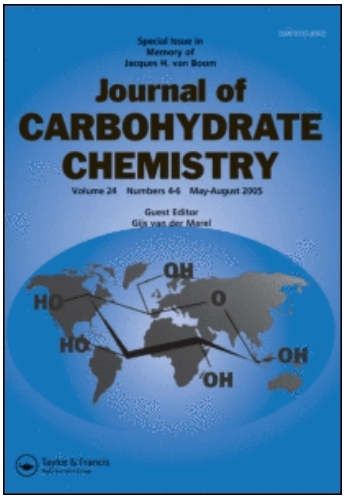

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OXIDATION OF METHYL 4,6-*O*-ISOPROPYLIDENE-α-D-GLUCOPYRANOSIDE AS A MODEL COMPOUND FOR STARCH

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ABSTRACT

The oxidation of methyl 4,6-*O*-isopropylidene-α-D-glucopyranoside (**1**) via various routes to the dicarboxylate **2** is described. This reaction is used as a model for the oxidation of starch to dicarboxylic starch, a material with very promising properties as a cobuilder in detergents. The best oxidant found for C_2-C_3 cleavage was RuO_4, prepared *in situ* by oxidation of a catalytic amount of Ru^{III} with NaOCl.

INTRODUCTION

Dicarboxylic starch has recently been reported to show very good performance as a cobuilder in detergent formulations.[1] One of the desired properties of detergent ingredients[2] is biodegradability, which is a characteristic feature of oxidised amylose. However, an economically viable process to produce dicarboxylic starch in bulk quantities is not yet available. Environmental and economic considerations exclude the use of metal oxidants in stoichiometric amounts, as well as oxidants like periodate.

In the course of a research programme directed towards conversion of starch into dicarboxylic starch, a model compound was necessary to simplify analytical problems. Because the amylose component of starch is a polymeric 1,4-linked glucopyranose, a glucopyranoside was needed that had protective groups on positions 1 and 4. The protection of

the primary hydroxyl function on C-6 of the model compound was also desired to allow us to compare the activity for glycol cleavage of various reaction systems. Starting from methyl α-D-glucopyranoside, protection of the 4- and 6-*O*-position could readily be accomplished in one step with an isopropylidene function. Therefore the model compound of choice was methyl 4,6-*O*-isopropylidene-α-D-glucopyranoside (**1**). Although **1** has a tendency to undergo hydrolysis, the same is true for starch.

By introducing an isopropylidene bridge between C_4-C_6, it was possible that the geometry of the pyranoside ring had been slightly altered. This would affect the distance between the hydroxyl functions of the vicinal diol. NMR spectral data from Debost *et al.*[3] show that the isopropylidene bridge has no significant influence on the conformation of the glucoside. To check this conclusion by an entirely different technique, a computer calculation using MM3 was performed on **1** and two other pyranosides, methyl α-D-glucopyranoside and 1,4,6-*O*-trimethyl α-D-glucopyranoside. No change of the OH-OH distance (2.84 Å) was found, nor was any difference between the torsion angles in the pyranoside ring of **1**, indicating that **1** could be used as model for the diol system in starch.

The aim of our investigations was to find an oxidation system for glycol cleavage in carbohydrates which was economically viable and environmentally friendly. This restricted our investigations to the use of catalytic amounts of redox metals in combination with inexpensive oxidants such as hydrogen peroxide, sodium hypochlorite and molecular oxygen. We now wish to report the C_2-C_3 cleavage of compound **1** to the disodium (5*R*)-[(*S*)-carboxylato (methoxy) methoxy]-2,2-dimethyl-[1,3-dioxane]-(4*R*)-carboxylate (**2**).

RESULTS AND DISCUSSION

The preparation of methyl 4,6-*O*-isopropylidene-α-D-glucopyranoside (**1**) has been reported by Jones *et al.*[4] and by Dasgupta *et al.*[5] in moderate yield (28 and 30%) from methyl α-D-glucopyranoside and acetone, using zinc or ferric chloride, respectively, as the Lewis acid catalysts. Preparation of the protected glucopyranoside according to the reaction shown in Figure 1 has been reported by Wolfrom *et al.*[6] to give **1** in 73% yield.

Debost *et al.*[3] used an optimised procedure which gave **1** in an improved yield of 90%. Copeland *et al.*[7] modified the method of Wolfrom to give high yields of the 4,6-*O*-protected manno-, gulo- and galactopyranosides.

