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Determination of the absolute configuration of sulfinyl glycosides: the role of the *exo*-anomeric effect

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Abstract

The diastereoselective synthesis and conformational study of α- and β-ethylsulfinylglycosides have been studied. It was found that while β-(S_S)-sulfinyl glycosides are flexible β-(R_S)-sulfinyl glycosides exists in a major conformation stabilized by the *exo*-anomeric effect. The generality of the hyperconjugative delocalisation gives rise to a general rule for the determination of the absolute configuration of sulfinyl glycosides by ^{1}H or ^{13}C NMR spectroscopy without need of chemical shift reagents. © 2000 Published by Elsevier Science Ltd.

Access to structurally diverse chiral sulfoxides is an important synthetic challenge, as the sulfinyl group promote high stereocontrol in a plethora of chemical transformations.[1] To the best of our knowledge there is no report on the utilisation of sulfinylglycosides with a chiral sugar backbone in such transformations. The main limitation for these applications relies on the absence of a simple and general method allowing the determination of the absolute configuration of the stereogenic sulfinyl sulfur. Beside X-ray crystallography, the widely used approach for the determination of absolute configuration of chiral sulfoxides has been the utilisation of NMR spectroscopy using chiral shift reagents.[2] The success of using chiral shift reagents as a tool for the elucidation of the configuration of sulfoxide depends on the stability of the complex formed by hydrogen bonds between their acidic OH groups and the basic sulfinic oxygen. Nevertheless the chemical shift differences between the diastereomeric complexes are usually very small or nonsystematic. As a part of our continuous interest in the synthesis of chiral sulfoxides[3] we report here a general study on the diastereoselective oxidation of thioglycoside, and a simple method for the determination of the absolute configurations of the obtained sulfinyl glycosides. The method is a simple analysis of ^{1}H or ^{13}C NMR data without using chiral shift reagents, based on the different conformation of the two diatereomeric sulfoxides and on

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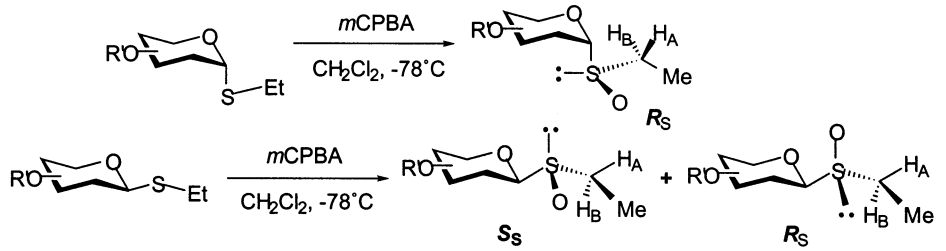
the *exo*-anomeric effect.[4] The synthesis of sulfinyl glycosides was achieved in high yield by oxidation of the parent thioglycosides in CH_2Cl_2 at −78°C in order to avoid the formation of the corresponding sulfone (Scheme 1).[5]



Scheme 1. Oxidation of α- and β-ethylthioglycosides with *meta*-chloro perbenzoic acid (*m*-CPBA)

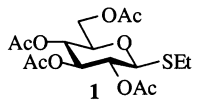
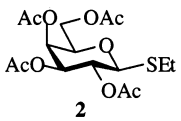
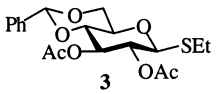
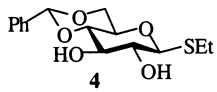
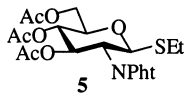
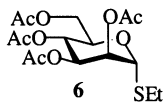
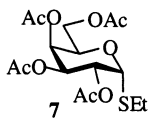
As can be seen in Table 1, the diastereoselectivity ranges from 0 to >95%, depending mainly on the configuration of the anomeric carbon (α or β), and on the substituent at the C-2 position in β anomers.[6] A major isomer is obtained in the oxidation of α-thioglycosides,[7] while a mixture of isomers is always obtained in the case of β-thioglycosides. We observed that the methylene protons α to the sulfinyl group exhibited quite different ^{1}H NMR signal patterns and chemical shifts (Table 1) depending on the configuration of the sulfinyl sulfur. It is a general feature that in all the obtained β-sulfinylglycosides, (Table 1, entry 1–6) the non-equivalence ($\delta\nu$) of the diastereotopic protons $H_{pro\text{-}R}$ and $H_{pro\text{-}S}$ vicinals to the sulfoxide group is larger in the minor isomer (around 170 Hz), than in the major isomer (around 30 Hz). The configuration of the sulfinyl sulfur of $3R_S$ and $3S_S$ is known,[2b] and that of the $4R_S$ and $4S_S$ has been determined in a previous study,[8] and confirmed by Zemplen deacetylation, allowing the correlation of the large and the small non-equivalence with the *R* and the *S* absolute configuration of the sulfinyl sulfur, respectively.

