Turk J Chem
26 (2002) , 317 – 322.

Steric Effects on the Oxidation Potential of 1-aryl Thioglycosides

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Received 21.08.2000

The electrochemical oxidation of several 1-arylthioglycosides has been studied by cyclic voltammetry in acetonitrile. We found that the oxidation potential of the α anomer always occurs at a less positive oxidation potential than of the β anomer. The difference in the oxidation potential depends on the substituent attached on the C-3 of the sugar moiety and is greatly influenced by the stability of the radical cation obtained after the first electron transfer.

Key Words: Thioglycosides, cyclic voltammetry, oxidation potentials, steric effects.

Introduction

There has been over the past ten years a considerable interest in the synthesis of modified nucleosides since the discovery of AZT (3'-azido-3'-deoxythymidine) and other sugar-modified nucleoside analogues, as potent antiviral agents against the human immunodeficiency virus (HIV).[1] Along with other popular methods, aryl or alkyl S-glycosides have been widely used to build desired molecules.[2] These starting materials are ideal precursors of three classes of reactive intermediates: anomeric carbeniums, anions and radicals. Thus, they play an important role in carbohydrate chemistry at the anomeric carbon atom. Thioglycosides have received considerable attention as glycosating agents because of their chemical stability during various chemical transformations, and relatively easy synthesis.[3] Usually, activation of the 1-thioglycosides involves the formation of a reactive sulphonium intermediate through a two-electron process, taking advantage of the well-known affinity of the sulphide group for soft electrophiles.[4,5] One of the easiest ways to generate a carbenium centre is through an electron transfer activation of the sulphide group to give a reactive radical cation. Such milder conditions have been elegantly developed by Amatore and Sinaÿ[6] for the preparation of *O*-glycosides and disaccharides; both chemical [with the commercially available tris(4-bromophenyl)ammoniumyl hexachloroantimonate radical cation[7]] and electrochemical activations were used. The principle of this glycosidation method can be written as follows:

$$\begin{aligned} \text{Ar-S-R} &\longrightarrow [\text{Ar-S-R}]^{+\cdot} + \text{`e'} \\ [\text{Ar-S-R}]^{+\cdot} &\longrightarrow \text{ArS}^{\cdot} + \text{R}^{+} \\ 2\ \text{ArS}^{\cdot} &\longrightarrow \text{Ar-S-S-Ar} \\ \text{R}^{+} + \text{NuH} &\longrightarrow \text{products} \end{aligned}$$

where 'e' = electrode or oxidising agent and NuH = H_2O, R'OH or CH_3CN

As a part of an ongoing program into the synthesis and biological evaluation of purine-like *C*-nucleosides[8], we became interested in the possibility of using the electrochemical approach to elaborate a new and more straightforward synthesis of such molecules. Our strategy was to use a series of 1-thioglycosides as starting materials for preparative electrochemical oxidation and to trap the oxocarbenium intermediate with purine and pyrimidine bases to obtain the desired *C*-nucleosides.

During our investigations on the cyclic voltammetric analyses of different α and β anomers of 1-thioglycosides, we found an interesting 'anomeric' effect on the oxidation potentials of the different thioglycosides. We wish to report herein our findings and a possible explanation of this difference of the oxidation potential, on the basis of the stability of the radical cation primarily obtained after the first electron transfer.

Experimental

NMR spectra were obtained on a Bruker AC 200 instrument operating at 200 MHz for ^{1}H NMR. All reactions and manipulations were conducted under a dry nitrogen atmosphere. Cyclic voltammetry was performed using a 'home-made' potentiostat [9] with positive feedback ohmic drop compensation and a Tacussel GSTP4 signal generator. The working electrode was a glassy carbon (Tokai Corp.) disc (3 mm diameter) and the reference electrode was Ag/$AgNO_3$ 10^{-2} M in CH_3CN. The supporting electrolyte was tetrabutylammonium hexafluorophosphate (NBu_4PF_6; Fluka *puriss.*). All solvents are of commercial origin and were used as such. Reactions were monitored by TLC on silica gel 60 F_{254} (Merck) with detection by charring with H_2SO_4. Flash column chromatography was performed on silica gel (40-60 μm, Merck). Sugar derivatives **1a** and **1b** were prepared according to procedures described in reference 16. Both anomers α and β were separated with the Chromatotrone (Harrison Research) technique. Derivatives **2a** and **2b** were prepared from the corresponding phenyl 3,5-di-*p*-nitrobenzoyl-2-deoxy-$\alpha(\beta)$-D-1-methoxy (itself prepared according to reference 11) according to reference 10. Compound **3** was prepared according to reference 12. Deprotected sugar derivatives **4a** and **4b** were prepared from the α/β mixture of **3** according to reference 19 and both anomers were separated by flash chromatography. Derivatives **5a** and **5b** were prepared according to reference 12 and deprotection was performed according to reference 13 to give sugar **6**.

