ELSEVIER

Carbohydrate Research 267 (1995) 65–77

CARBOHYDRATE RESEARCH

Selective alkaline oxidative degradation of mono- and di-saccharides by hydrogen peroxide using borate as catalyst and protecting group

Ron van den Berg, Joop A. Peters *, Herman van Bekkum

Laboratory of Organic Chemistry and Catalysis, Delft University of Technology, Julianalaan 136, 2628 BL Delft, Netherlands

Received 18 July 1994; accepted 5 September 1994

Abstract

Lactose, maltose, cellobiose, and galactose can be degraded selectively in one step and in high yield into the corresponding next lower aldose and formic acid by H_2O_2 in the presence of borate. The selectivity further improves when a small amount of EDTA is added, in order to suppress the influence of transition metal ions which catalyze the decomposition of H_2O_2 via radical pathways, leading to non-selective oxidative degradation of aldoses. The function of borate in the selective oxidative degradation of aldoses is two-fold: catalysis of the degradation of the starting aldose and protection of the next lower aldose against oxidation.

Keywords: Perborate; Aldoses; 3-*O*-β-D-Galactopyranosyl-D-arabinose (galarose); Lyxose; Arabinose

1. Introduction

It is well known [1] that aqueous alkaline hydrogen peroxide degrades aldohexoses and aldopentoses stepwise, and ultimately almost quantitavely to formic acid. The degradation takes place via the open form of the aldose. It would be interesting to degrade readily available aldohexoses selectively to the next lower aldopentose and formic acid, since aldopentoses are valuable starting compounds, for example, in the synthesis of riboflavin and lyxoflavin. Examples of selective oxidative degradations of aldoses in the literature are the Ruff method [2], the Wohl degradation [3], the hypochlorite method [4,5], and the nitrophenylhydrazone method [6]. All these syntheses are, however, two-step reactions with rather low overall yields ($<50\%$).

* Corresponding author.

SSDI 0008-6215(94)00282-7

It has been reported that borate causes an enhancement of selectivity in a variety of reactions with carbohydrates, such as isomerization (glucose → fructose) [7], esterification (benzoylation) and etherification (methylation) [8], isopropylidenation [9], bromine oxidation [10], hydrogenation [11], and dehydration [12]. Generally, the rationale for this selectivity enhancement is the formation of stable borate esters [13–16] of the desired product. For example, in the isomerization of lactose to lactulose, which is an industrial process, borate shifts the equilibrium towards lactulose because a stable borate ester can be formed at C-2 and C-3 of β-lactulofuranose, whereas the starting compound lactose does not form stable borate esters [16]. Moreover, borate exerts a protecting role with respect to degradation reactions.

Surprisingly, up to now no reports have appeared on the influence of borate on the alkaline oxidative degradation of aldohexoses by H_2O_2. It has been shown that addition of borate results in a decrease of the oxidation rate of reducing sugars with oxidants such as Cu^{2+}, Fe^{3+}, and I_2 [17]. This type of oxidation takes place via the cyclic form of the sugar [18]. One example of perborate oxidation in alkaline medium is the oxidation of primary aliphatic amines to aliphatic C-nitroso compounds [19].

Herein, we report on a new selective one-step alkaline oxidative degradation of reducing mono- and di-saccharides to the next lower aldose and formic acid by H_2O_2 in the presence of borate ions. The high selectivity of borate for particular diol configurations is exploited to catalyze these reactions and to protect reaction products against over-oxidation. The oxidative degradation of lactose (**1**) towards 3-*O*-β-D-galactopyranosyl-D-arabinose (galarose) has been studied in detail. A comparison is made with other di- and mono-saccharides.

2. Experimental

Materials.—All aldoses used in this study were from the D series; they were reagent grade, and were used without further purification. Lactose was purchased from Merck and contained 0.00005% Pb, 0.0025% Cu, 0.0025% Zn, and 0.0001% As. Boric acid was also purchased from Merck and contained < 0.0015% heavy metals (such as Pb) and < 0.0008% As.

NMR Measurements.—^{11}B NMR spectra were recorded at 25°C with a Varian VXR-400 S spectrometer at 128.3 MHz. The ^{11}B spectra were referenced with respect to a solution of 0.1 M boric acid in D_2O, pH 6.5 (substitution method). The boron concentration of the solutions was 0.1 M, the sugar concentration 0.1 M, and the H_2O_2 concentration 0.5 M. The samples were prepared by dissolution of the appropriate amounts of boric acid, sugar, and H_2O_2 in D_2O. The pH was adjusted with 2 M NaOH in H_2O and the total volume of each sample was 5 mL.

^{13}C NMR spectra were recorded at 25°C with a Nicolet NT-200 WB spectrometer at 50.31 MHz with *tert*-butyl alcohol as the internal reference.

General oxidative degradation procedure.—The appropriate amounts of aldose, 35% H_2O_2, and boric acid were dissolved in 60 mL water and heated to 40°C. The pH was adjusted to the desired value with 6 M NaOH. During the reaction, the pH was maintained at this value by dropwise addition of 6 M NaOH. After consumption of 1.0 mL of 6 M NaOH, the reaction was stopped by lowering the pH to 5 with 12 M HCl. The products

were analyzed with ^{13}C NMR and HPLC (Dionex system). The absolute amount of product (galarose, arabinose, or lyxose) was determined by HPLC (Dionex) by comparison with authentic samples.

Some reactions were performed in the presence of 50 mg ethylenediamine tetraacetic acid, disodium salt dihydrate (EDTA). Then, the temperature was kept at 50°C.

