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Conformational behavior of peracetylated β-D-mannopyranosyl methanesulfonamide: implications for the mechanism of sulfonamidoglycosylation of carbohydrate derivatives

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ABSTRACT

The conformational behavior of 2,3,4,6-tetra-*O*-acetyl-β-D-mannopyranosyl methanesulfonamide has been investigated from a combined theoretical and experimental point of view. The study of the conformational space of the glycosyl sulfonamide revealed that the β anomer is thermodynamically more stable than the α one. This fact suggests that the synthesis reaction could take place mainly under thermodynamic control as the main experimental product is the β-anomeric form of the sulfonamide. Several intramolecular hydrogen bonds were found in the stable conformers of the *N*-mannopyranosyl sulfonamide under study. A relationship was found to exist between them and the relative stability of the conformers. A detailed analysis of geometrical parameters shed light into the nature of the solid state structure of the novel 2,3,4,6-tetra-*O*-acetyl-β-D-mannopyranosyl methanesulfonamide in terms of *exo*- and *endo*-anomeric effects and antiperiplanar relationships. NBO calculations confirmed those findings. Calculated ^{1}H and ^{13}C NMR chemical shifts support previous findings concerning configuration and conformation assignments of the title sulfonamide.

Finally, an explanation of the stereochemical outcome of sulfonamidoglycosylations, was given in terms of *exo*- and *endo*-anomeric effects and steric factors.

1. Introduction

In many cases, use of carbohydrates as drugs has an important drawback: they are sensitive to the presence of enzymes and acidic or basic media. Thus, design of mimetics that bind to enzymes but are not processed to product in the usual way is an active area of research.[1] In recent years a variety of replacements for the glycosidic linkage have raised considerable interest as stable carbohydrate mimetics due to their enormous stability to enzymatic degradation and the resulting possibilities as enzyme inhibitors.[2] The most common modifications with respect to the linkage are S-glycosides, C-glycosides, and N-glycosides. An unusual enzyme-resistant replacement for the glycosidic linkage, is the sulfonamide corresponding to a glycosylamine carrying a sulfonyl group at nitrogen. However, glycosylamines are not stable and are very sensitive to hydrolysis and anomerization.[3] To overcome this problem, one of our groups has developed several syntheses of *N*-glycosyl sulfonamides by sulfonamidoglycosylation of carbohydrate derivatives.[4] These sulfonamidoglycosides have been shown to possess interesting biological activities. In that sense, recently we reported the synthesis of a series of α-D-hex-2-enopyranosyl sulfonamides, which were evaluated against human hepatocellular liver carcinoma (HepG2) and human lung adenocarcinoma (A549) cell lines and showed antiproliferative activity in the micromolar range.[5] Very recently we have prepared novel *N*-β-glycosyl sulfonamides and shown that they selectively target cancer-associated CAs (IX and XII) with K_Is in the low nanomolar range.[6]

The stereochemical outcome of sulfonamidoglycosylations is quite different depending on the reactives and products.[4] To shed some light on the mechanism of these reactions, we have studied the conformational behavior of peracetylated *N*-D-mannopyranosyl methanesulfonamide in solution, in the solid state and from a theoretical point of view.

2. Results and discussion

As anomers of 2,3,4,6-tetra-*O*-acetyl-D-mannopyranosyl methanesulfonamide could be present in two equilibrium

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conformations, namely $^1C_4$ and $^4C_1$, two different starting conformations of the glycosyl sulfonamide are considered for each anomer. These conformations are labeled **1**–**4**, see Figure 1.

The crystal structure of 2,3,4,6-tetra-*O*-acetyl-β-D-mannopyranosyl methanesulfonamide is shown in Figure 2. It can be seen that this anomer adopts a $^4C_1$ conformation and the acetoxymethyl group at C5 in an equatorial position in the crystal lattice.

