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Selective Oxidation of Primary Alcohols Mediated by Nitroxyl Radical in Aqueous Solution. Kinetics and Mechanism.

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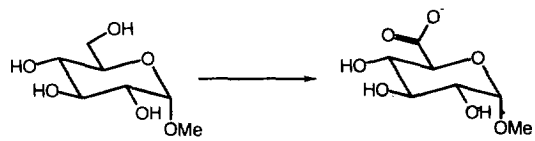
Abstract: The kinetics of the TEMPO-mediated oxidation of methyl α-D-glucopyranoside to sodium methyl α-D-glucopyranosiduronate were studied. An intermediate was found which was identified as the hydrated aldehyde. This was oxidised in the same manner as the alcohol, with pseudo first order rate constants ratio $k_{obs,ald}/k_{obs,alc} \approx 7$. The reaction mechanism is discussed with emphasis on steric factors and compared to literature data. Two different reaction pathways are postulated; under basic reaction conditions via a cyclic transition state **3** and under acid reaction conditions through an acyclic transition state **4**.

INTRODUCTION

It has been well established now that stable organic nitroxyl radicals like 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) can be applied as mediators for the oxidation of primary and secondary alcohols.[1-10] Several oxidants are able to oxidise the nitroxyl radical[11] to obtain the corresponding nitrosonium ion, which is the actual oxidant.[1] Conditions are generally very mild, which makes this method applicable to a variety of alcoholic substrates. However, there seems to be some inconsistency with respect to the product obtained from primary alcohol oxidation. Depending on the reaction conditions and the substrate, aldehyde[1-8] or carboxylate[2,6,9,10] is obtained. Also the selectivity with respect to primary and secondary alcohols differs substantially depending on the applied reaction conditions and the substrate. Some authors found a pronounced preference for primary alcohol oxidation,[4,6,7,9,10] while others found only little selectivity.[1-3,5,8] In this paper we address these ambiguities.

Previously, we investigated the TEMPO-mediated oxidation of various carbohydrates in water at pH 10-11 with hypobromite, formed by reaction of hypochlorite and bromide, as the regenerating oxidant.[10,12]

Under the applied conditions primary alcohols were oxidised more rapidly than secondary ones and only the carboxylate was found as the reaction product. Thus starch was selectively oxidised at the 6-position to obtain a polyglucuronate with >95% selectivity at complete conversion of the primary alcohol groups.[10] Here we report on the kinetics and mechanism of the oxidation of methyl α-D-glucopyranoside (MGP, **1**). Oxidation of this substrate proceeds with high regio-selectivity and no other product than methyl α-D-glucopyranosiduronate (**2**) could be detected.[12] Attention was focused on the mechanism of carboxylate formation. Furthermore, the reaction rate for various alcoholic substrates was investigated and the influence of steric factors on the transition state is discussed and compared to literature data.



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RESULTS AND DISCUSSION

We reported earlier that the oxidation of MGP with TEMPO/hypochlorite/bromide was first order with respect to MGP, TEMPO and NaBr.[12] Typical conversion-time curves for the oxidation of different concentrations MGP are shown in Fig. 1. After about 30% oxidation the formation of acid was first order with respect to the substrate (Fig. 2). This delay depended on several factors. Firstly, an induction period can be expected due to formation of an aldehyde intermediate (see below). Secondly, there has to be a build up of nitrosonium ion. Thirdly, it was found that hypochlorite delays the formation of acid as monitored with

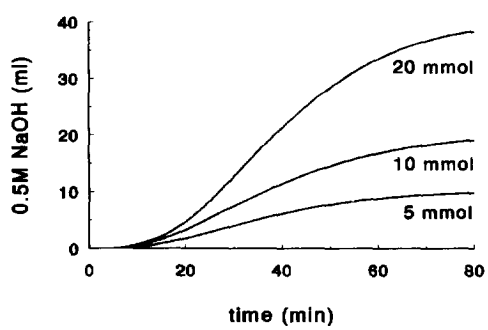


Figure 1. Typical plots for the oxidation of different concentrations MGP as measured with pH-stat. Conditions: substrate (5-20 mmol) in 520 ml water, 0.4 g NaBr, 0.02 g TEMPO, 30 ml 15% HOCl, pH 10, 1.5°C.

