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Bromide-free TEMPO-mediated oxidation of primary alcohol groups in starch and methyl α-D-glucopyranoside

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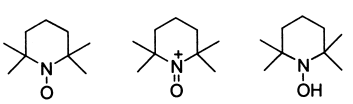
Abstract

TEMPO (2,2,6,6-tetramethylpiperidine-1-oxyl)-mediated oxidation of potato starch and methyl α-D-glucopyranoside (MGP) was performed in the absence of sodium bromide (NaBr) as co-catalyst, solely using sodium hypochlorite (NaOCl) as the primary oxidant. The low reaction rate associated with a bromide-free process was increased by performing the oxidation at increased temperatures. The reaction proceeded stoichiometrically and with high selectivity and with only minor depolymerisation, provided that temperature and pH were kept ≤ 20 °C and < 9.0, respectively. At 20 °C and pH 8.5, the reaction rate was comparable to that of a corresponding oxidation catalysed by NaBr at 2 °C. Consequently, this is a simple approach to raise the TEMPO/NaOCl reaction rate under bromide-free conditions while still maintaining good product properties. At higher oxidation temperatures (≥ 25 °C) and under more alkaline conditions (pH ≥ 9.0) degradation of the starch skeleton occurred. Simultaneously, side-reactions of the nitrosonium ion lowered the yield of the oxidation. Despite the absence of the NaBr catalyst, the reaction rate-controlling step was found to be the oxidation of the primary hydroxyl groups with the nitrosonium ion. The reaction was first-order in MGP and in TEMPO.

Keywords: TEMPO; Oxidation; Starch; Methyl α-D-glucopyranoside; Kinetics

1. Introduction

Stable nitroxyl radicals like TEMPO (2,2,6,6-tetramethylpiperidine-1-oxyl) (**I**) and its analogues have gained interest during the last 15 years as versatile and useful reagents for conversions of alcohols to carbonyl compounds [1]. The actual oxidising species is the nitrosonium ion (**II**) [2], the oxidised form of TEMPO.



I II III

Upon acting as oxidant species, **II** is converted into the hydroxylamine (**III**), the reduced form of TEMPO. In a TEMPO-mediated process regeneration of the nitrosonium ion takes place in situ by oxidants, such as *m*-chloroperbenzoic acid, copper salts, sodium bromite and sodium hypochlorite/sodium bromide [3–6]. Recently, additional

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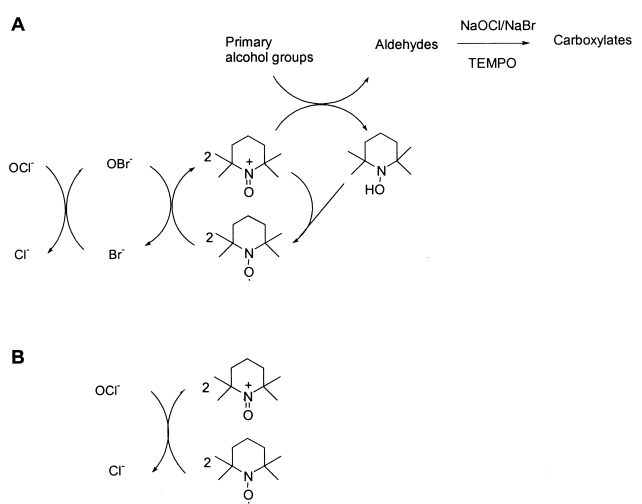
oxidants such as *N*-chlorosuccinimide and [bis(acetoxy)iodo]benzene were described [7,8]. The TEMPO oxidation process has been applied to the oxidation of various polysaccharides, including potato starch, inulin, guar gum, pullulan, dextrins, cellulose, carboxymethyl cellulose and chitosan, into the C-6 aldehyde and carboxy derivatives [9–13]. In all these studies, sodium hypochlorite/sodium bromide was used as the regenerating oxidising system of **II**, and hypobromite, which is the active oxidising species in this process, is formed in situ by oxidation of sodium bromide by sodium hypochlorite. TEMPO (**I**) is regenerated in situ via the hydroxylamine (**III**), which reacts with **II** to form TEMPO. It is generally accepted that catalytic cycle proceeds as depicted in Scheme 1(A). It cannot be ruled out that TEMPO is regenerated through a direct oxidation of the hydroxylamine by action of the primary oxidant [1]. Oxidation of the primary alcohol proceeds via a reactive C-6 aldehyde intermediate to the C-6 carboxy product. Both steps are probably catalysed by TEMPO [11]. In general, 10% sodium bromide (w/w) with respect to the substrate was added in previous works. From an industrial point of view, a process without sodium bromide would be more attractive, since its presence in the waste stream is highly undesired, due to environmental and corrosion concerns. Very recently, a procedure solely using hypochlorite as primary oxidant was described [14]. The low reaction rate associated with sodium bromide-free oxidation in conventional systems, was increased by the use of ultrasound. Independently, we have made a study of TEMPO oxidation in the absence of sodium bromide which we present here. In a bromide-free process, the nitrosonium ion is generated by direct oxidation by hypochlorite (Scheme 1(B)). In the previous studies, the TEMPO/sodium hypochlorite/sodium bromide oxidation was usually carried out at 0–5 °C. Our approach to accelerate the reaction was to perform the oxidation at increased, but still moderate temperatures (20–30 °C). In these experiments potato starch was used as the substrate. The implications on parameters like degree of oxidation, molecular weight and reaction rate were studied. For comparison, a few oxidations catalysed by sodium bromide were also performed at increased temperature. Furthermore, to elucidate reaction orders of the reactants and the rate-determining step in the absence of sodium bromide, a kinetic study was conducted, using methyl α-D-glucopyranoside as the substrate.



