Carbohydrate Research, 226 (1992) 253–260
Elsevier Science Publishers B.V., Amsterdam

The periodate oxidation of sucrose in aqueous *N,N*-dimethylformamide

Dirk de Wit, Ronald van den Berg, L. Anders M. Johansson, Fred van Rantwijk, Leendert Maat*, and Antonius P. G. Kieboom†

Delft University of Technology, Laboratory of Organic Chemistry, Julianalaan 136, 2628 BL Delft (The Netherlands)

(Received June 18th, 1991; accepted in revised form November 5th, 1991)

ABSTRACT

Sucrose has been oxidized with sodium periodate in 0–50% aqueous *N,N*-dimethylformamide (DMF). In 50% aqueous DMF the reaction is selective for the glucose ring, yielding a dialdehyde. The increased selectivity is not due to conformational factors but is ascribed to the dissociation of water from cyclic periodate ester species which makes the reaction via the acyclic ester on fructose unfavourable.

INTRODUCTION

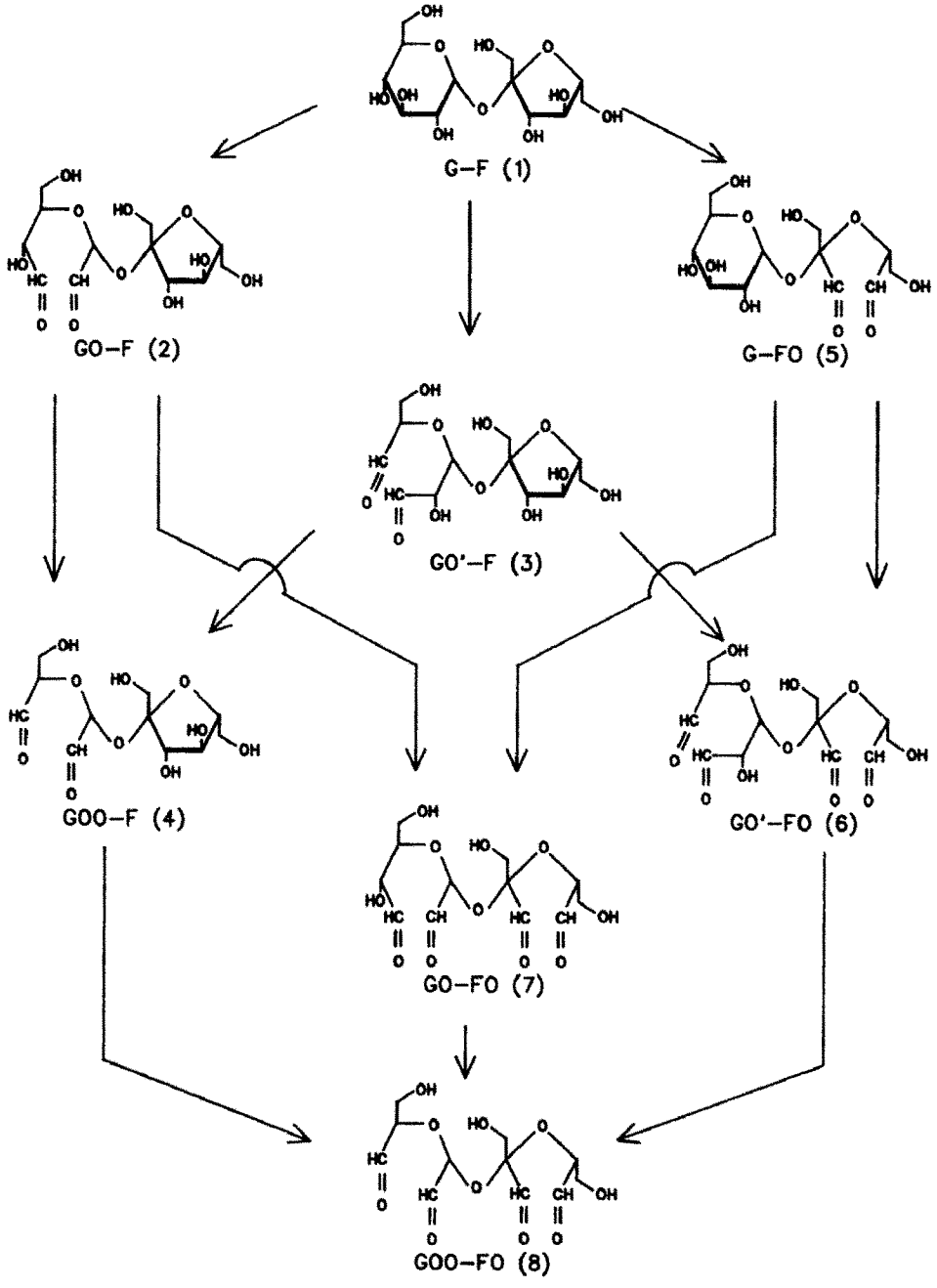
We reported recently on the oxidation (glycol cleavage) of sucrose by sodium periodate[1,2]. Of the seven possible oxidation products (Scheme 1), those bearing an unreacted sugar ring (**2**, **3**, **4**, and **5**) are of particular interest because of their potential use as chiral building blocks in further synthesis[3,4]. We have found[2] that the course of the reaction depends highly on the reaction temperature and pH. At 95° and pH 7 the dialdehyde derived from a double oxidation of the glucose ring (**4**) is formed selectively[2], whereas a ~ 1:1 mixture of glucose- and fructose-ring oxidized products is formed at 25° and pH 5 or 7.

