# Selective Alkaline Oxidative Degradation of Mono- and Di-saccharides by $H_2O_2$ with Borate as Catalyst and Protecting Group

**Ron van den Berg, Joop A. Peters and Herman van Bekkum**
*Laboratory of Organic Chemistry and Catalysis, Delft University of Technology, Julianalaan 136, 2628 BL Delft, The Netherlands*

Lactose, maltose, cellobiose and galactose are degraded selectively in one step and in a high yield into the corresponding next lower aldose and formic acid by $H_2O_2$ in the presence of borate.

Since it is well known[1] that aqueous alkaline hydrogen peroxide degrades aldohexoses and aldopentoses almost quantitatively to formic acid by a stepwise mechanism, we were interested in the possibilities of degrading readily available aldohexoses selectively to aldopentoses and formic acid, the former being valuable starting compounds in the synthesis of riboflavin and lyxoflavin. Unfortunately, all known selective oxidative degradations such as the Ruff method,[2] the Wohl degradation,[3] the hypochlorite method[4,5] and the nitrophenylhydrazone method[6] are two-step procedures and afford rather low yields of product (< 50%).

Here, we report on a new selective one-step alkaline oxidative degradation of mono- and di-saccharides to the next lower aldose and formic acid by $H_2O_2$ in the presence of borate ions. The essence of the method is that borate catalyzes the degradation of the reactant and protects the product against further degradation.

For example, in the oxidative degradation of lactose **1**, the presence of borate in the reaction mixture results in a dramatic increase in the selectivity and reaction rate. A non-selective, relatively slow reaction of lactose to 3-*O*-β-D-galactopyranosyl-D-arabinose (galarose) **2**, monosaccharides and formic acid took place when borate was absent (Table 1, expt. 1). Moreover, small amounts (< 5%) of lactulose and higher carboxylic acids were formed. After prolonged reaction times, only formic acid resulted. Expt. 2 shows that in the presence of borate there is an increase both in selectivity towards galarose and in degradation rate. An increase in the molar ratio borate : lactose (expts. 3 and 4) gave rise to a further increase in the selectivity, resulting in a conversion of lactose into galarose of 76% (expt. 4). Column chromatography on a cation exchange resin in the $Ca^{2+}$ form afforded pure galarose in 60% yield.

In these reactions borate acts both as a catalyst and as a protecting group. The catalytic action can be explained in terms of an increase of the open form of lactose (**3** + **4**) upon addition of borate,[7] a form 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.[8] In the presence of a large amount of borate (expt. 4) the β-galarofuranose produced is strongly protected by borate,[9] resulting in a slower degradation. Not only does the latter sugar form a very stable *cis*-1,2-diol furanose borate ester at C-1 and C-2 of the arabinose moiety **5**, but, further, has no favourable *threo* configuration in the open form. By contrast, lactose is not protected by borate against oxidative degradation, since it is predominantly in the pyranose form, which cannot form very stable borate esters. Thus, the ideal aldohexose in this new alkaline oxidative degradation procedure has a relatively high percentage of open form in the presence of borate, low stability constants for the borate esters of its cyclic forms and is converted into a sugar with the reverse stereochemical properties. Accordingly, this reaction could be successfully applied to maltose and cellobiose, but not to melibiose (6-*O*-α-D-galactopyranosyl-D-glucose); this is both because the last-named sugar forms a stable *cis*-1,2-diol furanose borate ester at C-1 and C-2 and because the expected product has a *threo* configuration in the open form.

In the degradation of galactose to lyxose and of glucose to arabinose enhanced selectivity is shown in the presence of borate, because of its ability to increase greatly the open form of glucose and galactose.[7] Although lyxose is obtained in a high yield (70%), the yield of arabinose is in only 30%, the absolute amount of the open form of glucose in the presence of borate being much lower than that of arabinose. Therefore, the degradation of arabinose is relatively fast compared to that of glucose.

From the results presented in Table 1, it is concluded that under the conditions employed, the temperature, the amount of $H_2O_2$ and the concentration have little influence on the product distribution. However, when the pH was raised to 11 (expts. 8 and 9), a small improvement of selectivity towards galarose was observed.

## Experimental

*General Procedure.*—Appropriate quantities of lactose **1**, 35% $H_2O_2$ and boric acid were dissolved in water (60 $cm^3$) and the solution was heated to 40 °C. The pH of the solution was adjusted to the desired value with 6 mol $dm^{-3}$ aqueous NaOH and was maintained at this during the reaction by the dropwise addition of further aqueous base. After consumption of 1.0 $cm^3$ of 6 mol $dm^{-3}$ aqueous NaOH the reaction was stopped by addition of 12 mol $dm^{-3}$ aqueous HCl to the mixture until it reached pH 5. The products were analysed by $^{13}C$ NMR spectroscopic and HPLC(DIONEX) techniques. The absolute amounts of galarose were determined by comparison with a standard sample of galarose.