In all the cases, the C2–H proton of the S_S diastereoisomers is more shielded as compared with C2–H proton of the R_S diastereoisomers. 1D DPFGSE NOESY experiments in $CDCl_3$ of compound $3R_S$ shows an intense transglycosidic NOE between the anomeric proton and the more shielded fragment of the ABX_3 system, together with a week transglycosidic NOE contact between H-1 and the deshielded part of the ABX_3 system. All together these data are indicative that the favoured conformation at equilibrium is the conformation stabilised by the *exo*-anomeric effect[9] (Fig. 1).

In this conformation, the anomeric proton is close to the H-proR, the O-5 is in a *syn* relationship with H-proS and is responsible for the splitting of the two protons, while the *syn* relationship of the sulfinyl oxygen and the H-2 proton is responsible for the deshielding effect observed for H-2 protons. In agreement with the assumption of an n-σ* hyperconjugative delocalisation in the R_S and not in S_S diastereomers (Fig. 1), is the observation of the shielding of the anomeric carbon observed for all the R_S sulfinyl glycosides (Table 1). This important experimental observation which supports the hyperconjugative origin of the *exo*-anomeric effect gives rise to a general empirical rule for the assignation of the absolute configuration of alkyl and aryl sulfinyl glycosides.[10]

The high diastereoselection observed in the oxidation of α-thioglycosides in favour of the R_S sulfinyl glycoside can be rationalised by the inaccessibility of the pro-*S* lone pair to the oxidant, dictated by steric effects and the imposed *exo*-anomeric conformation, as recently proposed in

Table 1
Diastereoselective oxidation of ethylthioglycosides: chemical shifts, data for the anomeric carbon and for the methylene protons α to the sulfinyl group in the obtained sulfinyl glycosides

Entry	thioglycoside	Major Product ($\Delta\nu = \delta_A - \delta_B$)[a] C-1 (δ ppm)	Minor Product ($\Delta\nu = \delta_A - \delta_B$) C-1 (δ ppm)	Ratio (S / R)[b]
1		**1**S_S (30.5 Hz) 89.8	**1**R_S (158.4 Hz) 86.5	2.3 / 1
2		**2**S_S (18.8 Hz) 90.3	**2**R_S (177.4 Hz) 87.0	2.2 / 1
3		**3**S_S (24.9 Hz) 90.3	**3**R_S (185.6 Hz) 87.3	1 / 1
4		**4**S_S (0 Hz) 89.4	**4**R_S (170 Hz) 89.0	9 / 1
5		**5**S_S (30.5 Hz) 85.0	**5**R_S (158.4 Hz) 83.4	3 / 1
6		**6**R_S (66.8 Hz), (65 Hz)[d] 90.7[d]	**6**S_S (225 Hz)[d] 87.1[d]	1 / 5
7		**7**R_S (61.2Hz), (20 Hz) 87.6	----[c]	0 / 1[c]

All reactions were carried out at -78°C in dry CH_2Cl_2, using 1.05 equ. of mCPBA, [a] Determined on the crude mixture,
[b] Determined by ^{1}H NMR analysis of the crude in $CDCl_3$,
[c] No trace of the S_S isomer was detected neither by ^{1}H NMR nor by ^{13}CNMR analysis of the crude.
[d] Data taken in C_6D_6.

