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Electrochemically-Promoted Reductive Cleavage of Glycosides

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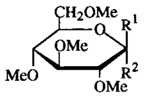
The "reductive-cleavage method" has been successfully used to simultaneously establish the identity, ratio, linkage position(s), and ring form of each glycosyl residue in glycans containing a wide variety of monosaccharides.[1] This method involves the regiospecific ionic hydrogenation of the glycosidic carbon−oxygen bonds of a fully methylated glycan with either Et_3SiH or $BH_3\cdot SMe_2$ and a Lewis acid promoter. Four Lewis acid promoters have been found to be suitable for reductive-cleavage, namely, $BF_3\cdot OEt_2$, TMSOTf, TMSOMs−$BF_3\cdot OEt_2$, and $BuSnCl_3$ (where TMS = trimethylsilyl, OTf = triflate, OMs = mesylate).[2] Among these, TMSOTf and TMSOMs−$BF_3\cdot OEt_2$ are used to achieve total reductive cleavage when Et_3SiH is used as the reducing agent, whereas $BF_3\cdot OEt_2$ and $BuSnCl_3$ result in total reductive cleavage when $BH_3\cdot SMe_2$ is used as the reducing agent. However, $BF_3\cdot OEt_2$ is quite selective as a promoter when Et_3SiH is used as the reducing agent and this selectivity has proven to be useful for sequencing carbohydrates.[3]

Despite the success of this method, it still suffers two drawbacks that limit its use. First, the reductive-cleavage reaction is very sensitive to the presence of trace amounts of water and great care to exclude water must be taken in order to prevent the rearrangement of 4-linked pyranosyl residues.[4] Second, its application to the sequence analysis of carbohydrates has been hampered by the lack of general, selective reductive-cleavage procedures. We therefore sought to develop an alternative method that might be experimentally easier to perform as well as capable of achieving selective reductive cleavage in a truly general fashion. Herein, we report the results obtained by carrying out reductive cleavage of glycosides using an electrogenerated acid as a promoter.

It is known that acidic media are formed in the vicinity of a platinum anode by the electrolysis of certain types of supporting electrolytes in organic solvents.[5] It is therefore possible to generate a strongly acidic environment in the vicinity of an anode surface, allowing acid-promoted reactions to occur even though the total electrochemical reaction system is kept neutral. Torii et al.[6] reported that ionic hydrogenation of acetals could be accomplished using Et_3SiH in the presence of an electrogenerated acid (EGA) produced in a CH_2Cl_2−$LiClO_4$−Bu_4NClO_4−(Pt) system. Noyori and Kurimoto[7] reported an electrochemical glycosylation method in which the glycosylation proceeds in a CH_3CN−$LiClO_4$−(Pt) system via a cyclic oxonium ion intermediate. These results suggested that it might be possible to accomplish the reductive cleavage of permethylated glycosides using an electrochemical method.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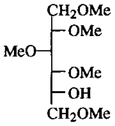
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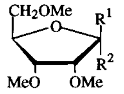
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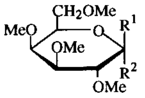
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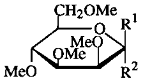
8, R^1 = R^2 = H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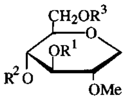
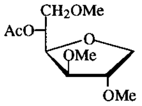
10, R^1 = R^2 = H


11, R^1 = Ac, R^2 = R^3 = Me
12, R^2 = Ac, R^1 = R^3 = Me
13, R^3 = Ac, R^1 = R^2 = Me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Methyl 2,3,4,6-tetra-*O*-methyl-*β*-D-glucopyranoside (**1**) was first chosen for study in order to explore the potential for promoting glycosidic reductive cleavage electrochemically. In a typical procedure, a solution (2.5 mL) containing the electrolyte (0.1 mmol), substrate (0.005 mmol), reducing reagent (0.1 mmol), and heptadecane (internal standard for integration) was placed in an undivided cell (5.0 mL), the cell was fitted with two Pt foil electrodes (0.7 × 0.7 cm each; 3 mm separation), and electricity was then passed through the cell at constant voltage with stirring at room temperature. The progress of the reaction was monitored by gas−liquid chromatography, after an aqueous $NaHCO_3$ quench, by integration of starting material and product relative to haptadecane and correction for molar response.[8]