Results and Discussion

The synthesis of the 2,3,5-tris-*O*-benzoyl-$(\alpha)\beta$-D-1-thiofuranosides have been described in the literature and both anomers were used as model substrates. Their structures are represented in Figure 1.

On a glassy carbon electrode, the 2,3,5-tris-*O*-benzoyl-α-D-1-thiofuranoside **1a** exhibits two close irreversible oxidation waves (E_{p1} = +1.17 V and E_{p2} = +1.28 V *vs* Ag/$AgNO_3$ 0.01 M, peak potential at 0.2 V s^{-1}; Figure 2a) in CH_3CN + 0.1M NBu_4PF_6. Both waves correspond to a one-electron transfer

(as compared to the one-electron reduction wave of 9-fluorenone in the same electrolytic medium). In contrast 2,3,5-tris-*O*-benzoyl-β-D-1-thiofuranoside **1b** exhibits only one bi-electronic irreversible oxidation wave located exactly at the same potential of the second electron transfer of the α anomer (E_p = + 1.28 V *vs* $Ag/AgNO_3$ 0.01 M, peak potential at 0.2V s^{-1}; Figure 2b). All oxidation steps remain irreversible up to 500 V s^{-1} demonstrating the instability of the radical-cation followed by a subsequent chemical step.

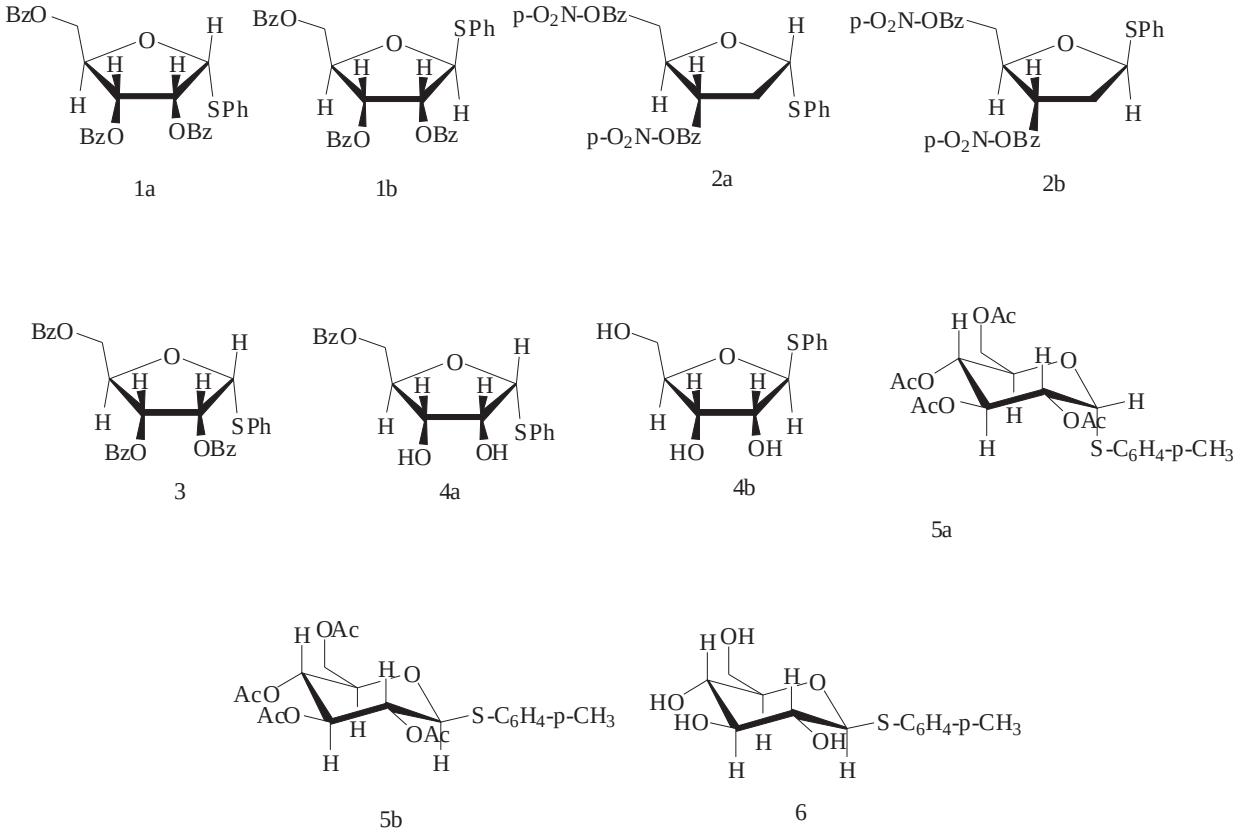


Figure 1. Structures of the sugar derivatives studied in this work (Bz = benzoyl, Ph = phenyl, Ac = acetyl)