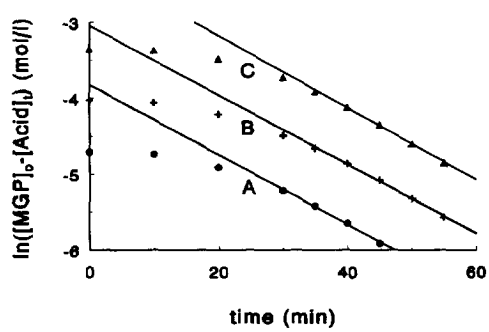


Figure 2. Plots of $\ln([MGP]_0-[Acid]_t)$ vs time. MGP_0=5(A), 10(B) and 20(C) mmol. Data from Fig. 1.

a pH-stat, probably due to influence of the equilibria HOCl/OCl$^-$ and HOBr/OBr$^-$. From experiments with MGP under standard conditions (see experimental section) with 15, 30, 60 or 120 mmol hypochlorite, it appeared that the [OCl$^-$] had no influence on the observed reaction rate. The fact that the concentration of primary oxidant had no influence on the reaction rate implies that the regeneration of the nitrosonium ion, which is thought to proceed according to reactions 1,2 and 4,[13] is more rapid than the oxidation of the substrate (reaction 3).

$$(H)OCl + Br^- \rightarrow (H)OBr + Cl^- \quad (1)$$

$$(H)OBr + 2TEMPO^{\cdot} + H_2O \rightarrow 2TEMPO^+ + 2OH^- + (H)Br \quad (2)$$

$$TEMPO^+ + OH^- + RCH_2OH \rightarrow TEMPOH + RCHO + H_2O \quad (3)$$

$$TEMPO^+ + OH^- + TEMPOH \rightarrow 2TEMPO^{\cdot} + H_2O \quad (4)$$

Hence the amount of oxidant (nitrosonium ion) can be considered as being constant during the reaction after circa 30% oxidation. Since the formation of acid was first order with respect to the substrate (Fig. 2), any intermediate reacts either much more slowly or much more rapidly than the primary alcohol. This was followed with high-performance anion-exchange chromatography (HPAEC, Fig. 3). The intermediate was

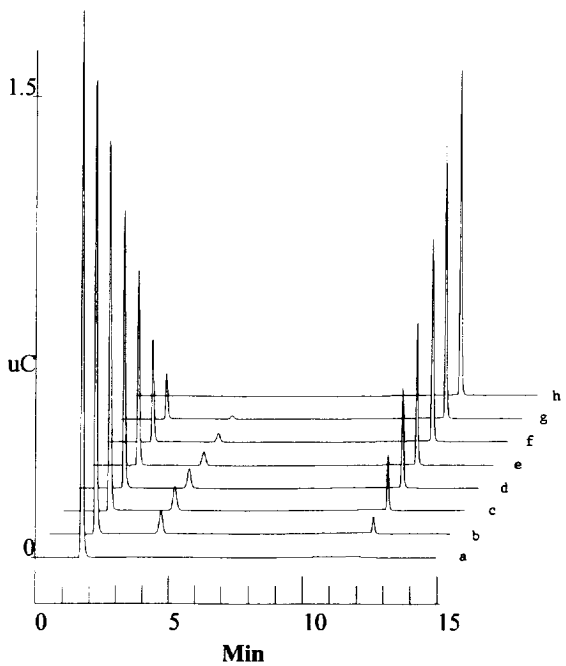


Figure 3. HPAEC plots of reaction products during the oxidation of MGP (10 mmol). A-h pertains to the amount of hypochlorite added; 0-14 ml 15% hypochlorite in steps of 2 ml. MGP (**1**): retention time is 1.7 min, hydrated aldehyde: retention time is 4.2 min and methyl α-D-glucopyranosiduronate (**2**): retention time is 12.1 min.