Electrolysis of **1** using both the CH_2Cl_2−$LiClO_4$−Bu_4NClO_4−Et_3SiH (8 V) and CH_3CN−$LiClO_4$−Et_3SiH (10 V) systems failed to give the expected product **2**. However, the reductive cleavage of **1** was accomplished in 84% yield when electrolysis was conducted at 10 V for 2 h using $BH_3\cdot SMe_2$ as the reducing agent and $Zn(ClO_4)_2\cdot 6H_2O$ [CAUTION: *Perchlorate salts with organic compounds are potentially explosive!*] as the electrolyte in CH_2Cl_2. In an effort to improve the yield of **2**, the reactions were subjected to pre-electrolysis in the absence of substrate for various periods of time, and then **1** was added and electrolysis was continued. These studies established that pre-electrolysis for 2 or more hours gave **2** in essentially quantitative yield. Analogous to the chemical method, a small amount of anomerization product **3** was formed during the reaction but was eventually converted to **2**.[2c,9] The product (**4**) arising by reductive cleavage of the endocyclic C−O bond of **1** was never observed in this study. Control experiments demonstrated that reductive cleavage proceeded slowly, if at all, in the absence of current. Moreover, addition of 0.5−1 equiv (to electrolyte) of H_2O to the reaction substantially decreased the reaction rate without affecting product yield, but both the rate and yield increased after pre-electrolysis for 24 h, presumably because pre-electrolysis destroyed the added H_2O.

Previous studies[2c] have shown that various types of glycosidic bonds display different susceptibilities to reductive cleavage when chemical procedures are employed, and indeed, they also display different reactivities to electrochemical reductive cleavage (Figure 1). Among the glycosides tested, fully methylated methyl *β*-D-ribofuranoside (**5**) was the most reactive followed by fully methylated methyl *β*-D-galactopyranoside (**7**). Fully methylated

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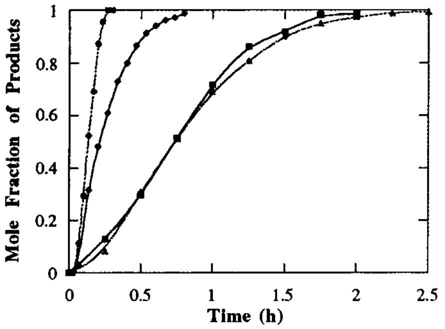

Figure 1. Time course for the formation of anhydroalditols using $Zn(ClO_4)_2 \cdot 6H_2O$ as an electrolyte. Electrolysis was conducted at 10 V with a 2 h pre-electrolysis. Substrates: **5** (●), **7** (◆), **1** (■), **9** (▲).

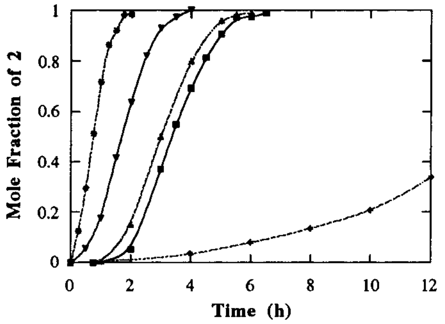

Figure 2. Time course for the reductive cleavage of **1** using different electrolytes. Electrolysis was conducted at 10 V with a 2 h pre-electrolysis. Electrolytes: $Zn(ClO_4)_2 \cdot 6H_2O$ (●), $Mn(ClO_4)_2 \cdot 6H_2O$ (▼), $Ni(ClO_4)_2 \cdot 6H_2O$ (▲), $Co(ClO_4)_2 \cdot 6H_2O$ (■), $LiClO_4$ (◆).

methyl β-D-glucopyranoside (**1**) and methyl α-D-mannopyranoside (**9**) were cleaved more slowly but at essentially the same rate. Therefore, these results demonstrate that it should be possible to accomplish electrochemical reductive cleavage of polysaccharides in a selective fashion by taking advantage of the susceptibilities of different types of glycosidic linkages to reduction.