Apart from temperature and pH, the use of water–organic solvent mixtures might be expected to influence the regioselectivity of the periodate oxidation of sucrose. The only report on this is that of Mitra and Perlin[5], showing a slight preference for the oxidation of the glucose ring in aqueous ethanol.

In order to examine potential solvent effects on both the reaction rate and regioselectivity, we have studied the periodate oxidation of sucrose in different water–dimethylformamide (DMF) mixtures.

* To whom correspondence should be addressed.
† Present address: Royal Gist-brocades N.V., R & D Group Chemistry and Analysis, P.O. Box 1, 2600 MA Delft, The Netherlands.

0008-6215/92/$ 05.00



Scheme 1. Oxidation of sucrose by periodate.

RESULTS

DMF is one of the few commonly used organic solvents that dissolves both sucrose and sodium periodate. However, glycol scission was observed only after the addition of an equal volume of water, indicating that water is required in the oxidation. This result agrees with the observation that the oxidation of 1,2-cyclohexanediol in aqueous DMF requires 50% water[6].

When periodate was used in a three-fold molar excess over sucrose in 50% aqueous DMF at 25°, no further precipitation of sodium iodate was observed after 2 h, which indicates that the conversion of the periodate is complete within this time. DMF was removed by lyophilization and the reaction mixture was analyzed by h.p.l.c. as described previously[1].

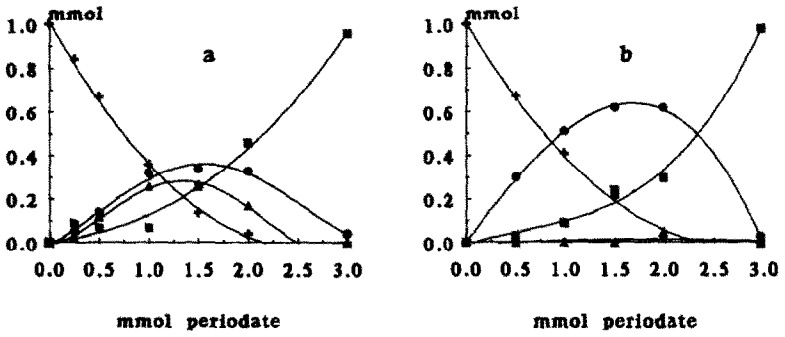


Fig. 1. Oxidation of 1 mmol sucrose (+) into G-FO (▲), GO(O)-F (●), and GO(O)-FO (■) as a function of the amount of periodate added (at 100% periodate consumption): (a) water, 25°, pH 5; (b) 50% (w/w) aqueous DMF, 25°.

