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Electrochemical Bromination of Peracetylated Glycals

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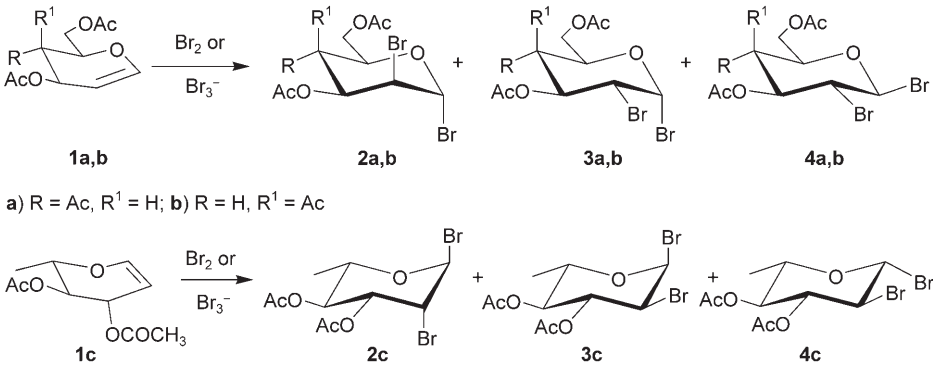
Abstract: Bromination of glycals with tribromides formed *in situ* from bromine and different bromide salts in dichloromethane (DCM) or acetonitrile (AN) was found to give predominantly the products of *anti* addition of bromine from the C-6 side in high yields. The same selectivity, which was much higher compared to bromination with bromine alone, was achieved in bromination of these substrates by anodic generation of bromine from the same salts.

Keywords: bromination; constant current electrolysis; glycals; tribromides

Due to the susceptibility of the carbon-halogen bond to be attacked by a wide range of reagents halogeno sugars represent an important class of compounds. First of all they are versatile starting materials in the synthesis of other carbohydrate derivatives, but also represent valuable chiral precursors in the syntheses of diverse non-sugar compounds. Among the halogeno sugars, those containing halogen atoms in positions 1 or/and 2 are of particular interest. Thus, according to the Koenigs–Knorr protocol[1] and its modifications, glycosyl bromides and chlorides have become by far the most frequently used glycosyl donors in *O*-glycosylation of both sugar and non-sugar compounds (aglycones).[2] Although the chemistry of carbohydrates has been dominated by this "natural" electrophilic reactivity of the anomeric carbon, glycosyl halides have been successfully applied also in the generation of the corresponding anomeric carbanions[3] and radicals.[4] 2-Halogenated sugars, on the other hand, are interesting as precursors for 2-deoxy sugars, since a halogen atom can be removed by reducing agents[5] or by photolysis.[6] Accordingly, 1,2-dihalogeno sugars also represent promising intermediates, as it has already been demonstrated.[7]

Although other methods have been reported,[8] addition of bromine to the corresponding glycals seems to be the simplest way to synthesize 1,2-dibromo sugars. However, this addition may lead to four possible diastereomeric products and the drawback of this methodology is the lack of stereoselectivity when free bromine is used. The first application of this reaction was reported by Fischer and co-workers in 1920,[9] who studied the addition of molecular bromine to 3,4,6-tri-*O*-acetyl-D-glucal. Nakamura and co-workers found, however, that these authors did not determine correctly the structure of the product(s)[10] and reported the formation of a mixture of D-*gluco*- and D-*manno* derivatives. At the same time Lemieux and Fraser-Reid reported that this reaction gave α-D-*gluco*- and α-D-*manno* derivatives in a 2:1 ratio.[11] They proposed a mechanism which leads to the products of thermodynamic control. Later investigations have shown, however, that the product distribution during bromination of peracylated glycals is under kinetic control, and that the stereoselectivity of the reaction depends on the polarity of solvents,[12] and even on the electron-withdrawing or -donating effect of the substituent at C-5.[12a] Considerably higher selectivity in the bromination of glycals was achieved by using quaternary ammonium tribromides as the bromine donating reagents.[13]

The inconvenience of handling elemental bromine, and even solid tribromides, prompted us to examine whether the electrochemical oxidation of bromides was a suitable way to perform the bromination of glycals. This was encouraged by recent successful application of bromine generated at the anode in the bromination of 5-unsaturated steroids[14] and estrogens.[15] In the present paper we report our first results obtained by studying the electrochemical bromination of three peracylated glycals, namely 3,4,6-tri-*O*-acetyl-D-glucal (**1a**), 3,4,6-tri-*O*-acetyl-D-galac-



Scheme 1. Bromination of glycals.

tal (**1b**), and 6-deoxy-3,4-di-*O*-acetyl-L-glucal (**1c**) (Scheme 1).