All the α anomers studied in this work (compounds **1a**, **2a**, **3**, **4a**, and **5a**) exhibit two close oxidation steps and the β anomers (compounds **1b**, **2b**, **4b**, **5b**, and **6**; Table) a bi-electronic oxidation wave. For the sugar derivatives **5a** and **5b**, having an acetyl group to protect the hydroxyl function, adsorption of the substrates (or of the oxidised products) was observed on glassy carbon and platinum electrodes. For compounds **2a** and **4a**, the two oxidation steps are not well resolved. From the literature, it is well known that alkyl phenyl sulphides (PhSR) are easily oxidised anodically to provide a radical-cation $(PhSR)^{\cdot +}$ which may undergo S-R bond cleavage to give the thiyl radical ($PhS^{\cdot}$) and the cation R^+.[14–19] In agreement with the literature, we found that the diphenyl disulphide exhibits two irreversible oxidation waves (E_{p1} = +1.27 V and E_{p2} = + 1.45 V *vs* $Ag/AgNO_3$ 0.01 M, peak potential at 0.2V s^{-1}; Figure 2c).

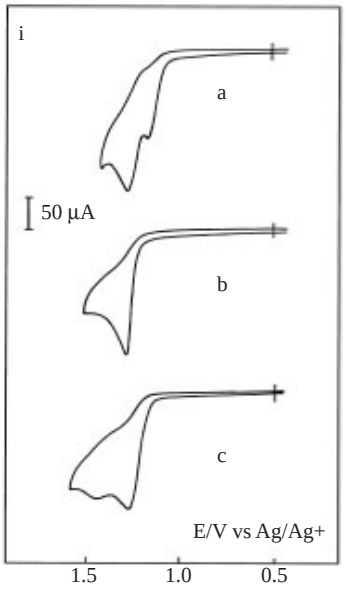


Figure 2. Cyclic voltammetry of the 2,3,5-tris-O-benzoyl-(α)β-D-1-thiofuranosides in CH_3CN + 0.1M NBu_4PF_6. (a) **1a** (C=2.1 mM), (b) **1b** (C=1.8 mM) and (c) PhSSPh (C=2.0 mM); glassy carbon electrode, scan rate 0.2 V s^{-1}.

Table 1. Oxidation potentials of the arylthioglycosides in CH_3CN + 0.1 M NBu_4PF_6. C = 2 mM, glassy carbon electrode, scan rate = 0.2 V s^{-1}.