To assess the potential of using the electrochemical method for selective reductive cleavage, the rates of reductive cleavage of permethylated methyl β-D-glucopyranoside (**1**) and methyl β-D-ribofuranoside (**5**) were examined using different electrolytes. As shown in Figure 2, the rate of cleavage of **1** in the presence of perchlorate salts was Zn(II) > Mn(II) > Ni(II) > Co(II) ≫ Li(I). Similarly, the rate of cleavage of permethylated methyl β-D-ribofuranoside (**5**) for Zn(II) salts (Figure 3) was $ClO_4^- > CF_3SO_3^- > BF_4^-$, possibly because of the order of activity of the parent acid in CH_2Cl_2.[10] On the basis of these results, we propose that electrolytes having different combinations of cations and anions can be used to achieve selective reductive cleavage of the glycosidic bonds in fully methylated glycans. It should be noted that this is the first report wherein transition-metal salts have been used as electrolytes for EGA generation. Indeed, transition-metal salts are much more reactive than Li salts, which were used previously.[5]

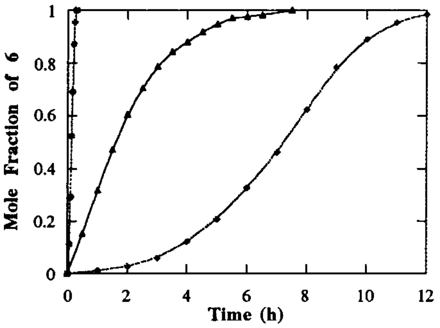

Figure 3. Time course for the reductive cleavage of **5** using different electrolytes. Electrolysis was conducted at 10 V with a 2 h pre-electrolysis. Electrolytes: $Zn(ClO_4)_2 \cdot 6H_2O$ (●), $Zn(CF_3SO_3)_2$ (▲), $Zn(BF_4) \cdot H_2O$ (◆).

Table 1. Mole Fractions of Products Derived by Electrochemically-Promoted Reductive Cleavage of Permethylated Glucans[a]

	mole fractions				
glucan	2	11	12	13	14
β-cyclodextrin			1.00		0.00
amylose	0.06		0.94		0.00
cellulose	0.03		0.97		0.00
nigeran	0.02	0.51	0.47		0.00
pullulan	0.06		0.63	0.31	0.00

[a] Electrolyzed at 10 V for 24 h with a 2 h pre-electrolysis using $Zn(ClO_4)_2 \cdot 6H_2O$ as the electrolyte and $BH_3 \cdot SMe_2$ as the reducing agent.

To examine the feasibility of using the electrochemical method for the analysis of polysaccharides, several glucans were subjected to electrochemical reductive cleavage and the products were identified by comparison to authentic standards.[11] Indeed, the results so-obtained (Table 1) are the same as those obtained using Lewis acids as promoters.[2a−c,9] However, in contrast to chemical methods, the electrochemical method tolerates traces of water. For example, compound **14**, which arises from 4-linked D-glucopyranosyl residues if traces of water are present,[2a,b] was not observed at all in the electrochemical method, even when a hydrated salt was used as the electrolyte. It should also be pointed out that the electrochemical procedure is experimentally much easier to perform than the chemical procedure and is much cleaner in an analytical sense.

In summary, reductive cleavage of permethylated carbohydrates can be achieved using an electrogenerated acid in the presence of $BH_3 \cdot SMe_2$. The electrochemical method is not moisture-sensitive and is easier and faster to perform than the chemical method. Furthermore, selective cleavage of glycosidic linkages may be achieved by the appropriate choice of electrolyte, and this may prove to be useful for sequencing polysaccharides.

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