The investigations were conceptualized as the electrolysis of bromides in the presence of glycals in appropriate systems of solvents and electrolytes. Tetraethylammonium bromide (TEAB) in dichloromethane (DCM) and lithium bromide and acetonitrile (AN) were chosen as the electrolysis media. These solvents were selected because they are aprotic and their polarities are very different (dielectric constants: $\varepsilon_{CH_2Cl_2} = 8.90$ and $\varepsilon_{CH_3CN} = 37.50$). It was interesting to examine whether the distribution of isomeric 1,2-dibromo sugars by electrochemical bromination of glycals would follow the selectivity of the bromination by tetraalkylammonium tribromide, or with molecular bromine. Since literature reports on the bromination of **1a** with bromine even in the same solvents were contradictory,[11,12a,13a,c] first we brominated each substrate (**1a–c**) in DCM and AN by non-electrochemical methods. In this way we had the possibility to compare classical chemical and electrochemical brominations under the same conditions, particularly considering the fact that bromination in aprotic media could be affected considerably by trace impurities, and a very careful control of the reaction conditions was needed to avoid scatter in the results.[16]

Thus, when we treated glycal **1a** with free bromine in DCM, two of the four possible isomeric 1,2-dibromo sugars, namely α-D-mannose (**2a**) and α-D-glucose derivative (**3a**; see Scheme 1), were obtained in a 93% overall yield. The ratio *manno/gluco* = 19:81 (see Table 1, run 1) pointed to the *syn* addition of bromine from the α-side as the main reaction pathway. This result is almost the same as that reported by Ruasse and co-workers for bromination in dichloroethane,[13c] and similar to Lemieux and Fraser-Reid's results on bromination in chloroform.[11] However, this finding differs considerably from other literature reports on bromination of the same substrate in dichloroethane, chloroform and ethyl acetate,[11,12,13a] particularly because we did not obtain the β-D-*gluco* derivative **4a**.

Table 1. Chemical bromination of glycals with molecular bromine without and with additives.

Run	Substrate	Solvent	Brominating agent	Product distribution [%][a,b]		
				2	**3**	**4**
1	**1a**	DCM	Br_2	19	81	
2	**1a**	DCM	Br_2/TEAB[c]	88	12	
3	**1a**	DCM	Br_2/TBAB[c]	89	11	
4	**1a**	DCM	Br_2/CTAB[c]	80	20	
5	**1a**	DCM	Br_2/KBr/18-crown-6[d]	77	23	
6	**1a**	AN	Br_2	72	28	
7	**1a**	AN	Br_2/LiBr[c]	90	10	
8	**1b**	DCM	Br_2	17	65	18
9	**1b**	DCM	Br_2/TEAB[c]	85	15	
10	**1b**	AN	Br_2/LiBr[c]	80	20	
11	**1c**	DCM	Br_2	31	60	
12	**1c**	DCM	Br_2/TEAB[c]	77	23	
13	**1c**	AN	Br_2/LiBr[c]	81	19	

[a] Overall yield up to 95%.
[b] Determined from ^{1}H NMR spectra of the reaction mixture.
[c] In a ratio 1:1.
[d] In a ratio 1:1:1.