*Isolation.*—Lactose **1** (5.55 mmol), 35% $H_2O_2$ (28.5 mmol) and boric acid (28.3 mmol) were dissolved in water (60 $cm^3$) and the solution heated to 40 °C. It was then brought to pH 10.5 with 6 mol $dm^{-3}$ aqueous NaOH. After 2 h, 1.5 $cm^3$ of 6 mol $dm^{-3}$ aqueous NaOH had been consumed and the reaction was, therefore, stopped by bringing the mixture to pH 3 with cation exchanger DOWEX 50X8-100. Borate was then removed from the mixture by addition of borate-specific anion exchanger (Amberlite IRA-743; 50 $cm^3$) after which the mixture was stored overnight. It was then filtered and evaporated to dryness. The residue, which contained mainly 3-*O*-β-D-galactopyranosyl-D-arabinose (galarose) **2** together with a small amount of monosaccharides, was dissolved in water (15 $cm^3$) and the solution applied to a column of cation exchange resin in the $Ca^{2+}$ form. The eluent was water and the fractions containing galarose were collected. Evaporation of the fractions gave

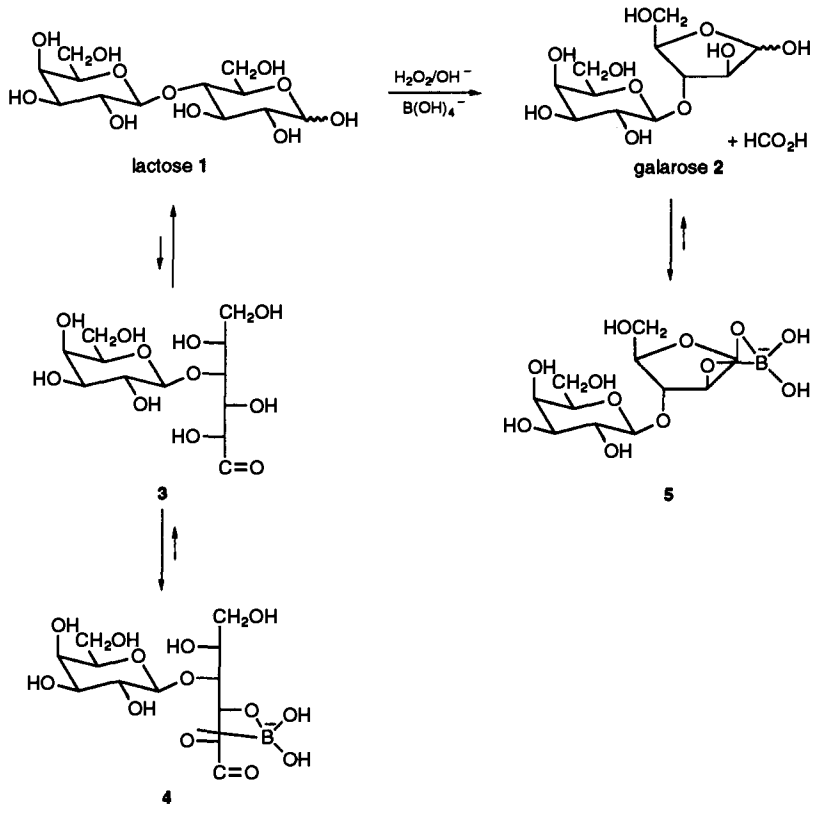


**Table 1** Oxidative Degradation of lactose (L) with $H_2O_2$ (H) and borate (B) to galarose (G)[a]

| | Reaction conditions | | | | | Yield, mmol (%)[d] | |
|---|---|---|---|---|---|---|---|
| Expt. | L:H:B[b] | L (mmol) | pH | $T$/°C | $t$/min[c] | L | G |
| 1 | 1:5:0 | 5.55 | 10.5 | 40 | 75 | 4.2 (76) | 0.6 (11) |
| 2 | 1:5:1 | 5.55 | 10.5 | 40 | 22 | 2.4 (43) | 2.6 (47) |
| 3 | 1:5:2 | 5.55 | 10.5 | 40 | 23 | 1.7 (31) | 3.4 (62) |
| 4 | 1:5:5 | 5.55 | 10.5 | 40 | 40 | 1.0 (18) | 4.2 (76) |
| 5 | 1:5:2 | 5.55 | 10.5 | 25 | 85 | 2.0 (36) | 3.2 (57) |
| 6 | 1:5:2 | 5.55 | 10.5 | 55 | 10 | 1.7 (31) | 3.4 (62) |
| 7 | 1:5:2 | 5.55 | 10 | 40 | 60 | 1.9 (34) | 3.3 (60) |
| 8 | 1:5:2 | 5.55 | 11 | 40 | 18 | 1.3 (24) | 3.8 (68) |
| 9 | 1:5:5 | 5.55 | 11 | 40 | 19 | 0.8 (15) | 4.4 (79) |
| 10 | 1:2:2 | 5.55 | 10.5 | 40 | 85 | 1.9 (34) | 3.3 (60) |
| 11 | 1:3:2 | 5.55 | 10.5 | 40 | 45 | 1.7 (31) | 3.4 (62) |
| 12 | 1:5:2 | 11.1 | 10.5 | 40 | 14 | 3.7 (33) | 6.7 (60) |
| 13 | 1:5:2 | 22.2 | 10.5 | 40 | 8 | 7.5 (34) | 13.3 (60) |

[a] For further conditions see Experimental section. [b] Molar ratio. [c] Time $t$, at which 1.0 $cm^3$ 6 mol $dm^{-3}$ NaOH (6 mmol) was consumed with respect to 5.55 mmol lactose. [d] Yield based on lactose, the remainder consists of monosaccharides and formic acid.

galarose (1.0 g, 3.2 mmol, 60%). 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.

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