The course of the oxidation reactions in 1:1 (w/w) DMF–water solution and in aqueous solution is depicted in Fig. 1. In water at 25° (pH 5) oxidations at the glucose and fructose sites occur at the same initial rate, as is apparent from the equal increase in the dialdehydes having only the glucose ring (**2–4**) and those having only the fructose oxidized **5** (Fig. 1a). In 50% aqueous DMF, however, formation of **5** is negligible, whereas formation of the tetraaldehydes **6–8** is comparable to that in water (Fig. 1b). Thus, the major pathway for the oxidation of sucrose in 50% aqueous DMF can be described by:

$$\text{G-F} \xrightarrow{k_1} \text{GO(O)-F} \xrightarrow{k_2} \text{GO(O)-FO}$$

with:

$$\frac{\mathrm{d[GO(O)\text{-}F]}}{\mathrm{d}t} = k_1 \cdot [\text{G-F}] - k_2 \cdot [\text{GO(O)-F}] \qquad (1)$$

and with the ratio of rate constants:

$$k_1/k_2 = \frac{[GO(O)\text{-}F]}{[G\text{-}F]} = 4.6 \qquad (2)$$

when [GO(O)-F] reaches its maximum.

The total oxidation of the glucose moiety (GO(O)-F + GO(O)-FO) as well as the oxidation of GO to GOO, in which formic acid is produced, is depicted in Fig. 2. The amount of GOO was measured by titration of the formic acid, whereas the amount of glucose-ring oxidation was assessed by h.p.l.c. from the amount of glucose formed after hydrolysis of the reaction mixture (see experimental). This result confirms that the reaction mixture contains singly and doubly oxidized glucose systems.

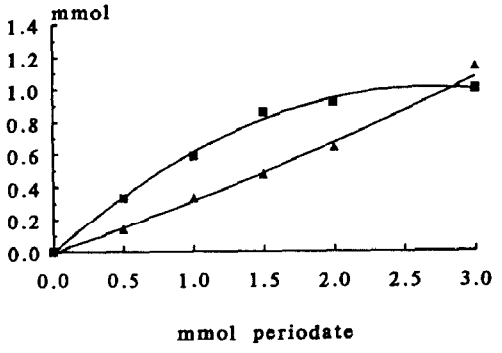
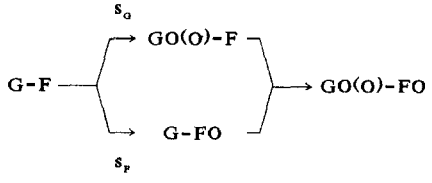


Fig. 2. Formic acid produced (▲) and total amount of glucose oxidized (GO(O)-F) + GO(O)-FO) (■) during the periodate oxidation of sucrose in 50% aqueous DMF, 25°.

The solvent effect of DMF was further investigated in a series of experiments in which equimolar amounts of periodate and sucrose were reacted at different DMF concentrations. On the basis of a simplified reaction scheme (Scheme 2), the reaction selectivity (consisting of s_G and s_F) is given in Fig. 3, where s_G = GO(O)-F/(GO(O)-F + G-FO) and s_F = G-FO/(GO(O)-F + G-FO). This treatment is valid because the amount of tetraaldehydes formed under these reaction conditions is small. Increasing the amount of DMF clearly enhances the reaction selectivity by suppressing oxidation at the fructose site (Fig. 3).



Scheme 2. Simplified reaction scheme of the oxidation of sucrose with periodate.

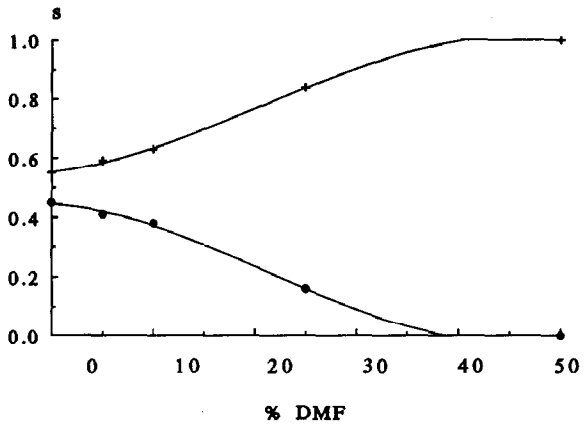


Fig. 3. $s_G(+)$ and $s_F(\bullet)$ as a function of the percentage of water in aqueous DMF mixtures.