Scheme 1. (A) Simplified pathway of the TEMPO oxidation cycle with NaOCl/NaBr as primary oxidant (the conversion of the aldehyde intermediate to carboxylate proceeds via the same reaction sequence). (B) Oxidation of TEMPO by hypochlorite to the nitrosonium ion in the absence of NaBr (the substrate oxidation is the same as in (A).

2. Experimental

General methods.—The molecular mass distribution was determined with a Pharmacia HPLC ÄKTA EXPLORER 10, equipped with a UV–Vis detector (UV-900). Uronic polysaccharides were monitored at 215 nm. The SEC-column system was a TOSOHAAS TSKgel G 4000 PW, MW 1000–700,000 connected in series with a TSKgel G 6000 PW, MW 500,000–50,000,000. As eluent, 0.05 M NaCl was used. Flow rate was set at 0.5 mL/min. Under the given conditions V_0 is ca. 12 mL. NMR spectra were recorded on a Varian VXR-400 S spectrometer using D_2O as solvent. As internal standard, *t*-BuOH was used (CH_3 at 31.2 ppm). Quantitative ^{13}C NMR spectra were recorded with a 0.33° flip angle, an acquisition delay of 10 s, 50,000 datapoints and ^{1}H decoupling during acquisition only. The uronic acid content in the oxidised mate-

rials was determined with the Blumenkrantz assay [15], which method allows quantitative determination without interfering with neutral sugars. The latter assay is assumed to represent the carboxylic groups arising from TEMPO–C-6 oxidation. The total carboxylic acid content of the oxidised materials (C-6–TEMPO oxidation and non-selective oxidation) was determined by acid–base titration. After dissolution of the oxidised starch (0.2 g) in distilled water, NaOH was added (15 mL 0.05 M) and the soln was back-titrated to pH 7 with 0.1 M HCl to give the carboxyl content.

Materials and reagents.—Potato starch (water content 18%) was obtained from AVEBE (Groningen, The Netherlands). Sodium hypochlorite ca. 15% (w/w) was obtained from Akzo Nobel (Arnhem, The Netherlands). TEMPO was obtained from Sigma (St. Louis, MO, USA). All other chemicals were of commercial grade and were used without further purification.