identified as the hydrated methyl α-D-*gluco*-hexodialdo-1,5-pyranoside by ^{1}H NMR (doublet H6 at 5.3 ppm in D_2O). No free aldehyde could be detected with ^{1}H NMR. This is in agreement with methyl ß-D-*galacto*-hexodialdo-1,5-pyranoside in aqueous solution, obtained from oxidation of methyl ß-D-galactopyranoside with D-galactose oxidase, which is also completely hydrated.[14] The intermediate could be reduced with sodium borohydride to obtain the starting compound, which is further evidence for the fact that it is an aldehyde. Another way of determining the amount of aldehyde formed was by adding known amounts of hypochlorite and following the amount of acid formed with pH-stat (Fig. 4). These results agree well with the results obtained from HPAEC.

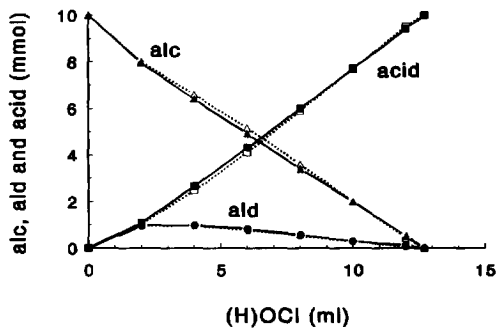


Figure 4. Amount of alcohol, aldehyde and acid present during the oxidation as followed by pH-stat (-) and HPAEC (···).

Attempts to stop the oxidation at the aldehyde stage at another pH did not succeed. In the range pH 8.5-11.5, the maximum concentration aldehyde was about 10%. Apparently, its oxidation is substantially more rapid than the oxidation of the alcohol, which gives the following consecutive first order reaction scheme:

$$[Alc] \xrightarrow{k_1} [Ald] + H_2O \rightleftharpoons [AldH_2O] \xrightarrow{k_2} [Acid], \quad \text{with } k_2 > k_1 \tag{5}$$

Here k_1 and k_2 are both first order rate constants with respect to the substrate and it is assumed that the hydration of the aldehyde is very rapid, so that this reaction has no influence on the observed reaction rate. For a consecutive first order reaction system with $k_2>k_1$, the following rate equations may be written:

$$[Alc]_t = [Alc]_o \exp(-k_1 t) \tag{6}$$

$$[Ald]_t = [Alc]_o \{k_1/(k_2-k_1)\}\{\exp(-k_1 t)-\exp(-k_2 t)\} \tag{7}$$

and as an approximation:

$$[Acid]_t \approx [Alc]_o \{1-\exp(-k_1 t)\} \tag{8}$$

From the results of HPAEC and the pH-stat experiments it follows that the ratio $k_2/k_1 \approx 7$ for the oxidation

of MGP. By applying the simplified equation 8 for the calculation of k_1 from the pH-stat experiments an error in the order of several percents is introduced which has no influence on the qualitative interpretation of the results.