DISCUSSION

Our present results show that the oxidation reaction in aqueous DMF proceeds at a lower rate than the reaction in water and favours the oxidation of the glucose ring. In water at 75° and pH 5 the reaction was selective in the same manner[2]. However, here the reaction rate was enhanced. Therefore, there is no direct relationship between reactivity and selectivity.

The question arises whether the average conformation[7] of sucrose in water changes upon addition of DMF, thereby affecting the course of the periodate oxidation

TABLE I

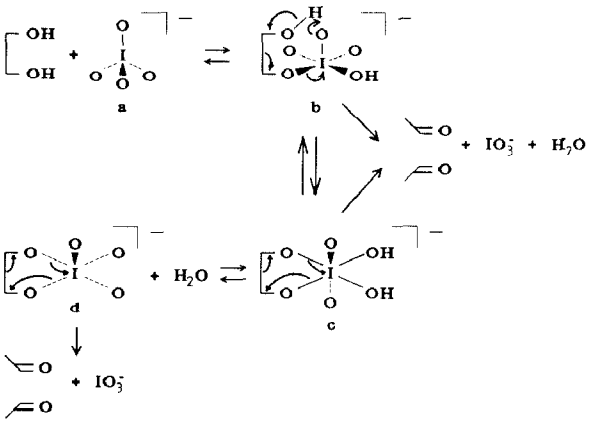
^{13}C N.m.r. relaxation times[a] for sucrose

C-atom	*H_2O–^2H_2O (9/1, w/w); 25°*		*^2H_2O; 25°*		*^2H_2O; 75°*		*^2H_2O; DMF-d_7 (1/1; w/w); 25°*	
	$T_1(s)$	$\bar{T}_1/2^b$	$T_1(s)$	$\bar{T}_1/2^b$	$T_1(s)$	$\bar{T}_1/2^b$	$T_1(s)$	$\bar{T}_1/2^b$
C-1[g]	0.490		0.426		0.920		0.236	
C-2[g]	0.505		0.453		0.918		0.243	
C-3[g]	0.510		0.451		1.074		0.251	
C-4[g]	0.510		0.458		1.054		0.246	
C-5[g]	0.513		0.443		0.920		0.239	
C-6[g]	0.308		0.263		0.624		0.152	
C-1[f]	0.291	0.249	0.253	0.219	0.574	0.486	0.142	0.121
C-3[f]	0.482		0.424		0.988		0.237	
C-4[f]	0.494		0.432		0.999		0.244	
C-5[f]	0.471		0.409		0.898		0.232	
C-6[f]	0.333		0.288		0.741		0.164	

[a] Accuracy ± 5%. [b] The half-average value of the methine carbon atoms in the glucose- and fructose-ring system.

reaction. In addition to earlier n.m.r. spectroscopic studies[8–10] we have measured the ^{13}C relaxation times of the primary and secondary carbon atoms in sucrose in 9:1 (w/w) H_2O–^2H_2O, ^2H_2O, and 1:1 (w/w) DMF-d_7–^2H_2O (Table I). The differences in the relaxation times measured in 9:1 H_2O–^2H_2O and neat ^2H_2O at ambient temperature are small. For that reason we assume that conclusions regarding the conformation of sucrose in ^2H_2O are also valid in H_2O. It becomes apparent from our measurements that the difference in relaxation time, between C-1^f and half the average relaxation time of the methine carbon atoms, remains small under all conditions. We conclude that the O-1^f···H···O-2^g hydrogen bond[9,10] remains intact when DMF is added or when the temperature is raised to 75°. Consequently, the observed selective oxidation of the glucose ring cannot be attributed to alterations in the average conformation of sucrose. We, therefore, conclude that the similar effects of both DMF addition and temperature increase (in H_2O) on the reaction is caused by differences in the mechanism of the periodate oxidation at the glucose and fructose rings.