Oxidation of potato starch.—If not otherwise stated, all experiments were carried out according to the following procedure: potato starch (12.2 g) was gelatinised in demi-water (450 mL) at ca. 95 °C under mechanical stirring. The soln was then slowly cooled to the oxidation temperature. In most experiments, the oxidation was performed at 20 ± 0.5 °C in a thermostatted water bath. TEMPO (4–8 mg TEMPO/g starch) was dissolved in the starch soln. NaOCl was added in portions of 2 mL throughout the oxidation in order to minimise unwanted side reactions, such as glycolic cleavage of the C-2–C-3 vicinal diol moiety. The pH was kept at 8.5 by addition of 0.5 M NaOH, controlled by a pH stat. After completion of the reaction, remaining carbonyl intermediates were reduced to hydroxyl groups by $NaBH_4$ (0.2 g). The oxidised materials were precipitated in 2 volumes of ethanol and then subsequently filtrated and rinsed with acetone. The materials were dried in a vacuum oven at 30 °C for 10–15 h. All materials were re-dissolved in water, ion-exchanged (Dowex 50WX8-100 cation exchanger, Sigma) and subsequently freeze dried in order to remove salts and to convert carboxylates to the protonated form.

Oxidation of methyl α-D-glucopyranoside (MGP).—All kinetic experiments were carried out using MGP as a model compound. After dissolution of MGP (1.94 g, 0.01 mol) in 250 mL of distilled water, NaOCl was added in 10% excess with respect to the amount needed for complete conversion of C-6 hydroxyl to carboxylic acids (11 mL of 15% NaOCl). The pH was adjusted to 8.5 and kept at this value throughout the oxidation by addition of 0.5 M NaOH, controlled by a pH stat. The reaction flask was kept under N_2 to avoid CO_2 contamination. The reaction was started by adding TEMPO (0.065 mmol from a 5 mg/mL soln). The oxidations were monitored by the consumption of NaOH as a function of time. This consumption was assumed to represent the formation of uronic acid. In some experiments aliquots were taken throughout the reaction and uronic acid formation was determined using the Blumenkrantz assay.

3. Results and discussion

TEMPO oxidation of potato starch — effect of temperature and pH.—In a comparative study, starch was oxidised by TEMPO/sodium hypochlorite with and without sodium bromide as the catalyst. The results are summarised in Table 1. As the starch samples only were partially oxidised (1 and 1.4 mol sodium hypochlorite/mol primary alcohol, respectively), some aldehydes will be present at the end of the oxidations. Consequently, the uronic acid content is expected not to exceed ca. 42 and 65 mol%, respectively. The results indicate that the oxidations have proceeded stoichiometrically in the absence of sodium bromide at all tested temperatures, except at 25–30 °C. At otherwise identical conditions, no variation of the uronic acid content was observed for different concentrations of TEMPO (4–8 mg TEMPO/g starch). The uronic content of the starch materials oxidised in the presence of the sodium bromide catalyst also suggested stoichiometric conversion, but the obtained values were somewhat higher.

In an attempt to further investigate the selectivity of the oxidations, the products were

Table 1
Test matrix for the TEMPO oxidation of potato starch at different temperatures with and without NaBr [a]

Experiment	TEMPO (g/g starch)	NaOCl (mol/mol) [b]	NaBr (% w/w)	Temperature (°C)	Time (min)	Uronic acid (mol%) [c]	$Carboxyl_{total}$ (mol%) [d]
1	4	1		2	115	48	44
2	8	1		2	110	46	48
3	4	1.4		2	330	72	62
4	8	1.4		2	275	70	68
5	4	1		10	120	49	46
6	8	1		10	100	45	42
7	4	1.4		10	250	65	62
8	8	1.4		10	180	63	60
9	4	1		20	65	42	45
10	8	1		20	45	43	45
11	4	1.4		20	185	61	66
12	8	1.4		20	120	60	65
13	4	1.4		25	140	60	70
14	4	1.4		30	115	62	70
15	4	1.4	10	2	170	72	74
16	4	1.4	10	10	108	73	75
17	4	1.4	10	20	64	78	70

[a] See Section 2 for further conditions.
[b] The amount of sodium hypochlorite added (mol NaOCl/mol primary alcohol), which is equivalent to an oxidation degree of 42 and 65 mol%, respectively.
[c] Determined by Blumenkrantz assay oxidation (taken as 6-CH_2OH oxidation).
[d] Determined by acid–base titration (total COOH content).