Having in mind the basic intention to generate bromine at the anode in bromide-containing media, we treated compound **1a** with Br_2 in dichloromethane in the presence of TEAB, in order to have the exact parameters for the comparison of classical and electrochemical methodologies. As we expected, the results were almost the same as those reported by Lafont[13a] and Ruasse[13c] for the bromination with solid tetraalkylammonium tribromides, that is, the main product was the α-D-*manno* derivative **2a**, as the result of an *anti* addition from the β-side. It pointed to the *in situ* formation of tetraethylammonium tribromide (TEATB) and its further action. Additional experiments were devoted to checking whether cations of *in situ* formed tribromide salts did or did not play any role in this reaction. Thus, we brominated **1a** in DCM

with bromine in the presence of tetrabutylammonium bromide (TBAB), cetyltrimethylammonium bromide (CTAB) and a KBr/18-crown-6 combination. It turned out that the stereochemistry of this reaction is almost independent of the character of cation, since the α-D-*manno* derivative **2a** was the predominant product (Table 1, runs 3–6).

Bromination of **1a** in AN with free bromine, without any additive gave results which were different from bromination in DCM. The main product in this case was the α-D-*manno* derivative **2a** (see Table 1, run 6). Selectivity in formation of this compound increased with the use of lithium bromide as an additive (Table 1, run 7).

The other two glycals, **1b** and **1c**, were brominated under conditions that we selected on the basis of above results as the most promising for the synthetic application. Namely, these substrates were subjected to bromination with bromine without any additive in DCM (in order to obtain predominantly the products of *syn*-addition from the α-side) and with Br_2/TEAB/DCM and Br_2/LiBr/AN combinations (in order to obtain predominantly the products of *anti*-addition from the β-side). The obtained results are listed in Table 1. As can be seen, galactal **1b** and glucal **1a** behave differently in bromination with bromine in DCM without a catalyst. In addition to the minor product of *anti* addition from the β-side (α-*talo* derivative **2b**), under these conditions **1b** gave both the *syn* and *anti* addition products from the α-side, that is, both anomers of per-*O*-acetylated 2-bromo-2-deoxy-D-galactopyranosyl bromides (**3b** and **4b**). The *talo*/*galacto* ratio in this bromination was, however, almost the same as the *manno*/*gluco* ratio in bromination of **1a** (17:83 *vs.* 19:81). Bromination of **1b** with bromine in the presence of bromide salts (TEAB in DCM and LiBr in AN) proceeded with high selectivity, giving mainly the α-*talo* derivative **2b**, as the product of an *anti* addition from the β-side, similarly to brominations with tetraalkylammonium tribromides.[13].

Bromination of substrate **1c** gave results very similar to **1a** (Table 1, runs 11–13).

Considering these results we conclude that the electrochemical bromination of glycals should proceed in a way similar to reactions of these substrates with bromine/bromide combinations, i.e., it should exhibit a selectivity similar to that reported in the literature for brominations with solid tetralkylammonium tribromides.[13a,c] Before the preparative electrochemical bromination we performed some cyclovoltammetric measurements. We examined the electrochemical behaviour of glucal **1a** in the presence of bromide in DCM and in AN. This substrate and bromide ions have first been analyzed separately. Figure 1 (dashed lines) displays the voltammograms of glycal at a Pt electrode. No oxidation or reduction wave appears in both solvents and therefore glycal is not electroactive in the potential window of interest. As shown in Figure 1 (solid lines), bromide ions (i.e., TEAB in DCM and LiBr in AN) exhibit two well-defined oxidation waves (O_1 and O_2 at 420 and 730 mV in DCM, i.e., 340 and 600 mV in AN, respectively) on the forward potential sweep and two reduction waves (R_1 and R_2 at −180 and 400 mV, that is, −70 and 460 mV).

Peak currents of waves O_1 and O_2 are in a 2:1 ratio for both solvents. In addition, anodic and cathodic waves are proportional to the concentration of bromide ions (data not shown). This behaviour is in good concordance with already reported data on the oxida-