Isolation of galarose(**2**).—Lactose (5.55 mmol), 35% H_2O_2 (28.5 mmol), and boric acid (28.3 mmol) were dissolved in 60 mL water and heated to 40°C. The pH was adjusted to 10.5 with 6 M NaOH. After 2 h, 1.5 mL of 6 M NaOH was consumed, after which the reaction was stopped by lowering the pH to 3 with cation-exchange resin (Dowex 50×8-100). Then, 50 mL of borate-specific anion-exchange resin (Amberlite IRA-743) was added in order to remove borate. After one night, the solution was filtered and evaporated to dryness. The residue, which contained mainly galarose together with a small amount of monosaccharides, was dissolved in 15 mL of water and applied to a column of cation-exchange resin (Ca^{2+} form). The eluent was water. The fractions containing galarose were collected. After evaporation of the solvent, 1.0 g (3.2 mmol, 60%) of galarose was obtained. Quantitative ^{13}C NMR and HPLC analysis (Dionex) showed that galarose was obtained with a purity of 95%. The identity of this compound was established by comparison of a ^{13}C NMR spectrum with that of an authentic sample.

3. Results and discussion

Oxidative degradation of disaccharides.—Table 1 summarizes our experiments on the H_2O_2–borate oxidative degradation of lactose, glucose, and galactose.

A non-selective, relatively slow reaction of lactose (**1**) to 3-*O*-β-D-galactopyranosyl-D-arabinose (galarose, **2**), monosaccharides, and formic acid took place when borate was absent (Table 1, Experiment 1). Only 10% of the formic acid formed originates from the degradation of lactose to galarose, the remainder results from over-oxidation. When a larger excess of H_2O_2 was used and after prolonged reaction times, lactose was completely converted into formic acid. In this paper, we define the selectivity of the reaction as the percentage of total formed formic acid which is produced by the degradation to the next lower aldose.

As can be seen in Table 1, the addition of borate results in a dramatic increase of the selectivity and reaction rate. Experiment 2 shows the increase in selectivity towards galarose and in the degradation rate upon addition of an equimolar amount of borate (with respect to lactose). Increasing the molar ratio borate:lactose to 5:1 (Experiment 5) gave rise to a further increase of the selectivity: 70% of the formic acid formed was produced by the degradation to galarose. Purification of the mixture via column chromatography on a cation-exchange resin (Ca^{2+} form) afforded essentially pure galarose in 60% yield.

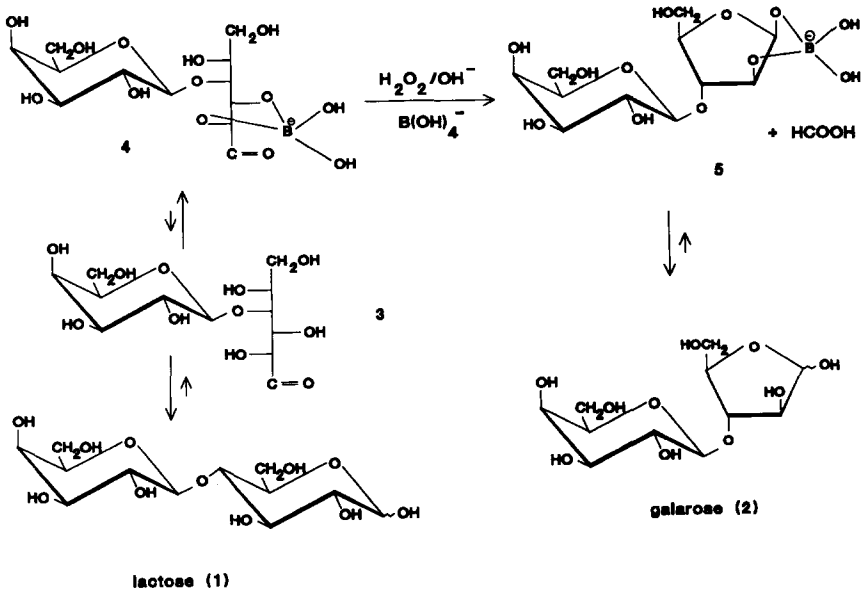
Furthermore, Table 1 (Experiments 7–8 and 12–15) shows that, within the applied limits, the temperature, the amount of H_2O_2, and the concentration do not have a significant influence on the product distribution. However, upon raising the pH to 11 (Experiments 10 and 11), a small increase of the selectivity to galarose was observed, which can be attributed to a shift of the equilibrium between boric acid and borate (pK_a boric acid = 9.0).

Table 1
Oxidative degradation of aldose (A) with H_2O_2 (H) and borate (B) to the next lower aldose (A-1) [a]