The periodate oxidation of glycols has generally been discussed, up to now, in terms of a cyclic ester intermediate[11]. Because this seems an oversimplification of the reaction mechanism, we have depicted in Scheme 3 the spatial structures of the possible intermediates. The inter-oxygen distances have been taken from periodate crystal structures[12].



Scheme 3. Spatial structures of periodate–diol intermediates: (**a**) tetrahedral, O–O: 287 pm; (**b**) square pyramidal, O–O: 262 or 252 pm; (**c**) octahedral, O–O: 262 pm; (**d**) square pyramidal.

The two cyclic bidentate esters **c** and **d** will, in general, be more stable than the monoester **b**. One would expect a shift of the equilibrium towards the dehydrated ester **d** when the water activity is low or at elevated temperatures (gain in entropy), analogous to the equilibrium:[13,14]

$$H_4IO_6^- \rightleftarrows IO_4^- + 2\,H_2O$$

This intermediate **d** is plausible with glucose (inter-oxygen distances of the two diol systems are 2.87 Å), but oxidation of the fructose system (inter-oxygen distance of the *trans*-diol is 3.13 Å)[15,16] should proceed via the acyclic intermediate **b**, because the cyclic ester is geometrically unfavourable*.

The results of this study suggest that the dissociation of water from cyclic periodate ester species dictates the course of sucrose oxidation, that is, the decomposing entity is a dehydrated intermediate. Conditions that make the dissociation of water energetically advantageous will favour the oxidation of glucose relative to that of fructose, with the former occurring via cyclic esters and the latter via acyclic esters.

EXPERIMENTAL

Reaction apparatus. — The oxidation experiments at pH 5 and 25 or 75° in water were performed in a 60-mL thermostatted glass reaction-vessel. During reaction, the pH was kept constant automatically using a pH meter (Metrohm 654), a pH controller (Metrohm 614) and a motor burette (Metrohm 665, 5 mL) containing 0.1M aq. NaOH.

Reactions in water. — Sucrose (342 mg, 1 mmol) was dissolved in a weighed amount of water (30.00 g) and stirred in the dark at 25 or 75° under a stream of N_2. To this mixture a 0.2M aqueous $NaIO_4$ solution was added at a rate of 1 mL/min using a motor burette (Metrohm 665, 10 mL) and at a constant pH of 5.0 (± 0.1). After each addition of the appropriate amount of $NaIO_4$ at 75° the mixture was cooled to 25° and the pH was brought to 7. It appeared that all of the periodate had reacted under these conditions. Further maintenance at higher temperature was not necessary. At pH 5 and 25°, the pH was brought to 7 when the addition of NaOH solution followed a straight line. Each reaction mixture containing a given amount of periodate was analyzed by h.p.l.c.

Reactions in water–DMF. — Sucrose (342 mg, 1 mmol) was dissolved in a weighed amount of DMF (15 g). The appropriate amount of periodate was added. To this solution 15 g of water was added. After 2 h the mixture was lyophilized twice. The residue was dissolved in 20 mL of water and analyzed. For the reactions with other DMF–water ratios, the volumes of the solvents concerned are adjusted.

H.p.l.c. apparatus. — The h.p.l.c. system consisted of a Millipore–Waters M6000A or M45 pump, a Perkin–Elmer ISS-100 autosampler, a Waters R 401 refractive index detector, and a Spectra-Physics 4270 integrator. The following h.p.l.c. columns were used: (*i*) a 9 × 250-mm column packed with 9–11 μm Aminex A-7 (Bio-Rad). This column was kept in a Spark Holland SpH 99 column oven at 60°; (*ii*) a 4.6 × 250-mm 5 μm RSIL-polyol column (Alltech) at ambient temperature.

Analysis procedures. — *A. Determination of sucrose.* To 0.50 g of the reaction mixture, 0.50 g of a cyclomaltoheptaose solution (10 mg/mL water) as the internal

* Oxidation of sucrose with lead tetraacetate (estimated inter-oxygen distance 3.1 Å) yields[5] the dialdehyde G-FO. Apparently in this route the cyclic ester is favoured on the fructose ring by fitting onto its diol system (3.13 Å).

standard and 1.00 g of MeCN were added; 70 μL of the resulting solution [1:1 (v/v) MeCN–water] was injected onto the RSIL-polyol column with an eluent flow [7:3 (v/v) MeCN water] of 1.0 mL/min.