We have used the oxidation of **1** to the corresponding dicarboxylate **2** (Fig. 2) as a model reaction for C_2-C_3 cleavage in glucopyranoside structures. The usual reagent for glycol cleavage is periodate,[8] forming the dialdehyde which can be further oxidised to the diacid with chlorite/H_2O_2.[9] To our surprise the substrate reacted only slowly with periodate

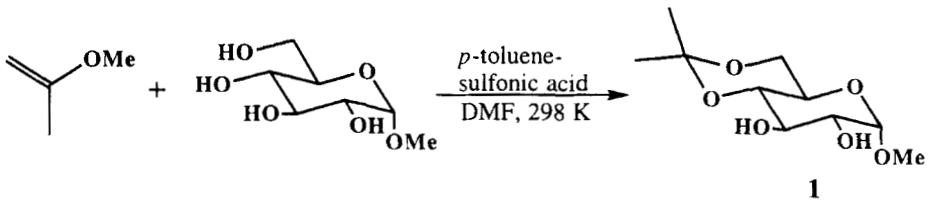

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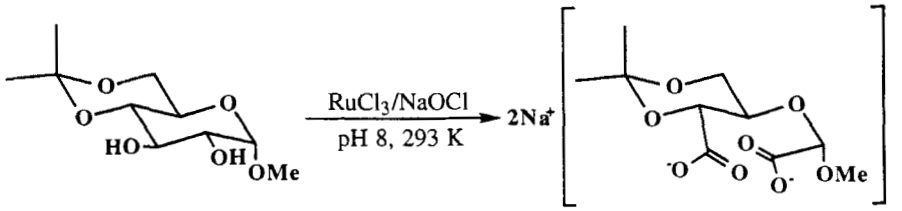
Fig. 1 Synthesis of methyl 4,6-*O*-isopropylidene-α-D-glucopyranoside



1 2

Fig. 2 Glycol cleavage

under typical reaction conditions[4] and total conversion could not be accomplished. However, we prepared the dicarboxylate **2**, using the method developed by Emons *et al.*[10] Cleavage occurred, using ruthenium as catalyst and sodium hypochlorite as oxidant to oxidise Ru^{III} to Ru^{VIII}, RuO_4 being a well known reagent for glycol cleavage.[11,12,13] After isolation of the dicarboxylate **2**, an HPLC method was developed and several reactions with various catalysts and oxidants[14] were monitored.

A number of catalytic and non-catalytic oxidation procedures were tested for glycol cleavage of **1** (Table 1). Using only sodium hypochlorite as the oxidising agent, the reaction was very slow. Besides **2**, a number of unidentified products were present. The selectivity toward cleavage as well as the reaction rate were increased by catalytic amounts of ruthenium.[10] Slow addition of the oxidant NaOCl at constant pH also had a beneficial effect. When ruthenium on carbon was used as a heterogeneous catalyst, hypochlorite dissolved the ruthenium[15] by oxidising it to Ru^{VIII}, hence the reaction became homogeneous and gave the same results as obtained with $RuCl_3$. Afterwards the metal could be precipitated on the carbon by quenching with methanol.

Another method for selective glycol cleavage was recently published by Besemer.[16] Potassium bromide was used as catalyst in combination with NaOCl as oxidant. The results

TABLE 1. Results of Oxidation Experiments (293K)

Oxidant	Catalyst	pH	time (h)	% yield 2[a]	% Conv.[a]
NaOCl	--	10	11	4	5
NaOCl	KBr	10	7	62	65
NaOCl	$RuCl_3$	8	7.5	67	68
NaOCl	Ru/C [b]	8	0.6	80	92
H_2O_2	--[c]	7	79	3	15
H_2O_2	Ru, Ru/C [d]	7	48	2	5
H_2O_2	TS-1 Eurocat	6	72	0	10
H_2O_2	Ti Mordenite	7	66	2	18
$NaIO_4$	--	6-7	21	0 [e]	57
O_2	Ru-pyrochl. ox	11	6	0	3

a. Values (%) obtained from HPLC chromatograms.
b. Ruthenium dissolves when using NaOCl
c. Degradation probably by OH radicals[21] at pH higher than 7
d. Decomposition of H_2O_2
e. Dialdehyde is formed

of this method on the oxidation of **1** were very promising: the dicarboxylate was formed with very good selectivity.

The use of hydrogen peroxide as oxidant would render the advantage that the product is obtained free of salt. Reaction with hydrogen peroxide without catalyst resulted in degradation of **1** without significant cleavage of the C_2-C_3 bond. Catalysis of the desired reaction with ruthenium was not effective and glycol cleavage did not take place, even when H_2O_2 was slowly added to the aqueous solution of substrate and catalyst. We tentatively conclude that H_2O_2 is not able to oxidise Ru^{III} to Ru^{VIII}. We also noticed that H_2O_2 decomposed rapidly upon contact with ruthenium.

Titanium is known to be an effective catalyst for the cleavage of diols with H_2O_2.[17] Titanium-substituted molecular sieves[18] were not effective in the oxidation of **1** with H_2O_2, probably because the pores in the zeolites were too small to allow **1** to enter. Attempts with titanium on amorphous silicalite were also not successful, but once large pore zeolites become available,[19] oxidation with Ti-zeolites and hydrogen peroxide may give better results.

Oxidation with molecular oxygen was tried in combination with ruthenium pyrochlore oxide as a heterogeneous metal catalyst. Although this catalyst has been reported[20] to cleave 1,2-cyclohexanediol, no product of glycol cleavage of **1** could be detected.