Expt	Reaction conditions					Reaction products yield, mmol (%) [d]		HCOOH (%) [e]
	A:H:B [b]	A (mmol)	pH	T (°C)	t (min) [c]	A	A−1	
Lactose								
1	1:5:0	5.55	10.5	40	75	4.2 (76)	0.6 (11)	10
2	1:5:1	5.55	10.5	40	22	2.4 (43)	2.6 (47)	43
3	1:5:2	5.55	10.5	40	23	1.7 (31)	3.4 (62)	57
4 [f]	1:5:2	5.55	11	50	75	1.1 (20)	3.9 (70)	65
5	1:5:5	5.55	10.5	40	40	1.0 (18)	4.2 (76)	70
6 [f]	1:5:5	5.55	11	50	95	0.4 (8)	4.8 (86)	80
7	1:5:2	5.55	10.5	25	85	2.0 (36)	3.2 (57)	53
8	1:5:2	5.55	10.5	55	10	1.7 (31)	3.4 (62)	57
9	1:5:2	5.55	10	40	60	1.9 (34)	3.3 (60)	55
10	1:5:2	5.55	11	40	18	1.3 (24)	3.8 (68)	63
11	1:5:5	5.55	11	40	19	0.8 (15)	4.4 (79)	73
12	1:2:2	5.55	10.5	40	85	1.9 (34)	3.3 (60)	55
13	1:3:2	5.55	10.5	40	45	1.7 (31)	3.4 (62)	57
14	1:5:2	11.1	10.5	40	14	3.7 (33)	6.7 (60)	56
15	1:5:2	22.2	10.5	40	8	7.5 (34)	13.3 (60)	55
Maltose								
16	1:5:0	5.55	10.5	40	300	4.0 (72)	0.6 (11)	10
17	1:5:2	5.55	10.5	40	25	1.3 (23)	3.7 (67)	62
Cellobiose								
18	1:5:0	5.85	11.5	45	150	4.4 (75)	0.7 (12)	12
19	1:5:2	5.85	10.5	40	17	1.9 (32)	3.6 (61)	59
Glucose								
20	1:5:0	5.55	10.5	40	90	3.9 (70)	0.3 (5)	5
21 [f]	1:5:0	5.55	11	50	80	3.3 (60)	0.3 (5)	5
22	1:5:1	5.55	10.5	40	25	3.6 (65)	1.1 (20)	19
23 [f]	1:5:1	5.55	11	50	40	2.2 (40)	1.4 (25)	23
24	1:5:5	5.55	10.5	40	100	3.6 (65)	0.8 (15)	14
25 [f]	1:5:5	5.55	11	50	85	3.0 (55)	1.1 (20)	19
Galactose								
26	1:5:0	5.55	10.5	40	45	3.6 (65)	0.8 (15)	14
27	1:5:1.5	5.55	10.5	40	20	1.9 (35)	2.8 (50)	46
28	1:5:5	5.55	10.5	40	45	1.7 (30)	3.0 (55)	51
29 [f]	1:5:5	5.55	11	50	35	1.1 (20)	3.6 (65)	60

[a] For further details, see the Experimental section.
[b] Molar ratio.
[c] Time t, at which 1.0 mL 6 M NaOH (6 mmol) was consumed with respect to 5.55 mmol aldose.
[d] Yield based on starting aldose, the remainder consists of monosaccharides and formic acid.
[e] Percentage of total formic acid formed produced by degradation to the next lower aldose.
[f] With addition of 50 mg (0.024 mol/mol aldose) EDTA.

Since it is known that traces of transition metal ions may catalyze oxidative degradations with H_2O_2 [1], Experiments 4 and 6 were carried out in the presence of 50 mg EDTA (0.024 mol/mol lactose). These reactions appeared to be much slower. The selectivity,



Scheme 1. Oxidative degradation of lactose by H_2O_2 in the presence of borate.

however, was higher. Optimal results were obtained in Experiment 6, where 80% of the resulting formic acid was produced by degradation to galarose. The effect of several cations is under further investigation.

It should be noted that the way in which we have defined the selectivity of the reaction, viz., the percentage of total formic acid formed which is produced by the degradation to the next lower aldose, over-emphasizes the over-oxidation. When the selectivity is expressed as the molar percentage of starting aldose converted into the next lower aldose the selectivities of Experiments 3–15 are all in the range of 88–93%. Apparently, after the first step in the over-oxidation reaction path, borate is no longer capable of protecting against further oxidation, until lactose has been degraded to galactose, which can again be protected by borate. This is in agreement with the detection of small amounts ($<5\%$) of galactose and lyxose as side products.

Similarly, maltose and cellobiose were converted into the corresponding next lower aldoses (3-*O*-α-D-glucopyranosyl-D-arabinose and 3-*O*-β-D-glucopyranosyl-D-arabinose, respectively). By applying the formulations and conditions of Experiments 1 and 3, comparable results were obtained as with lactose (Table 1, Experiments 16–19). To degrade cellobiose *without* borate (Experiment 18), more extreme conditions were needed (pH 11.5, 45°C). Apparently, no transition metal ions were present.

However, this procedure was not successful with melibiose. In that case, under the conditions of Experiment 3, mainly starting material was recovered, only minor amounts of galactose and lyxose were formed.

Oxidative degradation of monosaccharides.—In the series of monosaccharides, an investigation was made into their degradation rate with H_2O_2 in the presence of various amounts of borate (Fig. 1).

It can be seen from Fig. 1 that only ribose shows a continuous decrease of degradation rate upon increase of the molar ratio of borate to the reactants. The other aldoses investigated

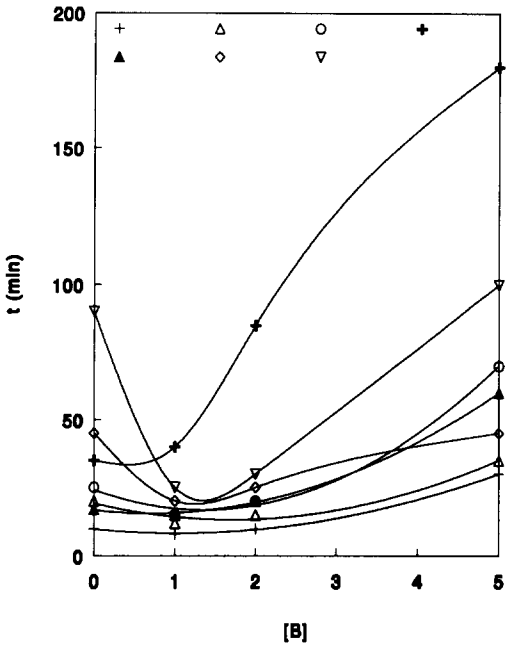


Fig. 1. Reaction rate of the oxidative degradation of monoaldoses with H_2O_2 in the presence of borate: t (min) = time t, at which 1.0 mL 6 M NaOH (6 mmol) was consumed with respect to 5.55 mmol aldose at 40°C and pH 10.5; [B] = molar amount of boric acid, with $[H_2O_2] = 5$ and [aldose] = 1; +, xylose; △, arabinose; ○, lyxose; +, ribose; ▲, mannose; ◇, galactose; ▽, glucose.

show an increase in degradation rate upon addition of an equimolar amount of borate, and a decrease, when an excess of boric acid is used.