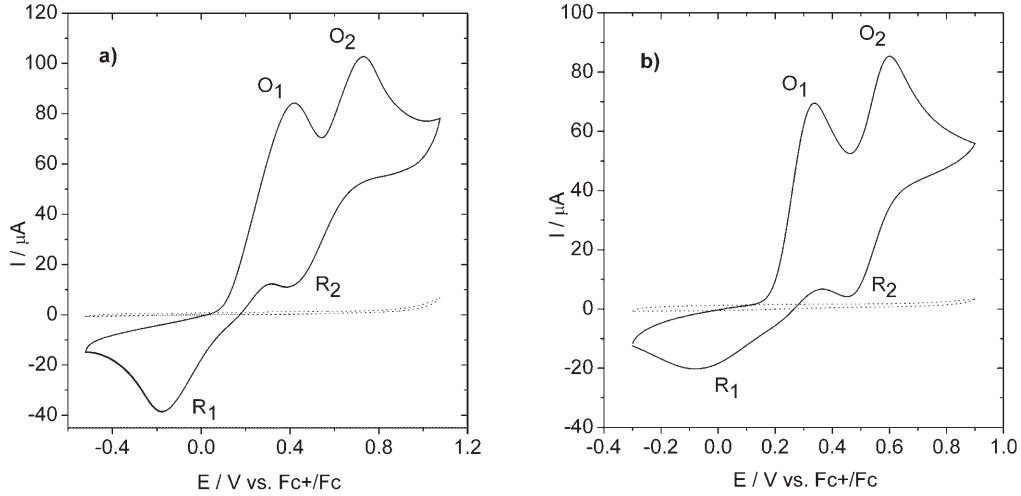


Figure 1. Cyclic voltammograms for the oxidation of 5 mM bromide (**a**) in dichloromethane and (**b**) in acetonitrile. Also shown are the voltammograms (dashed lines) for 2 mM glucal **1a** alone (**a**) in dichloromethane and (**b**) in acetonitrile. All solutions contained 0.05 M Et_4NClO_4 as supporting electrolyte. Scan rate: 0.1 $V \cdot s^{-1}$. Electrode: Pt (2 mm diameter). Counter-electrode: Pt wire.

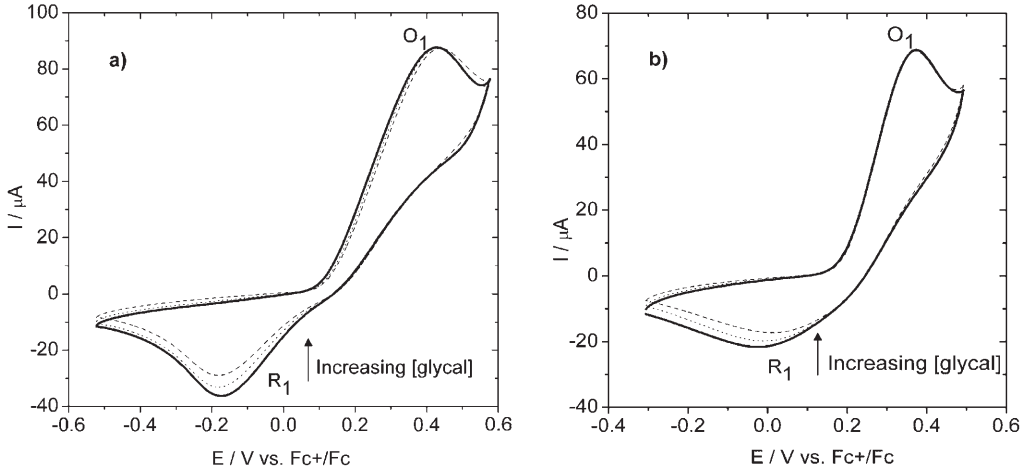


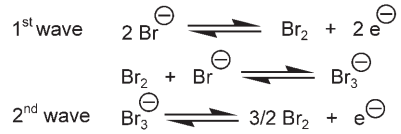
Figure 2. Cyclic voltammograms of (**a**) 5 mM TEAB in dichloromethane and of (**b**) 5 mM LiBr in acetonitrile with increasing glycal concentrations. Solid line: no glycal; dotted line: 1 mM glycal; dashed line: 2 mM glycal. All solutions contain 0.05 M Et_4NClO_4 as supporting electrolyte. Scan rate: 0.1 V·s^{-1}. Electrode: Pt (2 mm diameter). Counter-electrode: Pt wire.

tion of bromide at Pt electrode in different solvents.[17] The O_1 wave corresponds to the electro-oxidation of bromide which leads to the formation of molecular bromine, Br_2. This heterogeneous reaction is followed by the addition of bromide to the electrogenerated bromine forming thus the tribromide anion, Br_3^-. At the higher potentials corresponding to the O_2 wave, tribromide dissociates and forms Br_2.[17] On the backward potential sweep, the R_1 and the R_2 waves are due to the corresponding reverse processes. The shape of the R_1 wave is less well-defined probably because a chemical step follows the electron transfer reaction. All these processes are summarized below.