the oxidation of α-mannosyl thioglycosides (Fig. 2). The observed non-equivalence (around 70 Hz) is a consequence of the relative flexibility of C1–S due to the absence of the stabilising *exo*-anomeric effect.[11]

In conclusion, we have demonstrated that the difference in the chemical shift of the diastereotopic protons α to the sulfinyl sulfur serves as conformational probe (Fig. 2) to indicate either the flexibility or the rigidity of the glycosides and give rise to a general rule to determine the absolute configuration of sulfinyl glycosides by NMR spectroscopy. In the case of the rigid β-(R_S)-sulfinyl glycosides, the shielding of the anomeric carbon support an hyperconjugative delocalisation of the lone pair of the sulfinyl sulfur to σ* orbital of the C1–O5 bond. The easy determination of the sulfinyl sulfur configuration will stimulate the synthetic utilisation of

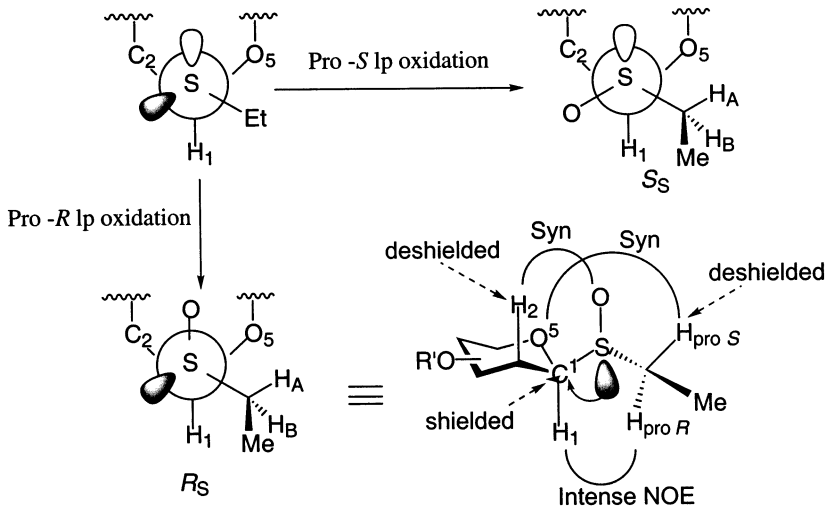


Figure 1. Newman projection of β-ehylthioglycoside, β-(R_S)-sulfinyl glycosides and β-(S_S)-sulfinyl glycosides

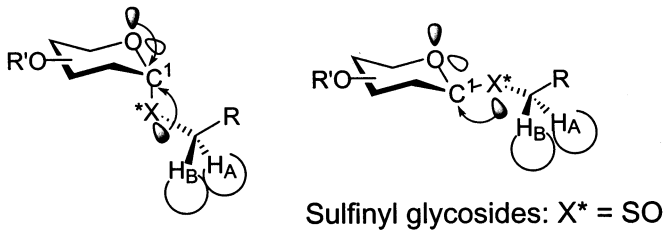


Figure 2. H_A and H_B as NMR sensitive probe to visualise the *exo*-anomeric effect

sulfinyl glycosides in fields such as in asymmetric synthesis, as ligands of transition metals, as well as in molecular recognition as chiral receptors. These aspects are currently being investigated in our group.

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8. It is assumed that the proposed approach is controlled by hydrogen bonding with OH-2.[6] The high d.e. observed in this case can be explained by the conformational stability of the starting thioglycoside due to *exo*-anomeric effect, associated with the favoured transition state implying three *trans*-fused six member rings.
9. In this regard, we have noticed that the crystalline sulfoxide $4R_S$, reported in the literature,[2] adopts the conformation with the *exo*-anomeric effect, in spite of the unfavorable *gauche* relationship between the C1–O5 and the S–O dipoles.
10. We have noticed that in the case of aryl glycosides **1**, **3** and **5** reported in Ref. 6, this rule is operative as the anomeric carbon is more shielded by 2.2, 3.6 and 7.2 ppm, respectively, in the R_S isomers.
11. In the case of α-thioglycosides it is the oxidation of the pro-*S* lone pair leading to α-(S_S)-sulfinyl glycosides which maintains the stabilising n-σ* hyperconjugative delocalisation.