The experiments were repeated in the presence of EDTA (0.024 mol/mol aldose) to suppress the influence of transition metal ions upon the oxidative degradation (Fig. 2).

A somewhat higher reaction temperature (50°C instead of 40°C) was needed in this case, as was seen before with lactose. The degradation rates of the experiments without borate (1:5:0) now agreed very well with the percentages of open forms, as given in the literature [20]. Thus, ribose has the highest percentage of open form (0.05%) and the highest degradation rate, while glucose has the lowest percentage (0.002%) and the lowest degradation rate. In the presence of borate, the same trends were observed as in the experiments without EDTA (Fig. 1). Remarkably, in the presence of EDTA, the aldohexoses showed a significantly larger increase in the degradation rate upon addition of borate (1:5:0 to 1:5:1) than the aldopentoses.

The oxidative degradations of the aldohexoses glucose and galactose in the presence of borate were investigated in more detail. The results are included in Table 1. It was found that galactose can be degraded selectively to lyxose upon addition of borate. The more borate added, the higher the selectivity was. In the presence of EDTA, an even higher selectivity to lyxose was obtained. Glucose also showed an enhancement of selectivity upon addition of borate (Table 1), but in comparison with galactose, a lower selectivity to the

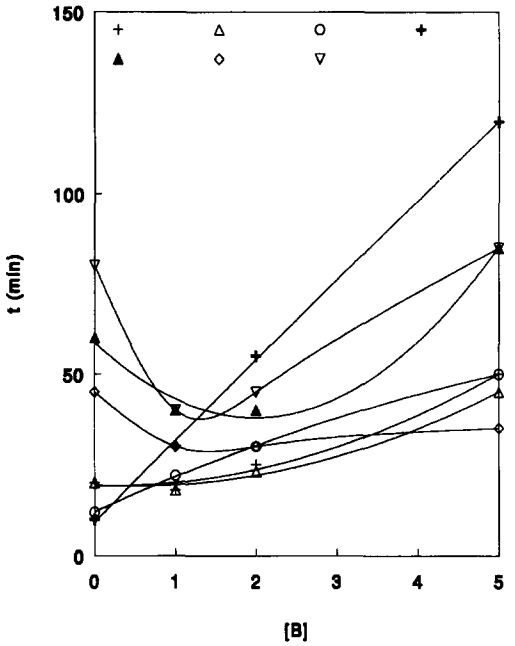
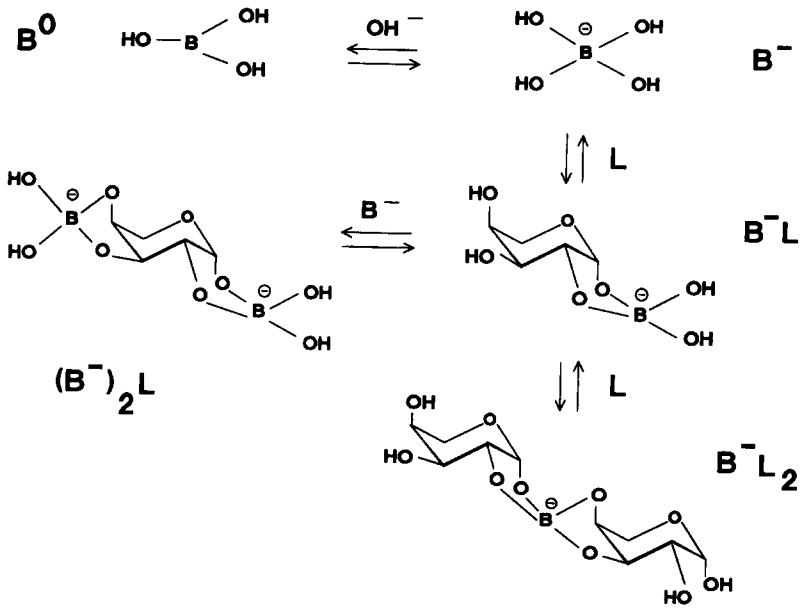


Fig. 2. Reaction rate of the oxidative degradation of monoaldoses with H_2O_2 in the presence of borate and EDTA: t (min) = time t, at which 1.0 mL 6 M NaOH (6 mmol) was consumed with respect to 5.55 mmol aldose at 50°C and pH 11; [B] = molar amount of boric acid, with $[H_2O_2] = 5$ and [aldose] = 1; +, xylose; △, arabinose; ○, lyxose; +, ribose; ▲, mannose; ◇, galactose; ▽, glucose.

next lower aldose (arabinose) was obtained. An optimum selectivity was obtained with a relatively small amount of borate. Once again, addition of EDTA gave rise to a small improvement in selectivity. Mannose behaved similarly to glucose.

Reaction mechanisms.—The interaction of boric acid and sugars in aqueous solution has been investigated for more than a century [21,22]. Borate mono- and di-esters (B^-L and B^-L_2) can be formed in alkaline medium both at vicinal 1,2-diol and at 1,3-diol functions (Scheme 2).