The study of the conformational space of 2,3,4,6-tetra-*O*-acetyl-D-mannopyranosyl methanesulfonamide leads to six different conformations both in the gas phase and after solvent effects are included. Three of those conformations belong to the β anomeric form, whereas the remaining ones represent the α anomer. Table 1 lists some selected geometrical parameters for the stable conformations. Gibbs free energies, also shown in Table 1, are slightly affected by the inclusion of solvent effects. Conformer **3c** becomes less stable by more than 1 kcal mol^{-1} relative to the more stable conformer when solvent effects are accounted for, whereas conformers **2a** and **1a** invert their relative order. Gibbs free energies calculated in the gas phase indicate that the relative composition at 298.15 K is about 97% of the β anomer of peracetylated *N*-D-mannopyranosyl methanesulfonamide and about 3% of the α form. When solvent effects are taken into account, the relative composition is almost unaffected with about 98% for the β anomer and the remaining 2% for the α anomer, a result which is in excellent agreement with experimental reports.[7] It is very interesting to note that the inclusion of solvent effects has little impact on the gas phase geometries, see Table 1. Conformational behavior about the C5–C6 bond in carbohydrates leads to three staggered orientations namely *gauche-gauche* (*gg*), *trans-gauche* (*tg*), and *gauche-trans* (*gt*). All these conformations correspond to local minima on the molecular surface of the corresponding carbohydrate. Conformers **3a**, **3b**, **1a**, and the solid state structure, show preference for conformation *gt* while *gg* is preferred for conformer **3c**, and *tg* is preferred for conformers **2a** and **2b**. It should also be noted that four stable conformers (**3a**–**c**, **1a**) reported in this work exhibited the $^4C_1$ conformation with τ(C1–O5–C5–C4), τ(O5–C1–C2–C3), and τ(C2–C3–C4–C5–O5) dihedral angles around the ideal value of +60°; τ(C1–C2–C3–C4), τ(C5–O5–C1–C2) around −60° and the acetoxymethyl group at C5 in a equatorial position. On the other hand the conformers **2a** and **2b** showed a $^1C_4$ conformation with the acetoxymethyl group at C5 in an axial position. It can also be seen from the table that other torsion angles such as τ(N1–C1–C2–C3), τ(N1–C1–O5–C5), τ(C2–C1–N1–S1), and τ(O5–C1–N1–S1) indicate that the solid structure adopts the β anomeric form. It is also of interest to compare some selected bond lengths and bond angles involving the O5–C1–N1 acetal moiety in the different conformers with experimental data. The calculated O5–C1–N1 bond angle in the three equatorially substituted conformers **3**

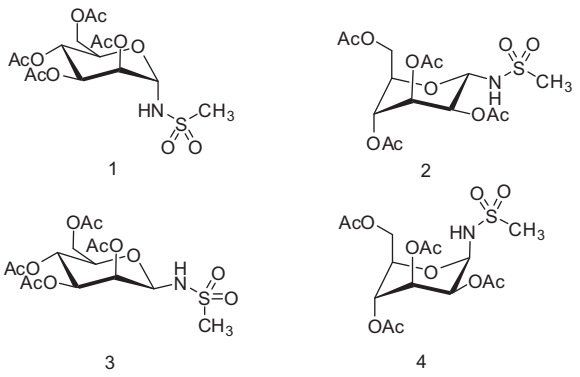

Figure 1. Schematic representation of the four starting conformations of 2,3,4,6-tetra-*O*-acetyl-D-mannopyranosyl methanesulfonamide. 1 and 2 correspond to the α anomeric form and 3 and 4 represent the β one.