Initially, it was expected that the aldehyde intermediate was oxidised by hypobromite to obtain the acid. However, from the oxidation of butanal with and without TEMPO, it appeared that the oxidation with TEMPO added was much more rapid (Table 1, entries 1 and 2). In organic solvents without water or with only a low concentration of water the reaction stops at the aldehyde stage, which indicates that water is necessary for the TEMPO-mediated oxidation of the aldehyde. It is thus concluded that the hydrated aldehyde intermediate is oxidised in the same way as the alcohol. This is supported by the fact that the ratio k_2/k_1 for the oxidation of MGP was not pH dependent in the range pH 8.5-11.5. At pH 8.5 and 11.5, the observed reaction rate was much lower than at pH 10. At pH 8.5 the rate limiting step might be the abstraction of a proton in the complex formed between the alcohol and $TEMPO^+$ (see below). We found that at pH 11.5, [(H)OCl] becomes rate limiting. Probably reaction 1 is then retarded, as was also found by other authors.[15] At this pH, the delay period is also substantially lengthened. From Table 1 it can be seen that $k_{obs,butanal}/k_{obs,n\text{-}butanol}$ is smaller than 7 (entries 1 and 3). This is attributed to the fact that butanal is only hydrated for about 32% in water.[16] The error in the calculation of $k_{obs,n\text{-}butanol}$ according to equation 8 will also be substantial in this case.

From an Eyring plot (Fig. 5) in the range of 1.5-23°C for MGP the activation parameters were calculated. Although the entropy of activation (-93 $JK^{-1}mol^{-1}$, 1.5°C) term is highly negative, the reaction is rapid due to a relatively low enthalpy of activation (58 $kJmol^{-1}$). The negative entropy of activation indicates an organised bimolecular transition state.

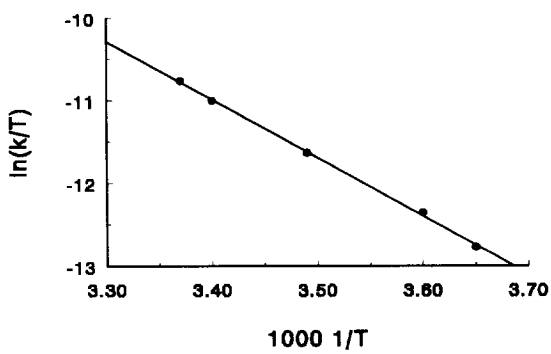
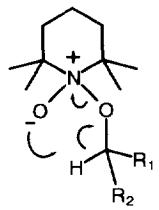


Figure 5. Eyring plot for the oxidation of MGP in the range 1.5-23°C.

The mechanism of the actual oxidation (reaction 3) is still not clear. Semmelhack *et al.*[17] proposed a concerted mechanism with a cyclic transition state **3**, which would be much more sterically confining than the acyclic transition state **4**, proposed by Ma and Bobbit.[8] These authors found only few steric effects in



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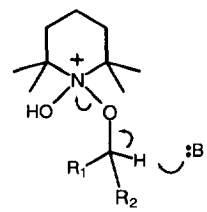

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the TEMPO-mediated oxidation of alcohols. It can be expected however, that the observed regio-selectivity for MGP is due to sterical hindrance caused by the four methyl groups in TEMPO. To investigate the influence of steric factors, several substrates were oxidised (Table 1). We were especially interested in the influence of the ring size because it was found that primary alcohols in pyranosides were oxidised more selectively than those in furanosides.[10] To test this, the model substrates cyclohexanol and cyclopentanol were oxidised (Table 1). Indeed it was found that the secondary alcohol on the five-membered ring was oxidised four times as fast as the secondary alcohol on the six-membered ring. During the oxidation of cyclohexanol and cyclopentanol, a small amount of acid was formed (0.25-0.75 mmol per 20 mmol substrate