Table 2
^{13}C NMR data for oxidised starch samples (δ in ppm)

Temperature (°C)	NaBr (% w/w)	pH	C-1	(C-2–C-5) [a]	C-6	$C\text{-}6_{ox}$	$C\text{-}6_{ox}/(C\text{-}6_{ox}+C\text{-}6)$ area ratio of integrals (%)
2		8.5	98.5	73.2–74.5	61.7	177.6	75
20		8.5	99.8	73.5–75.5	62.0	177.6	68
2	10	8.5	99.2	73.0–74.6	62.0	177.6	70
20	10	8.5	99.8	72.0–74.5	62.0	177.6	67
20		10	100.5	172.0–176.2	59.2–62.0 [b]	176.0–180.0 [b]	46

[a] No attempts were made to assign the four ring carbon signals.
[b] Several small signals.

investigated by ^{13}C NMR (Table 2), since pyranoside saccharides can be oxidised by hypohalites at near neutral pH to give 2,3-dicarboxy-systems [16–19]. However, in all the oxidised samples partially C-6 oxidised starch was the only product that could be detected. The integrals of the $C\text{-}6_{ox}$ and C-6 peaks also indicated stoichiometric conversions of the reactions. Consequently, the specificity for C-6 oxidation is not seriously deteriorated at sodium bromide-free conditions when the temperature is kept at ≤ 20 °C.

The differences in uronic acid and total carboxylic acid content are to be attributed to the accuracy of the methods. The rate of sodium bromide-free oxidation at 15–20 °C was in the same range as for the corresponding sodium bromide catalysed oxidation at 2 °C (Table 1). The concentration of TEMPO and the pH also have a large influence on the

Table 3
Test matrix and results for the TEMPO/NaOCl oxidation of potato starch at different pH

pH	NaOCl (mol%) [a]	Temperature (°C)	Time (min)	Uronic acid (mol%) [b]
8.5	1.4	20	185	66
9	1.4	20	135	58
9.5	1.4	20	213	44
10	1.4	20	180	29

[a] Equivalent to an oxidation degree of ca. 65 mol%.
[b] Determined by the Blumenkrantz assay.

reaction rate (see Section 3.2), but an increase of temperature is probably the most simple approach to increase the reaction rate in a sodium bromide-free process. Some oxidations in the absence of sodium bromide were carried out at higher pH (up to 10) and gave materials with a lower degree of oxidation while the effect was more pronounced at higher pH (Table 3).

This trend is probably not due to non-selective oxidation or to disproportionation of hypochlorite, since the optimum rate of both reactions is ca. pH 7 [20,21]. Instead, the likely explanation is that the reaction yield of the TEMPO-mediated oxidation is lower at more alkaline pH. The pH dependence is discussed more detailed in the reaction kinetics section below. Furthermore, there appears to be a major depolymerisation at higher pH since the ^{13}C NMR C-1, C-6_{ox} and C-6 signals in the sample oxidised at pH 10 were splitted into several smaller peaks. As alkalinity and temperature were expected to affect the extent of polysaccharide degradation, all oxidised potato starch materials were analysed by size exclusion chromatography (SEC) to determine the molecular mass distribution. It was seen that starch, oxidised in the absence of sodium bromide at pH 8.5 at ≤ 20 °C, degrades only to a limited extent (Fig. 1). Materials which were oxidised in the presence of sodium bromide under the same conditions appear to be slightly more degraded. A broadening of the signal occurs at 20 °C (Fig. 2). At higher pH, there is a severe depolymerisation (Fig. 3). It is well known that C-6 oxidised glucopyranosides are susceptible to β-alkoxy elimination reactions under alkaline conditions [22].

TEMPO/(H)OCl oxidation of methyl α-D-glucopyranoside (MGP) — kinetics and mechanism.—In the absence of TEMPO, no consumption of NaOH could be detected at the given conditions (pH 8.5). Therefore, in the kinetic experiments presented below glycolic cleavage of C-2, C-3 diols or any other side reactions are not taken into consideration. Further, an experiment was conducted to investigate whether sodium bromide-free

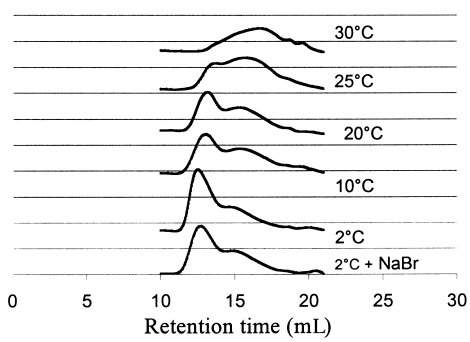


Fig. 1. Relative molecular mass distribution (SEC retention time vs. absorbance at 215 nm) for TEMPO/NaOCl oxidised starch at different temperatures at pH 8.5. For comparison, a spectrum of a reference sample oxidised at 2 °C with 10% NaBr (w/w) is given.

