is the formation of a tertiary carbonium ion that thermodynamically favors the reaction. This feature will be common to the acid-catalyzed reactions of any ketose or ketoside.

EXPERIMENTAL

Pure, dry Me_2SO was prepared by distillation from calcium hydride under diminished pressure, and stored over calcium hydride for several days. It was then redistilled onto a fresh quantity of calcium hydride, only the center fraction being taken, and stored with exclusion of moisture. Pure, dry DMF was prepared by the same procedure. The water used was triply distilled from glass. Analar sucrose was finely ground, and dried *in vacuo* at 40° over phosphorus pentaoxide.

Solutions of acid were prepared by adding weighed quantities of 98% sulfuric acid to weighed volumes of the chosen solvent, to give a stock solution. Calculated amounts of these stock solutions were then weighed into vials containing a weighed amount of dry sucrose in Me_2SO or other solvent.

The reactions were performed in Teflon-sealed, glass vials suspended in an oil bath maintained at the desired temperature ($\pm 0.1°$). At intervals, small samples were taken by hypodermic syringe, per(trimethylsilyl)ated, and the ethers examined by g.l.c., as previously described[1].

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