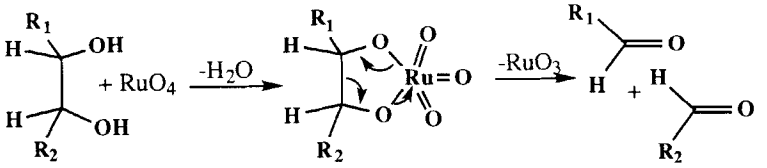


Fig. 3 Presumed mechanism of Ru-catalyzed diol cleavage

In short, the best results were obtained with $RuCl_3$/NaOCl. Glycol cleavage with this reagent is assumed[13,22] to proceed via the mechanism shown in figure 3.

Presumably the dialdehyde which is formed as the primary product is immediately further oxidised to the dicarboxylate. No dialdehyde or hydroxy-keto intermediates were found in the analysis of the reaction mixtures of oxidation of **1** with NaOCl and $RuCl_3$.

Furthermore, we have demonstrated that the catalyst can be recycled. When Ru/C was used in combination with NaOCl, the ruthenium was precipitated on the carbon after the oxidation and could be filtered and recycled. When $RuCl_3$/NaOCl was used, the ruthenium was precipitated by adding a little methanol. After filtration the catalyst could be reused by simply adding some hypochlorite solution to redissolve the ruthenium.

In conclusion, the use of hypochlorite in the presence of catalytic amounts of ruthenium appears to have considerable practical utility for the oxidative cleavage of vicinal diol moieties in carbohydrates.

EXPERIMENTAL

General procedures. All oxidation experiments were performed in a magnetically stirred, thermostatted glass reaction vessel of 60 or 500 ml. During the oxidations the pH was kept constant using a pH meter (Metrohm 654), a pH controller (Metrohm 614) and a motor burette (Metrohm 655) containing 0.100 M or 1.00 M aqueous sodium hydroxide.

Samples were analyzed by HPLC on a system consisting of a Millipore M590 pump and M717 autosampler, an Erma ERC-7510 RI detector, a Shimadzu SPD-2A UV detector at 215 nm, and a Spectra Physics SP4400 integrator. A 4 μ Novapak C_{18} 8x100 mm column contained in a Millipore module was used with an aqueous 0.05 M phosphate buffer with 0.5 % MeOH as the mobile phase.

^1H NMR and ^{13}C NMR spectra were recorded on a Varian VRX-400S spectrometer, using D_2O as solvent and *tert*-butyl alcohol as internal reference.

Table 2: ^{1}H NMR from Disodium (5*R*)-[(*S*)-carboxylato (methoxy) methoxy]-2,2-dimethyl-[1,3-dioxane]-(4*R*)-carboxylate (2)

δ (ppm)	signal	H's	structure	no.	J (H_a,H_b)	J (Hz)
1.38, 1.48	2s	3H, 3H	$C(CH_3)_2$	10, 11		
3.26	s	3H	OCH_3	9		
4.18	d	1H	HC-4	4	(4,5)	8.3
3.87	m	1H	HC-5	5	(5,6), (5,6')	4.3, 7.5
3.79	dd	1H	H_XC-6	6	(6,6')	11.6
4.00	dd	1H	H_YC-6	6'		
4.76	s	1H	$C\underline{H}OCH_3$	1		

^{13}C NMR: δ 177.8, 175.6 [COO^- (C-2, C-3)], 101.6 [$O_2\underline{C}(CH_3)_2$], 100.7 [C-1], 75.9 [C-4], 72.2 [C-5], 63.2 [C-6], 54.7 [OCH_3], 27.9, 21.6 [$C(\underline{C}H_3)_2$];

IR: ν^{KBr}: 1600 cm^{-1}: COO^-

MS (FAB): *m/z*: 309 (M^++1, 15), 293 (5), 115 (100), 69 (40), 67 (22).

Synthesis of Methyl 4,6-*O*-isopropylidene-α-D-glucopyranoside (1). Methyl 4,6-*O*-isopropylidene-α-D-glucopyranoside was prepared according to the method of Wolfrom *et al.*,[6] with modifications of Copeland[7] (yield: 12.1 g of product, 52 mmol, 95%). NMR spectral data were fully in accordance with the results of Debost.[3]

Preparation of Disodium (5*R*)-[(*S*)-carboxylato (methoxy) methoxy]-2,2-dimethyl-[1,3-dioxane]-(4*R*)-carboxylate (2). In a typical oxidation reaction, 150 mg (0.64 mmol) of **1** was dissolved in 30 mL of water; 6 mg (0.023 mmol) of $RuCl_3.3H_2O$ was dissolved in 2 mL of water and added to the solution of **1**. During the addition time of about 2 minutes, the pH was kept between 6 and 9 by co-adding some hypochlorite solution to prevent hydrolysis of the substrate. An additional amount of 25 mL of 0.14 M NaOCl (3.5 mmol) solution was slowly added during 2 hours, maintaining the pH at 8. The reaction was followed using HPLC. Dicarboxylate **2** was isolated from the oxidation product of **1** at pH 8 with $RuCl_3$/NaOCl by evaporation of water from the reaction mixture. The remaining solid was extracted twice with 75 mL of boiling 100% EtOH and the hot EtOH was filtered. After concentrating the raw product to 30 mL the dicarboxylate precipitated (not optimized yield: 30%).

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