Recently, we determined the structure and (local) stability constants of the borate esters of several mono- and di-saccharides by ^{11}B and ^{13}C NMR [16]. It appeared that B^-L, B^-L_2, and $(B^-)_2L$ esters are formed. B^-L_2 esters dominate with an excess of sugar and $(B^-)_2L$ esters with an excess of borate. The order of local stability constants $K_{loc}(B^-L)$ is: *cis*-1,2-diol-furanose (2500–45000 L/mol) > > exocyclic-1,2-diol-pyranose (250–1500) > exocyclic-1,2-diol-furanose (50–100) > *cis*-1,2-diol-pyranose (10–20) > exocyclic *cis*/*trans*-4,6-diol-pyranose (3–6) > > *trans*-1,2-diol-pyranose/furanose (0). Thus, pyranose structures do not form very stable borate esters, while furanose structures do form very stable borate esters when a *cis*-1,2-diol configuration is present. The interaction of borate with the open form of the saccharides cannot be measured directly by NMR, as these forms occur only in very small amounts. However, from previous studies on polyhydroxycarboxylates and polyols [15], it can be concluded that the *threo* configuration is very



Scheme 2. Equilibria between boric acid, borate, and a sugar compound in aqueous medium.

favourable for borate ester formation [$K(B^-L) = 200$–1200 L/mol]. From a combination of these data and the known overall association constants $K(B^-L)$ [16] of the sugars, the effect of borate on the amount of open form (free sugar + borate ester) can be estimated. It can be concluded that lactose, glucose, galactose, and mannose show a large increase in the amount of the open form upon addition of an equimolar amount of borate. By contrast, ribose, which has a favourable *cis*-1,2-diol-furanose structure and no *threo* configuration, shows a large decrease in the amount of open form. This is in good agreement with the results of a study by Roy et al. [23]

From Fig. 3A it can be concluded that hydrogen peroxide forms relatively strong complexes with borate. The signals at δ −15.1 and −16.5 can be assigned to the peroxoborates $(OH)_2B(OOH)_2^-$ and $(OH)_3BOOH^-$, respectively. Pizer and Tihal [24] have investigated the interaction of boric acid (0.1 M) and H_2O_2 (1 M) before and found that $K(B^-L)$ of H_2O_2 is 20 L/mol.

In samples with a sugar, H_2O_2, and borate, all possible borate–sugar, borate–H_2O_2, and borate–H_2O_2–sugar species were observed by ^{11}B NMR. Apparently competition occurs between hydrogen peroxide and saccharide for borate. It depends on the various stability constants which species will dominate. Thus, in the case of lactose, which has a relatively low affinity for borate [$K(B^-L) \approx 25$ L/mol] [16], the borate–H_2O_2 species are most important (Fig. 3B). The lactose–borate combination gave peaks at δ −9.7, −13.6, −14.0, and −18.2 [16]. The new, small peaks in the ^{11}B NMR spectrum at δ −12.2 and −12.7 can be attributed to the perborate esters of C-3′–C-4′ and C-1–C-2, respectively. The chemical shifts of the corresponding borate esters are δ −13.6 and −14.0. In the case of galarose, equal amounts of borate–H_2O_2 and borate–sugar species were found (Fig. 3C). This can be explained by the stability constant of the borate monoester $K(B^-L)$ of galarose (≈ 100 L/mol) and that of H_2O_2 (20 L/mol) [24], taking into consideration the 5 times