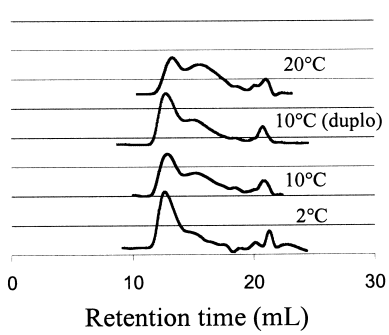


Fig. 2. Relative molecular mass distribution (SEC retention time vs. absorbance at 215 nm) for TEMPO/NaOCl oxidised starch catalysed by NaBr at different temperatures at pH 8.5. The amount of NaBr is 10% (w/w) with respect to the substrate.

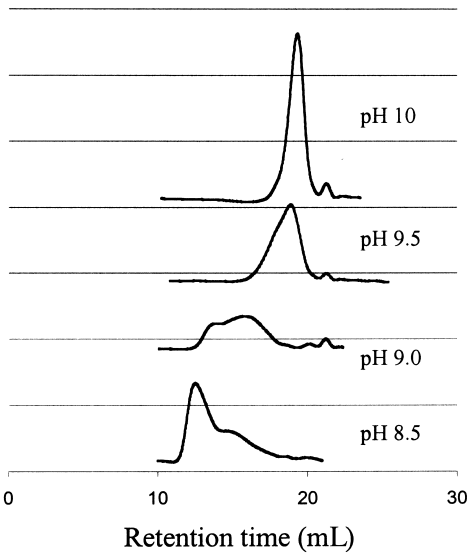


Fig. 3. Relative molecular mass distribution (SEC retention time vs. absorbance at 215 nm) for TEMPO/NaOCl oxidised starch at different pH at 20 °C.

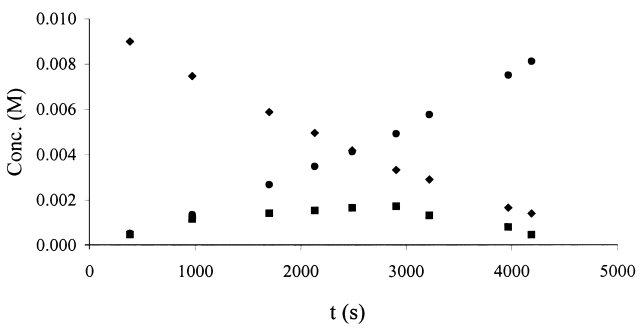


Fig. 4. Course of the TEMPO/NaOCl oxidation at 20 °C and pH 8.5. ◆, MGP; ■, aldehyde intermediate; ●, 1-*o*-methyl-α-D-glucuronic acid.

TEMPO oxidation proceeds as a consecutive two-step reaction via the C-6 carbonyl intermediate to the C-6 carboxy product. Aliquots were taken throughout the reaction and quenched in 95% ethanol. Uronic acid ($[acid_t]$) was determined with the Blumenkrantz assay. Consumed hypochlorite was determined with iodometric titration and subsequently correlated to concentrations of formed uronic acid and aldehyde with $[ald]_t = [NaOCl] - 2[acid]_t$. Non-reacted alcoholic substrate was calculated with $[MGP]_t = [MGP]_0 - [ald]_t - [acid]_t$. It followed from this experiment that the carbonyl intermediate reaches its maximum concentration at ca. 30–50% reaction, in agreement with the theory for first-order consecutive reactions (Fig. 4).