B. Determination of glucose and fructose. An aqueous solution of diethylene glycol dimethyl ether (0.50 g; 20 mg/mL) was added to 0.50 g of the reaction mixture, followed by 0.50 mL of a 0.8M aqueous solution of $NaBH_4$ in 0.1M NaOH. After 24 h at room temperature, the resulting solution was hydrolyzed by adding 0.06 mL of trifluoroacetic acid and the resulting mixture was stored overnight at 60°. Analysis was performed on the Aminex A-7 (H^+) column at 60° with an eluent flow (0.01M trifluoroacetic acid in water) of 0.6 mL/min.

N.m.r. measurements. — All n.m.r. experiments were performed on a Varian VXR-400S spectrometer. The longitudinal ^{13}C relaxation-times were measured in ^2H_2O at 25° and 75°, in 9:1 (w/w) water–^2H_2O at 25°, and in 1:1 (w/w) ^2H_2O–DMF at 25°. A 0.3M solution of sucrose in a 5-mm tube containing 1 mL was used for the measurements. The relaxation times were obtained with an inversion-recovery method [(90^0_x 180^0_y 90^0_x – t – 90^0_x) pulse sequence]. The magnetization curves were fitted with a three-parameter equation suggested by Levy and Peat[17] to correct for inhomogeneous H1 fields which produce incomplete inversion by the 180° pulse.

ACKNOWLEDGMENTS

We are greatly indebted to Dr. J. A. Peters for valuable discussions and performing the n.m.r. experiments. Experimental assistance by Mr. E. Le Grand is gratefully acknowledged.

REFERENCES

1 D. de Wit, F. van Rantwijk, L. Maat, and A. P. G. Kieboom, *Recl. Trav. Chim. Pays-Bas*, 108 (1989) 335–338.
2 D. de Wit, F. van Rantwijk, L. Maat, and A. P. G. Kieboom, *Recl. Trav. Chim. Pays-Bas*, 109 (1990) 518–522.
3 K. J. Hale, L. Hough and A. C. Richardson, *Tetrahedron Lett.* 28 (1987) 891–897.
4 K. J. Hale, L. Hough and A. C. Richardson, *Chem. Ind.* (1988) 268–269.
5 A. K. Mitra and A. S. Perlin, *Can. J. Chem.*, 37 (1959) 2047–2052.
6 R. D. Guthrie, *Chem. Ind.*, (1960) 691.
7 C. H. du Penhoat, A. Imberty, N. Roques, V. Michon, J. Mentech, G. Descotes, and S. Pérez, *J. Am. Chem. Soc.* 113 (1991) 3720–3727.
8 A. Allerhand, D. Doddrell, and R. Komoroski, *J. Chem. Phys.*, 55 (1971) 189–198.
9 K. Bock and R. U. Lemieux, *Carbohydr. Res.*, 100 (1982) 63–74.
10 D. C. McCain and J. L. Markley, *Carbohydr. Res.*, 152 (1986) 73–80.
11 A. S. Perlin, in W. Pigman and D. Horton (Eds.), *The Carbohydrates, Chemistry and Biochemistry*, Vol. 1b, Academic Press, New York, 1980, pp. 1168–1169.
12 N. N. Greenwood and A. Earnshaw, *Chemistry of the Elements*, Pergamon Press, Oxford, 1985, pp. 1022–1023.
13 R. M. Kren, H. W. Dodgen, and C. J. Nyman, *Inorg. Chem.*, 7 (1968) 446–451.
14 C. E. Crouthamel, A. M. Hayes, and D. S. Martin, *J. Am. Chem. Soc.*, 73 (1951) 82–87.
15 G. M. Brown and H. A. Levy, *Acta Cryst.*, B29 (1973) 790–797.
16 J. C. Hanson, L. C. Sieker, and L. H. Jensen, *Acta Cryst.*, B29 (1973) 797–808.
17 G. C. Levy and I. R. Peat, *J. Magn. Reson.*, 18 (1975) 500–521.