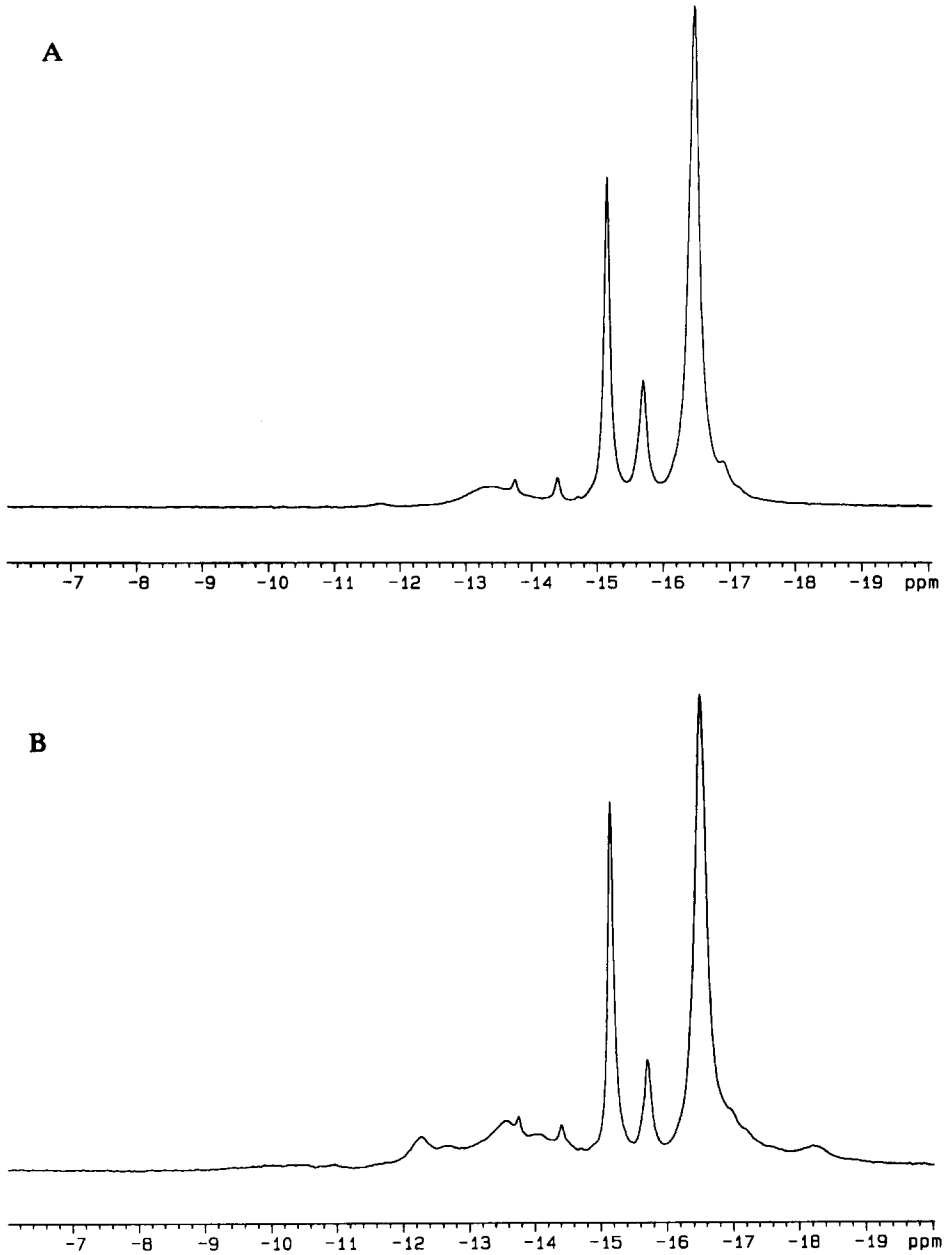


Fig. 3. ^{11}B NMR spectra of (A) 0.10 M boric acid–0.5 M H_2O_2, pH 10.25, (B) 0.10 M boric acid–0.5 M H_2O_2–0.10 M lactose, pH 10.40, and (C) 0.10 M boric acid–0.5 M H_2O_2–0.10 M galarose, pH 10.85

higher concentration of H_2O_2. Galarose and borate showed peaks in the ^{11}B NMR spectrum at δ −8.9, −12.9, −13.5, −13.8, and −18.2. It is possible to assign these peaks by analogy with lactulose [16]. The peak at δ −8.9 belongs to the B^-L_2 ester of β-galarofuranose at C-1 and C-2. The B^-L ester of this sugar has a chemical shift of δ −13.8, and

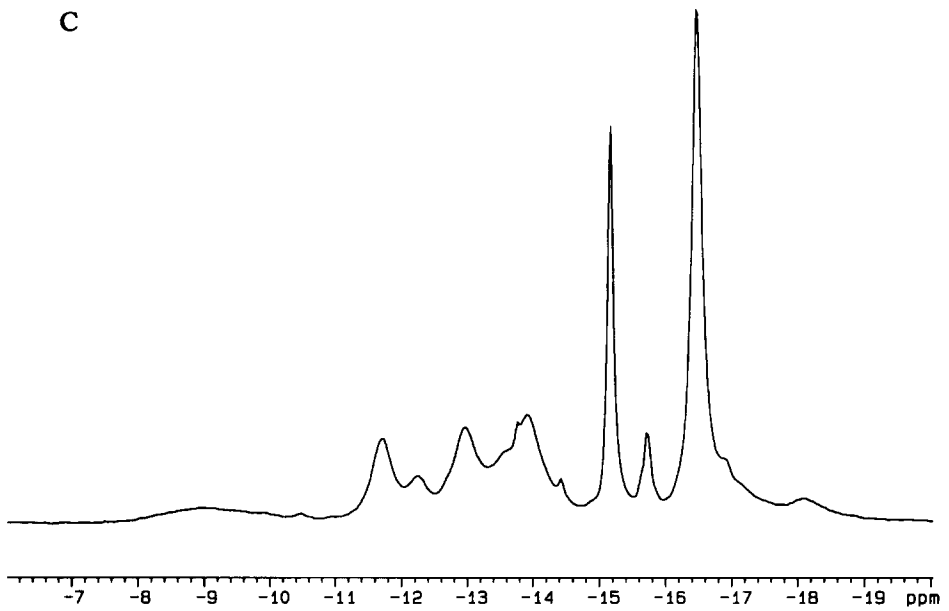


Fig. 3 (continued).

the corresponding tridentate ester on C-1–C-2–C-5 is visible at δ −12.9. The smaller peaks at δ −13.5 and −18.2 can be assigned to B^-L esters on the galactose moiety of galarose on C-3–C-4 and C-4–C-6, respectively. ^{11}B NMR spectra of a galarose–H_2O_2–borate solution exhibited two new peaks for the perborate esters: a peak at δ −12.2, which can be assigned to the C-3′–C-4′ ester, as observed with lactose, and another at δ −11.7 for the C-1–C-2 ester of β-galarofuranose. The ratio borate ester:perborate ester of galarose was ca. 70:30, while the amount of borate, under the conditions used, was much lower than the amount of perborate [24]. Because galarose has about the most favourable configuration (*cis*-1,2-diol-furanose) for borate ester formation, it can be concluded that, in general, borate esters of sugars will be more stable than perborate esters of sugars.

According to Isbell et al. [1], the alkaline oxidative degradation of aldoses is initiated by addition of the nucleophilic hydroperoxide anion (pK_a $H_2O_2 = 11.6$), resulting in an acyclic carbohydrate peroxide. This may decompose either by an α-hydroxy hydroperoxide cleavage mechanism or an ester mechanism.