It was assumed that the TEMPO-mediated reaction is responsible for both consecutive oxidation steps [11]. Furthermore, when sodium bromide was present, De Nooy et al. [11] observed that oxidation of the aldehyde to the carboxylic acid is ca. seven times faster than the oxidation of the primary alcohol to the carbonyl intermediate. In order to simplify the kinetic expression, a steady state approximation was applied here and, after an initial brief period, the rate of formation and disappearance of reactive carbonyl intermediate is assumed to be balanced. It was also assumed that the reaction rate-determining step is the oxidation of methyl α-D-glucopyranoside with the nitrosonium ion (**II**). The following kinetic expression applies:

$$-\frac{d}{dt} = k[MGP]_t[\text{nitrosonium}]_t \quad (1)$$

TEMPO is cycled in the course of the reaction. Consequently, the concentration of **II** is assumed to be constant and the expression simplifies to

$$-\frac{d}{dt} = k_{obs}[MGP]_t \quad (2)$$

Integration gives

$$\ln\left\{\frac{[MGP]_0 - [\text{uronic acid}]_t}{[MGP]_0}\right\} = k_{obs}t \quad (3)$$

where

$$[MGP]_t = [MGP]_0 - [\text{uronic acid}]_t \quad (4)$$

Both the influence of pH and of the respective concentrations of TEMPO, sodium hypochlorite, and methyl α-D-glucopyranoside on the rate of methyl α-D-glucopyranoside oxidation was studied. The progress of the oxidation for an experiment performed under standard conditions (20 °C, pH 8.5) is shown in Fig. 5. The consumption of NaOH gave a good estimation of uronic acid formation throughout the reaction. Thus, this technique has been used in the experiments when otherwise not stated.

Apart from the initial phase of the reaction, possibly due to building up the steady-state concentration of nitrosonium ion, the oxidations appear to be first-order in substrate (Fig. 6). Accordingly, k_{obs} in Eq. (2) is independent

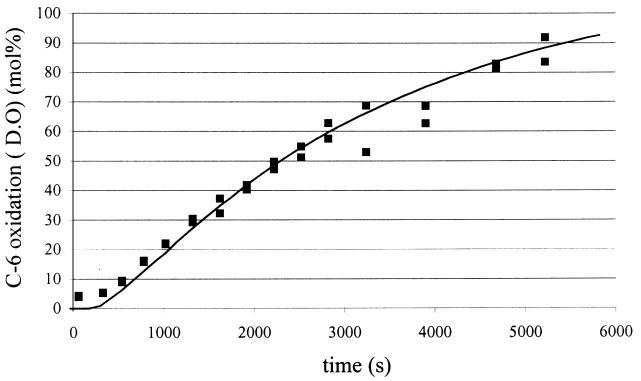


Fig. 5. Uronic acid formation vs. time in the TEMPO/NaOCl oxidation of MGP as monitored by the Blumenkrantz assay (■) and by the consumption of NaOH (—).

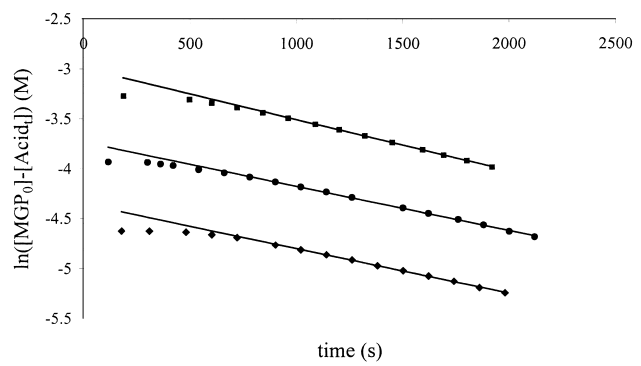


Fig. 6. $\ln([MGP_0] - [acid_t])$ vs. time for three initial concentrations of MGP: ■, 0.01 M; ●, 0.04 M; ◆, 0.064 M.