The reactivity of the electrogenerated bromine has been studied in the presence of various concentrations of glycal in both solvents. Typical voltammograms are represented on Figure 2.

The influence of glycal on waves R_1 and R_2 has been investigated using cyclic voltammetry. By adding glycal to the solution, the peak current of wave O_1 remains constant since glucal **1a** is not electroactive as seen on Figure 1 while the peak current of wave R_1 decreases. This decrease is directly related to glycal. The voltammograms are affected in the same manner for both solvents (Figure 2 a and b). The cathodic R_2 wave is not modified by the addition of glycal (data not shown). In the presence of glucal **1a**, the decrease of the R_1 wave arose as a consequence of the partial homogeneous reaction of the electrogenerated product with **1a**. This shows that tribromide is the chemical species reacting directly with glucal **1a**.

According to Scheme 2, both bromine and tribromide exist in the solution through the electrolysis of a bromide salt. As our results in brominations of glycals with bromine without and in the presence of bromides showed, the reaction of bromine with the bromide to form tribromide is a faster process than addition of free bromine to glycal. Knowing that, we started the preparative electrochemical bromination of glycals by the simplest way – compound **1a** was submitted to constant current electrolysis (50 mA, 2 F/mol) in 0.05 M solution of TEAB in DCM, using an undivided cell, supplied by platinum and aluminum plates as an anode and a cathode, respectively. Analysis of the reaction mixture showed that more than 50 % of the starting substrate remained unchanged, but the consumed part of it was converted mainly into the *manno* derivative **2a**. Apparently, an important part of the flowed electric charge was spent by some side reactions, possibly by cathodic reduction of the species formed by anodic processes. In general, such a problem could be solved by electrolysis in a divided electrolytic cell. Thus, when constant current electrolysis (20 mA) was performed in the cell in which the platinum anode was separated from the aluminum cathode by the membrane (a ceramic probe) the substrate **1a** placed in the anodic compartment was completely brominated after consuming 2 F/mol charge. Selectivity of the reaction was the same as in the cases of bromination of this substrate with tetraalkylammonium tribromides[13a,c] and with bromine in the presence of bromide salts (Table 2, run 1). The electrolysis in which the combination KBr/18-crown-6 = 1:1 as the electrolyte was used in the same solvent gave also **2a** as the main product.



Scheme 2. Electrode reactions.

Table 2. Electrochemical bromination of glycals.

Run	Substrate	Solvent	Electrolyte	Product distribution[a,b]	
				2	**3**
1	**1a**	DCM	0.05 M TEAB	90	10
2	**1a**	DCM	0.05 M KBr/18-crown-6	93	7
3	**1a**	AN	0.2 M LiBr	90	10
4	**1b**	DCM	0.05 M TEAB	92	8
5	**1b**	DCM	0.05 M KBr/18-crown-6	95	5
6	**1b**	AN	0.2 M LiBr	88	12
7	**1c**	DCM	0.05 M TEAB	82	18
8	**1c**	DCM	0.05 M KBr/18-crown-6	84	16
9	**1c**	AN	0.2 M LiBr	82	18

[a] Overall yield up to 95%.
[b] Determined from ^{1}H NMR spectra of the reaction mixture.
[c] In the anodic compartment 1.1 mol of TEAB per mol of the substrate was added.

Electrochemical experiments in which AN has been used as the solvent and LiBr as the electrolyte gave completely the same results as those performed in DCM, as well as those performed in AN using the bromine/LiBr combination in classical chemical methods.

This electrochemical methodology was applied to the bromination of the other two substrates. The obtained results are given in Table 2, and exhibit that this method leads to the same products as the classical ones, that is, the main products of bromination of glycals were products of an *anti* addition from the β-side (**2b**, **c**).