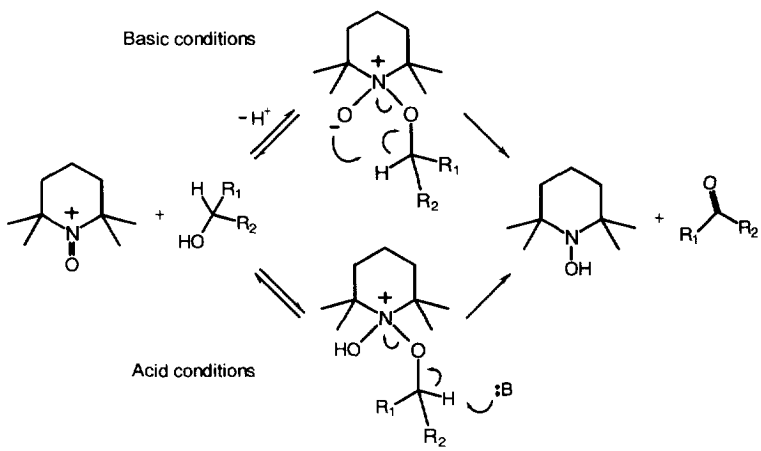
Table 1. Rate constants for the oxidation of various substrates.*

Entry	Substrate	TEMPO (g)	$10^4 xk_{obs}$ (s^{-1})
1	butanal[a]	0.02	18
2	butanal[a]	-	1.1
3	n-butanol[a]	0.02	12
4	n-butanol[a,b]	-	<0.01
5	cyclohexanol[b]	0.02	0.52
6	cyclohexanol[b]	-	0.05
7	cyclopentanol[b]	0.02	2.1
8	cyclopentanol[b]	-	0.05
9	3-methylcyclohexanol[b] (cis/trans mixture)	0.02	0.52
10	2-methylcyclohexanol[b] (cis/trans mixture)	0.02	0.08
11	methyl α-D-glucopyranoside[a]	0.02	7.8
12	methyl ß-D-glucopyranoside[a]	0.02	12
13	octyl α-D-glucopyranoside[a]	0.02	7.8
14	methyl α-D-galactopyranoside[a]	0.02	7.7

* Conditions: 20 mmol substrate in 520 ml water, 0.4 g NaBr, 30 ml 15% OCl^-, pH 10, 1.5 °C. [a] Reaction followed by monitoring the consumption of NaOH. [b] Reaction followed by the consumption of hypochlorite.

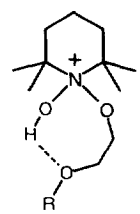
conversion) which indicates overoxidation of the substrate. 3-Methylcyclohexanol (cis/trans mixture) was oxidised with the same reaction rate as cyclohexanol, whereas the more hindered alcohol in 2-methylcyclohexanol (cis/trans mixture) was oxidised more slowly. Note that the secondary alcohols tested were oxidised faster with TEMPO added to the reaction mixture than with only hypobromite. However, this difference becomes smaller with more sterically hindered secondary alcohols like 2-methylcyclohexanol. Simple primary alcohols like n-butanol were oxidised rapidly and quantitatively to the corresponding carboxylates. Without TEMPO added to the reaction mixture, no reaction was observed for eight hours. In the oxidation of various pyranosides (entries 11-14) it appeared that the substituent on the anomeric centre did not have much influence on the reaction rate. However, the anomeric configuration, in contrast to the configuration at C-4, had a substantial influence on the reaction rate. The reasons remain to be clarified.

Obviously, under the applied conditions, primary alcohols are oxidised more rapidly than secondary ones. With primary/secondary polyol substrates, the selectivity for the primary hydroxyl depends on the sterical demand of the secondary alcohol. For example, in contrast to several pyranosides, the acyclic substrates 1,3-butanediol and mannitol could not be oxidised selectively. The reaction was followed with HPLC, and even in the initial stage of the reaction, more than one product peak was found. In general, the observed regio-selectivity for different substrates under the applied conditions depends on the accessibility of the alcohol, which would favour the more sterically confining transition state **3**. A study of the literature on nitroxyl-mediated oxidation of alcohols reveals that this sterically directed selectivity only occurs under basic reaction conditions,[4,6,7,9,10] while under acid reaction conditions[1-3,5,8] this selectivity disappears and secondary alcohols may be oxidised more rapidly. This leads us to propose two different reaction pathways. The one under basic conditions based on the cyclic transition state **3** and the one under acid conditions based on the acyclic transition state **4**:



Scheme 1

In addition to the difference in selectivity obtained, a second indication for two different reaction pathways stems from the work by Yamaguchi *et al.*[18] They found that a ß-oxygen in the alcohol inhibits the oxidation. A probable explanation of this was given by Ma and Bobbitt,[8] who reasoned that a complex formed between the positive nitrogen and the ß-oxygen might be responsible for this decreased reactivity. They found, for example, that ethylene glycol was completely unreactive under their conditions. Under our conditions this substrate was rapidly oxidised. Since both Yamaguchi *et al.* and Ma and Bobbitt worked under acid conditions,[19] such a complex is conceivable, while in **3** such a complexation is less probable due to the negative oxygen. Another perhaps more probable ß-oxygen interaction is shown in formula **5**. The hydrogen bond is expected to lower the positive charge on the nitrogen, which would be the driving force in this reaction pathway. Thus the reaction leading towards the products would be less favourable. Besides the observed difference in selectivity, another general difference is that the oxidation under basic conditions is more rapid than under acid conditions. The latter is usually performed with stoichiometric amounts of radical, while the former oxidation is mainly performed with catalytic amounts (for the influence of the TEMPO concentration on the reaction rate, see ref. 12). Obviously, base will facilitate the proton abstraction step present in both mechanisms, which also is thought to be the rate-limiting step in both pathways.



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EXPERIMENTAL SECTION

All chemicals used were commercially available and used without further purification, except for octyl α-D-glucopyranoside, which was synthesised according to a previously reported method.[20] ^{1}H, ^{13}C NMR and HPAEC were performed as described previously.[12] The structures of all oxidised pyranosides were confirmed with ^{1}H and ^{13}C NMR and reported elsewhere,[12] except for sodium methyl α-D-galactopyranosiduronate: ^{1}H NMR (D_2O) δ 4.82 (H1, d, $J_{1,2}$=3.0 Hz); ^{13}C NMR (D_2O) δ 56.8, 69.4, 71.2, 72.3, 72.9, 100.9, 177.3 and sodium octyl α-D-glucopyranosiduronate: ^{1}H NMR (D_2O) δ 4.87 (H1, d, $J_{1,2}$=3.9 Hz); ^{13}C NMR (D_2O) δ 15.0, 23.6, 26.9, 29.9, 30.0, 30.2, 32.6, 70.1, 72.7, 73.5, 73.6, 74.5, 99.6, 178.2.

General procedures: All kinetic data were average values of at least three experiments. Oxidation of secondary alcohols was followed by measuring the amount of hypochlorite consumed. Aliquots were taken and added to an acidified 1M KI solution, which was subsequently titrated against 0.1 M sodium

thiosulphate. Oxidation of primary alcohols was followed with pH-stat. Formation of uronic acid during the oxidation of the carbohydrates was followed with a colorimetric method[21] and HPAEC.

General oxidation procedure: The substrate (20 mmol) was dissolved in water (520 ml) and NaBr (0.4 g, 3.9 mmol) and TEMPO (0.02 g, 0.13 mmol) were added. The solution was cooled in an ice-bath and a solution of hypochlorite (30 ml, *ca* 60 mmol) was brought to pH 10 and also cooled. The reaction was started at time=0 by adding the hypochlorite solution at once to the other solution. The temperature was 1.5±1°C during the reaction and the pH was maintained at 10 by adding 0.5M NaOH with a pH-stat. When the reaction was finished, excess hypochlorite was quenched by adding ethanol (5 ml) and the pH was brought to 7-8 by adding 4M HCl.

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19. It should be noted that Yamaguchi *et al.*[18] added Na_2CO_3 as acid scavenger. However, since this salt is not soluble in CH_2Cl_2, it is not expected to have influence on the reactions as shown in Scheme 1. Probably only when acid is liberated, it will react with the heterogeneous acid scavenger.
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