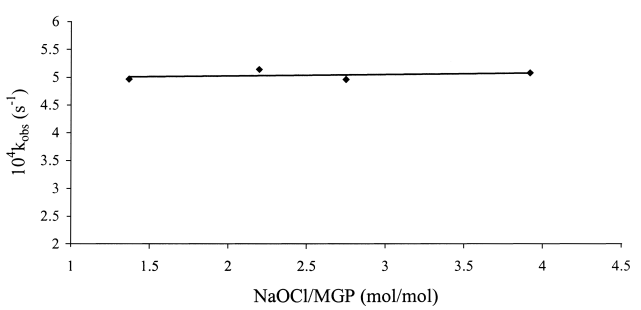


Fig. 7. Rate constants ($10^4 k_{obs}$ (s^{-1})) vs. NaOCl/MGP (molar ratio).

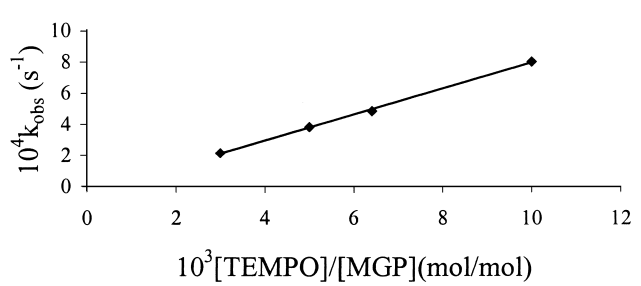
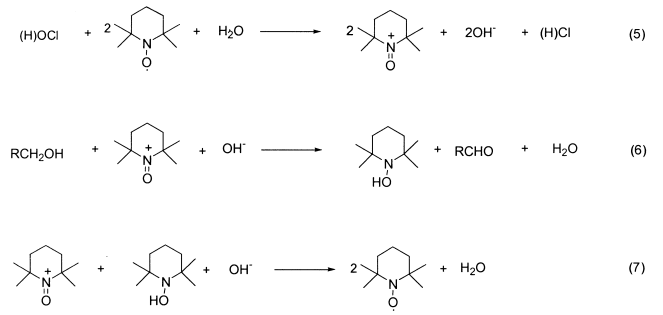


Fig. 8. Rate constants ($10^4 k_{obs}$) vs. 10^3[TEMPO]/[MGP].



Scheme 2.

of the initial concentration of methyl α-D-glucopyranoside within the tested concentration interval (10–64 mM). The oxidation rate appears also to be independent of the amount of sodium hypochlorite (the molar ratio of sodium hypochlorite/methyl α-D-glucopyranoside varied between 1.4 and 3.9) (Fig. 7). There is a linear dependence between the overall rate constant (k_{obs}) and the amount of TEMPO (the molar ratio of TEMPO/methyl α-D-glucopyranoside varied between 0.003 and 0.012), in accordance with Eq. (1) (Fig. 8).

Under the conditions described, the rate-determining step of the TEMPO/sodium hypochlorite oxidation is the oxidation of the alcohol to the carbonyl intermediate by the nitrosonium ion. Thus steps (5) and (7) are distinctly faster than step (6) (Scheme 2). The same behaviour was observed by De Nooy et al. in the presence of sodium bromide [11]. At forehand, we presumed that oxidation of TEMPO to the nitrosonium ion using sodium hypochlorite would be much slower in the absence of NaOBr, becoming the rate-determining step and responsible for the lower rate in a bromide-free experiment. However, also in the absence of sodium bromide the results clearly show that step (6) is rate determining. The catalytic effect of sodium bromide in a TEMPO/(H)OCl mediated oxidation remains to be explained.

Effects of pH on the reaction rate.—The pH has a large impact on the rate of oxidation both in the presence and absence of sodium bromide. An increase of pH starting from mildly alkaline conditions is accompanied by a distinct increase of the reaction rate. However, under more severe alkaline conditions, the rate is lowered again. The pH optimum is somewhat lower in the absence of sodium

bromide (ca. 9.3 compared to ca. 10.5 for a sodium bromide-catalysed oxidation) (Fig. 9). This is advantageous in connection with the occurrence of β-alkoxy elimination reactions. De Nooy et al. [10] observed that the reaction was retarded at higher alkaline pH, but no actual pH optimum was found. The retardation at higher pH was ascribed to the low concentration of hypochlorous acid due to virtually complete dissociation to hypochlorite at pH 11 and it was suspected that step (5) would be retarded and would become rate limiting under these conditions.