The degradation is catalyzed by traces of transition metal ion species such as Fe(II), because they decompose H_2O_2 in alkaline media via a radical mechanism [1,25]. This is in agreement with the observation that sequestering of traces of metal ions by addition of EDTA to the degradation reaction of lactose, glucose, and galactose gives rise to a decrease in the reaction rate and an increase in the selectivity.

When borate was applied as an additive in the oxidative degradation of aldoses, an improved selectivity to the next lower aldose was found. In the case of lactose, borate acts as a catalyst for the degradation of lactose and as a dynamic protecting group for galarose. The catalytic action can be explained by an increase of the open form of lactose (**3** + **4**) (Scheme 1) upon addition of borate [23], which has been shown to be the reactive tautomer in the oxidative degradation [1]. The reason for this increase is the relatively high affinity

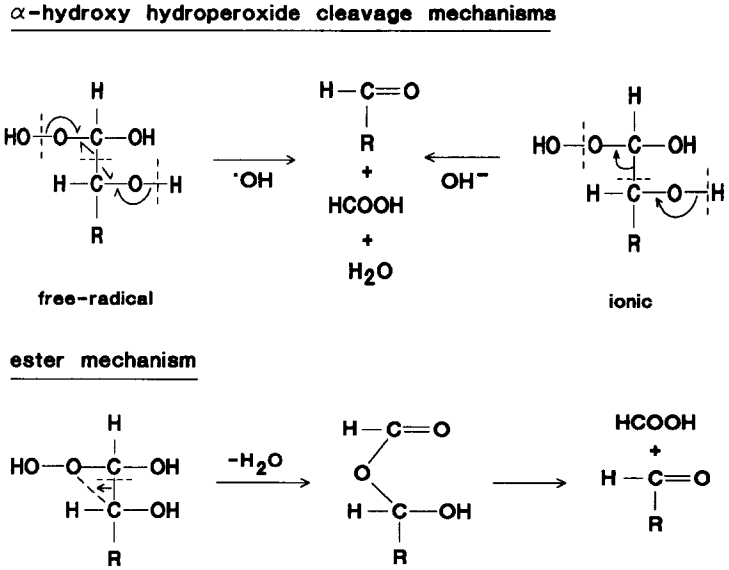
of borate for the *threo* C-2–C-3 diol function in the open form [15] [$K_{loc}(B^-L) \approx 200$ L/mol] and the relatively low overall association constant $K(B^-L)$ (25 L/mol) [16] of lactose. This is because lactose is predominantly in the pyranose form, which cannot form very stable borate esters. Galarose is protected by borate because, on the one hand, it does not have a favourable *threo* configuration in the open form and on the other hand it can form a very stable *cis*-1,2-diol furanose borate ester at C-1 and C-2 [$K_{loc}(B^-L) \approx 5000$ L/mol] of the arabinose moiety (**5**) [16]. These properties result in a decrease of the amount of open form of galarose upon addition of borate. As a consequence, lactose can be degraded selectively to galarose in the presence of borate. This selectivity even improves when EDTA is added to suppress the influence of transition metal ions, catalyzing H_2O_2 homolysis towards hydroxyl radicals.

A selective oxidative degradation in the presence of borate also could be successfully applied to the lactose-related disaccharides maltose and cellobiose, but not to melibiose (6-*O*-α-D-galactopyranosyl-D-glucose), because the latter sugar can form a stable *cis*-1,2-diol-furanose borate ester at C-1 and C-2 and because the expected product also has a *threo* configuration in the open form. The consequence of these properties is that only melibiose, galactose, and lyxose were detected by ^{13}C NMR spectroscopy, when melibiose was degraded under the same conditions as used in Experiment 3 (Table 1).

Galactose can be degraded selectively to lyxose in the presence of borate. The main reason for this behaviour is the presence of two *threo* configurations at C-2–C-3 and C-4–C-5 in the open form, which results in an increase of the open form of galactose upon addition of borate. By contrast, lyxose has favourable configurations for borate in the furanose form and cannot form a stable $(B^-)_2L$ borate ester in the open form.

Both glucose and mannose degrade to arabinose. When an equimolar amount of borate was added, with respect to lactose, an enhancement of selectivity of glucose (and mannose) to arabinose was observed (Table 1), which can be explained by a substantial increase of the open form of glucose upon addition of an equimolar amount of borate [23]. We can estimate this increase by making use of the overall association constant $K(B^-L)$ for glucose which is 65 L/mol [16]. From the overall association constant $K(B^-L)$ for D-gluconate [15], we estimate that $K(B^-L)$ for the open form of glucose is ca. 300 L/mol. It can then be calculated that the amount of the open form of glucose (free + borate ester) increases by a factor of 5 upon addition of an equimolar amount of borate (Roy et al. reported a factor of 9 [23]). It must be emphasized that this increase of the open form is smaller in the presence of H_2O_2, because of the competition between H_2O_2 and glucose for borate. Both the overall association constant of arabinose [16] and the overall association constant of D-arabinonate [15] are ca. 100 L/mol, which means that addition of an equimolar amount of borate will have no influence on the amount of the open form of arabinose. This is confirmed by Roy et al. [23] and by the observed very small increase of the degradation rate of arabinose (Figs. 1 and 2) when an equimolar amount of borate was added.

However, when a large excess of borate was applied (1:5:5 molar ratio), a decrease of selectivity to arabinose occurred, because glucose (and mannose) can form more stable $(B^-)_2L$ borate esters with the furanose forms than with the open form. Thus, oxidative degradation of glucose and mannose in the presence of borate results in a relatively small yield of arabinose, which reaches a maximum upon addition of an equimolar amount of borate.



Scheme 3. Oxidative degradation of the acyclic peroxide of an aldose.