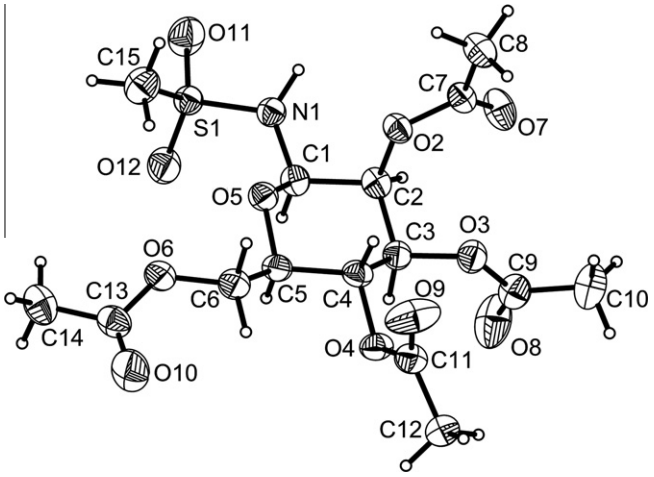

Figure 2. Drawing of 2,3,4,6-tetra-*O*-acetyl-β-D-mannopyranosyl methanesulfonamide showing the labeling of the non-H atoms and their displacement ellipsoids at the 30% probability level.

agrees very well with the crystal structure results (**3a**: 109.8° (110°); **3b**: 109.6° (109.6°), and **3c**: 109.6° (109.6°); experimental: 109.3°, calculated values in acetonitrile are in parenthesis). On the other hand, the O5–C1–N1 bond angle calculated for the axially substituted conformer **1a** (111.2° (111.0°)) is considerably higher than the experimental value. These facts are in good agreement with previous studies of bond angle variations in acetals.[8] It is important to point out that conformers **2a** and **2b** exhibited the $^1C_4$ conformation and the substituent at the anomeric center adopts an equatorial position so the O5–C1–N1 bond angle resembles the values found in the β-anomers. The C1–N1 bond length in conformers **3** (**3a**: 1.430 Å (1.440 Å); **3b**: 1.431 Å (1.439 Å); **3c**: 1.431 Å (1.441 Å)), in the solid-state conformation of the β anomer (1.431 Å) and conformers of α-anomer with a $^1C_4$ conformation (**2a**: 1.428 Å (1.435 Å); **2b** 1.428 (1.436 Å)) are shorter than the value in conformer **1a** (1.464 Å (1.469 Å)). These findings could be explained in terms of a competition between a $n_{N1} \rightarrow \sigma^*_{C1-O5}$ orbital interaction (*exo*-anomeric effect) and a $n_{O1} \rightarrow \sigma^*_{C1-N1}$ interaction (*endo*-anomeric effect) in $^4C_1$ conformer of α anomer (**1a**). In the conformers **3** of the β anomer, and the $^1C_4$ conformers of α anomer (**2**a and **2b**) the *endo*-anomeric effect is not present, and then, a dominant $n_{N1} \rightarrow \sigma^*_{C1-O5}$ leads to a shorter C1-N1 bond. As can be seen in Table 1 the values of the torsion angle τ(C2–C1–N1–S1) show an antiperiplanar relationship in conformers **3**, **2a**, **2b**, and in the solid state, in agreement with the $n_{N1} \rightarrow \sigma^*_{C1-O5}$ orbital interaction associated with the exo-anomeric effect. The NBO analysis presented in Table 2 shows that the $n_{N1} \rightarrow \sigma^*_{C1-O5}$ is similar for both anomers except for conformer **1a**, whereas $n_{O5} \rightarrow \sigma^*_{C1-N1}$ orbital interaction is higher in this conformer, thus supporting the experimental findings.

The conformational preference of the β anomer in solution is similar to that in the solid state since spin-spin coupling constant data indicate a value of 10.5 Hz for $J_{N1H-C1H}$,[7] which is consistent with the presence of an antiperiplanar relationship between N1H and H atom bound to C1. Thus, conformations predicted about the glycosyl linkage in conformers **3** are in very good agreement with the experimental data both in solution and in solid state.

Table 3 shows some characteristic geometric parameters and topological properties of intramolecular hydrogen bonds found for the stable conformers of the title compound. The values of the density and the Laplacian of the density at the bond critical points indicate that these are effectively hydrogen bonds. The evaluation of the stabilization energy as a consequence of the formation of an intramolecular hydrogen bond is a controversial