However, in addition to the retardation of step (5), we also believe that side-reactions of the nitrosonium ion account for the rate decrease. Endo et al. [23] reported that nitrosonium ion reacts with hydroxyl ions under alkaline conditions (pH > 9) and reverts to the TEMPO radical, while forming hydrogen peroxide (Scheme 3).

The latter reaction could explain the considerable deviations from the first-order kinetics occurring at alkaline conditions. In the absence of sodium bromide this effect becomes significant above ca. pH 9.5, and in the presence of sodium bromide above pH 10. Deviations from the first-order kinetics occur also at pH ≤ 7, probably due to the slower regeneration of TEMPO (step (7)) at neutral or lower pH. Another explanation is that side reactions, such as the glycolic cleavage of C-2–C-3 diols might contribute to the overall hydroxide consumption at this pH, and thus cause deviations.

Semmelhack et al. [24] proposed that reaction between an alcoholic substrate and nitrosonium ion takes place through a nucleophilic addition following a cyclic elimination (Scheme 4). De Nooy et al. [11] postulated that this pathway is likely under alkaline conditions. The hydroxyl ion could facilitate the rate-determining step by adopting a proton from the CH_2OH group, thus explaining the pH dependence of the oxidation under weakly alkaline conditions.

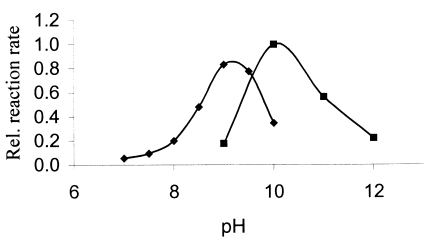
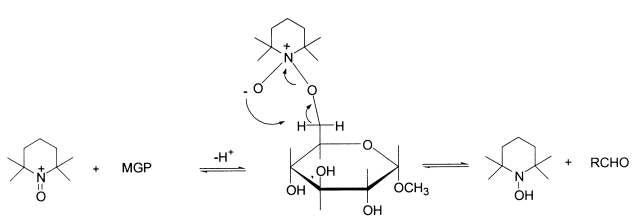


Fig. 9. Relative oxidation rate vs. pH at 20 °C for TEMPO/(H)OCl (◆) and TEMPO/(H)OCl/NaBr (■). The oxidations catalysed by NaBr (10% (w/w)) were carried out at 2 °C, in order to avoid competitive hypohalite oxidations.

Scheme 3. Reaction of nitrosonium ion with hydroxyl groups at high pH.



Scheme 4. The reactive intermediate formed in the oxidation of the CH_2OH group of MGP to the C-6 aldehyde.

4. Conclusions

In the present study, starch and methyl α-D-glucopyranoside have been selectively oxidised by the bromide-free TEMPO/(H)OCl system at somewhat higher temperatures (5–30 °C), in order to increase the reaction rate. In the oxidation of starch, the temperature had to be increased to 20 °C to obtain similar reaction rate as a bromide-catalysed system at 2 °C. An increased reaction rate was also obtained at higher concentrations of TEMPO. The oxidation of potato starch was found to proceed stoichiometrically to C-6 carboxy starch, except at more alkaline conditions (pH ≥ 9.0), presumably due to side reactions of the nitrosonium ion. The specificity for C-6 oxidation was not lost at bromide-free conditions when the temperature was kept at ≤ 20 °C and pH < 9.0. Analogously, at temperatures ≤ 20 °C and pH < 9.0, the depolymerisation of the polysaccharide backbone was only minor, but at higher temperatures and more alkaline conditions severe depolymerisation occurred. Fortunately, pH 8.5 is near the optimal pH to activate the system. Thus, good product properties and reaction rates can be obtained after a

careful choice of experimental conditions. Some kinetic experiments on TEMPO oxidation of methyl α-D-glucopyranoside revealed that the reaction is first-order in methyl α-D-glucopyranoside and first-order in TEMPO. It was concluded that the rate-determining step is the oxidation of the substrate with the nitrosonium ion. The obtained first-order kinetics apply only to weakly alkaline conditions (pH 8.5–9.0). At lower, near neutral pH, large deviations occur as the regeneration step of TEMPO radical becomes rate limiting. Under more alkaline conditions, the nitrosonium ion reverts to the TEMPO radical causing large deviations.

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