Compound	$Ep_{(ox)}$ (V vs Ag/Ag^+ 0.01 M)	$\Delta Ep_{(ox)}(\alpha, \beta)$ (mV)
1a	1.170 ; 1.280	
1b	1.280	110
2a	1.175 ; 1.210	
2b	1.210	35
3	1.170	-
4a	1.010 ; 1.140	
4b	1.140	130
5a	1.172 ; 1.275	
5b	1.275	103
6	1.160	-

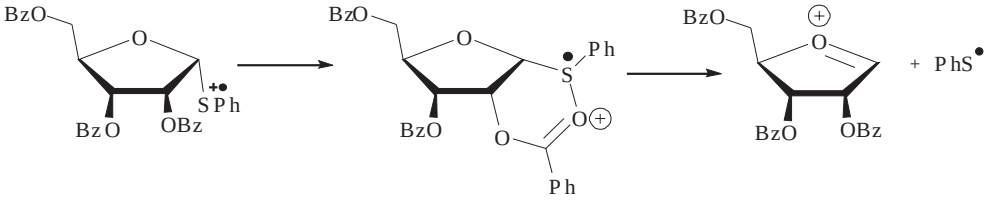
Oxidation of the arylthioglycosides should lead to the formation of the radical $PhS^{\cdot}$, which undergoes fast dimerisation giving PhSSPh, and also to the formation of the oxocarbenium cation. The oxocarbenium cation as well as the PhS cation can then undergo further chemical reactions with nucleophiles such as water or acetonitrile. In the case of the β anomers, potentials E_1 and E_2 are similar, which means the oxidation of the starting arylthioglycoside and PhSSPh occur at the same potential. In the case of the α anomers, the starting arylthioglycosides are easier to oxidise than PhSSPh: $E_1 < E_2$ (Scheme 1).

$$
\begin{aligned}
\text{RSAr - 1e} &\xrightarrow{E_1} \text{RSAr}^{+\bullet} \\
\text{RSAr}^{+\bullet} &\xrightarrow{k_1} \text{R}^{\oplus} + \text{ArS}^{\bullet} \\
\text{2 ArS}^{\bullet} &\longrightarrow \text{ArSSAr} \\
\text{ArSSAr - 1e} &\xrightarrow{E_2} \text{ArS}^{+} + \text{ArS}^{\bullet} \\
\hline
\text{RSAr - 2e} &\longrightarrow \text{R}^{\oplus} + \text{ArS}^{+}
\end{aligned}
$$

Scheme 1

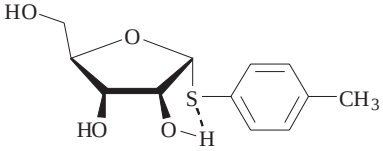
For the phenyl-2,3,5-tris-O-benzoyl-D-thiofuranoside, as well as for the thiopyranosides, β anomers are oxidised at a more positive potential than the α anomers (the peak potential difference is usually close to 100 mV).

The α anomer is probably easier to oxidise because of a stabilising effect from the radical cation with the oxygen of the benzoyl group and, therefore, cleavage of the C-S bond becomes more difficult (Scheme 2).



Scheme 2

For the β anomers, the oxygen atom of the benzoyl group is far from the sulphur atom, therefore facilitating the cleavage of the radical cation. For compounds **2a** and **2b** (the deoxy sugar derivatives), we would have expected a similar oxidation potential for both α and β anomers, but the experiments showed that there is in fact a small peak potential difference (35 mV, Table). Molecular models show that the oxygen of the benzoyl group is close to the sulphur in the radical cation intermediate, but that stabilisation is not strong enough due to a longer O-S distance. In the case of compound **3**, the methyl substituent of the thiotoluyl ring facilitates in some extent the stabilisation of the radical cation; its oxidation potential is 110 mV, more positive than **1a**. In the case of compounds **4a** and **4b**, the peak potential difference observed can be explained by a hydrogen bond formation in the anomer α:



The acetyl protecting group has the same stabilising effect for compounds **5a** and **5b** compared with the benzoyl group.

In all cases, the β anomers of the sugar derivatives were found to be oxidised at more positive potentials than their α anomers. Such a difference could be interpreted in terms of a stabilisation effect of the radical cation or on steric effects depending on the protecting group of the hydroxyl substituents.

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