The phenomena described present strong evidence that the oxidative degradation in the presence of borate occurs via the open form of a borate ester of the sugar, but the question arises which mechanism is involved. In Scheme 1, it is suggested that **4** is the most important borate ester in the open form. Then it is likely that the acyclic peroxide decomposes via the ester mechanism, because an α-hydroxy hydroperoxide cleavage mechanism does involve the blocked C-2 group (Scheme 3). An alternative explanation is that a peroxide in a $(HO)_3BOOH^-$ or a $(OH)_2B(OOH)_2^-$ perborate ester at C-2 and C-3 is involved in the degradation of lactose. This is less likely since the distance between the carbonyl C-atom and the closest perborate oxygen is probably too large for an intramolecular attack.

4. Conclusions

An enhancement of selectivity to the next lower aldose is observed when borate is added during the alkaline oxidative degradation by H_2O_2 of lactose, maltose, cellobiose, galactose, glucose, and mannose. In this article, we define the selectivity as the percentage of total formic acid formed which is produced by the degradation to the next lower aldose, which over-emphasizes the over-oxidation. Very high selectivity (> 70%, i.e., > 90% on lactose), at high conversion (> 80%) is achieved with lactose, maltose, and cellobiose, which even improves when traces of contaminating transition metal ions are sequestered by a small amount of EDTA. The cause for this high selectivity is two-fold. First, the degradation of these disaccharides is catalyzed by borate because of an increase of the open form and secondly borate acts as a protecting group for the product, because of a decrease of the open form. The achieved selectivity of the degradation of galactose to lyxose is 60% at a conversion of 80%. The main reason for this high selectivity is the double *threo* configuration

on the open form of galactose so that a very stable $(B^-)_2L$ ester can be formed. Glucose and mannose do not give high selectivity to arabinose, because the absolute amounts of open form of these two aldohexoses in the presence of borate remain much lower than that of arabinose.

Acknowledgements

This investigation was carried out with the support of the Dutch National Innovation Oriented Program Carbohydrates (IOP-k), Solvay-Duphar B.V. (Weesp), and DMV International (Veghel).

References

[1] H.S. Isbell, H.L. Frush, and E.T. Martin, *Carbohydr. Res.*, 26 (1973) 287–295; H.S. Isbell and H.L. Frush, *ibid.*, 161 (1987) 181–193.
[2] O. Ruff and G. Ollendorf, *Ber.*, 33 (1900) 1798–1810.
[3] G. Zemplén, *Ber.*, 60 (1927) 1309–1312.
[4] E. Hardegger, K. Kreis, and H. El Khadem, *Helv. Chim. Acta*, 35 (1952) 618–623.
[5] R.L. Whistler and K. Yagi, *J. Org. Chem.*, 26 (1961) 1050–1052; R.L. Whistler and R. Schweiger, *J. Am. Chem. Soc.*, 81 (1959) 5190–5192.
[6] L. Petrus, V. Bilik, K. Linek, and M. Misiková, *Chem. Zvesti*, 32 (1978) 701–705; V. Bilik, P. Biely, and M. Matulová, *ibid.*, 33 (1979) 782–784; V. Bilik, J. Alföldi, and R. Sandtnerová, *ibid.*, 35 (1981) 829–833.
[7] K.B. Hicks, E.V. Symanski, and P.E. Pfeffer, *Carbohydr. Res.*, 112 (1983) 37–50.
[8] R.J. Ferrier, *Adv. Carbohydr. Chem.*, 35 (1978) 31–80.
[9] C.J. Griffiths and H. Weigel, *Carbohydr. Res.*, 81 (1980) 17–21.
[10] B. Augustinsson and E. Scholander, *Carbohydr. Res.*, 126 (1984) 162–164.
[11] M. Makkee, A.P.G. Kieboom, and H. van Bekkum, *Carbohydr. Res.*, 138 (1985) 237–245.
[12] J.E. McMurry and M.D. Evion, *J. Am. Chem. Soc.*, 107 (1985) 2712–2720.
[13] J.F. Verchère and M. Hlaibi, *Polyhedron*, 6 (1987) 1415–1420.
[14] S. Chapelle and J.F. Verchère, *Tetrahedron*, 44 (1988) 4469–4482.
[15] M. van Duin, J.A. Peters, A.P.G. Kieboom, and H. van Bekkum, *Tetrahedron*, 41 (1985) 3411–3421.
[16] R. van den Berg, J.A. Peters, and H. van Bekkum, *Carbohydr. Res.*, 253 (1994) 1–12.
[17] W. Kliegel, *Bor in Biologie, Medizin und Pharmazie*, Springer-Verlag, Berlin, 1980, p 75.
[18] J. Lehmann, *Chemie der Kohlenhydrate*, Georg Thieme Verlag, Stuttgart, 1976, pp 85–88.
[19] W.W. Zajac, M.G. Darcy, A.P. Subong, and J.H. Buzby, *Tetrahedron Lett.*, 30 (1989) 6495–6496.
[20] S.J. Angyal, *Adv. Carbohydr. Chem. Biochem.*, 41 (1983) 27–65.
[21] L. Vignon, *C.R. Acad. Sci.*, 78 (1874) 31–50.
[22] J. Boëseken, *Adv. Carbohydr. Chem.*, 4 (1949) 189–210.
[23] R. Roy, R.E. Williams, and H.J. Jennings, *Carbohydr. Res.*, 127 (1984) 165–169.
[24] R. Pizer and C. Tihal, *Inorg. Chem.*, 26 (1987) 3639–3642.
[25] J. Gierer and K. Jansbo, *J. Wood Chem. Technol.*, 13 (1993) 561–581.