In conclusion, our investigations showed that bromination of glycals could be performed using *in situ* formed tribromides with the same selectivity as it was reported for bromination with solid teraalkylammonium tribromides. Moreover, we showed that this bromination could be achieved with the same selectivity by electrochemical oxidation of bromides to bromine. This electrochemical method is very simple and does not require complex and expensive equipment. Although tetraalkylammonium tribromides (used in the existing methods for bromination of glycals) are commercially available, they are irritant and sensitive reagents. Their storage and handling requires serious caution. The main advantage of the present electrochemical method is that these salts, as well as potassium and lithium tribromides could be formed *in situ*, avoiding the mentioned problems. Bearing in mind also an excellent dosage control (by simple current control) in this case, what is not easy in many classical methods when a solid should be gradually introduced into the reaction mixture, this procedure might be recommended as the superior one.

Experimental Section

All chemicals were commercially available and used as received, except that the solvents were purified by distillation. Cyclic voltammetry curves were obtained by using a CH Instruments (Austin, TX) potentiostat CHI760b Electrochemical Workstation. A standard three-electrode cell (5 mL), equipped with a platinum wire and a silver wire immersed in 0.1 M TEAB solution in CH_3CN as the counter and reference electrode, respectively. A platinum disk ($d = 2$ mm) was used as the working electrode, and all potentials are given with respect to the Fc^+/Fc couple. A cylindrical glass vessel equipped with a magnetic stirrer, a cylindrical platinum foil as the anode (Ø = 2.5 cm), a ceramic tube as the membrane (Ø = 1.5 cm), and an aluminum spiral as the cathode was assembled as the divided electrochemical cell for preparative electrolysis. A Uniwatt Beha Labor-Netzgerät (NG 394) was used as a direct current source for the electrolysis. NMR spectra were recorded on a Varian Gemini (200 MHz) spectrometer, using $CDCl_3$ as the solvent and TMS as the internal standard. Chemical shifts are expressed in δ (ppm). For TLC, silica gel 60 on Al plates, layer thickness 0.2 mm (Merck), was used.

General Procedure for Chemical Bromination of Glycals

A glycal (1 mmol) without or with the additive (1.1 mmol; see Table 1) was dissolved in DCM or AN (10 mL), protected from the light, and cooled in an ice bath. To this mixture 1.1 mmol of Br_2 dissolved in 0.22 mL of DCM was added in one portion, and stirring continued for 2 h. If DCM was used as the solvent, the reaction mixture was successively washed with a 1 M aqueous solution of $Na_2S_2O_3$, water and brine, and dried over anhydrous Na_2SO_4. Evaporation of the solvent gave a mixture of dibromides in 90–95% overall yields. The mixtures were analyzed by NMR spectroscopy without separation. 18-Crown-6, when used, was separated from the sugar derivatives by column chromatography (SiO_2/toluene-ethyl acetate, 9:1). If the reaction was carried out in AN, the solvent was evaporated, water (10 mL) added to the rest and the mixture extracted with DCM (2 × 10 mL). The obtained DCM solution was treated as described above.

Compounds **2a–c** and **3a–c** are known, and their spectra were in agreement with those given in the literature.[8,11,12a,b,13a]

In the ^{1}H NMR spectrum of the mixture obtained from **1b** by bromination in DCM without additives (Table 1, run 1), in addition to signals belonging to known dibromides **2b** and **3b**, a doublet appeared at 5.60 ppm. On the basis of the chemical shift and coupling constant (9.6 Hz) we concluded that it corresponded to an axial anomeric H atom, neighbouring to another axial H atom, that is, it belongs to 3,4,6-tri-*O*-acetyl-2-bromo-2-deoxy-β-D-galactopyranosyl bromide (**4b**). In the ^{13}C NMR spectrum of this mixture the signal at 81.9 ppm should belong to C-1 of **4b**.

General Procedure for Electrochemical Bromination of Glycals

0.5 mmol of a substrate **1a–c** and 25 mL of a solution of the corresponding electrolyte (see Table 2) were placed in the anodic compartment of the cell (outside the ceramic tube). The same solution of the electrolyte (3 mL) was used as the catholyte. The constant current electrolysis (20 mA) was stopped after 85 min (calculated to provide 5% more than 2 F/mol charge). The resulting reaction mixture was worked up as in the case of above described classic experiments.

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