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Preparation and structural determination of methyl 3-*C*-*p*-tolylsulfonyl-2-*C*-*p*-tolylthio-β-D-glucopyanoside derivatives and their 5a-carba-DL-analogs having non-chair conformation in solutions

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Abstract—Methyl 4,6-*O*-benzylidene-2,3-dideoxy-3-*C*-*p*-tolylsulfonyl-2-*C*-*p*-tolylthio-β-D-glucopyranoside and its 5a-carba-DL-analog exit mainly in a non-chair conformation in solutions, but the latter occupies a chair conformation in a solid state.

It is generally accepted that D-glucopyranoside occupies a chair conformation ($^4C_1$),[1] except specific cases.[2] Therefore, we assigned the *manno* configuration for the adduct **1**, formed exclusively in the reaction of methyl 4,6-*O*-benzylidene-2,3-dideoxy-3-*C*-*p*-tolylsulfonyl-β-D-*erythro*-hex-2-enopyranoside (**3**) with *p*-toluenethiol, from the coupling constants: $J_{1,2}$ 4.0, $J_{2,3}$ 4.8, $J_{3,4}$ 9.5, $J_{4,5}$ 9.9 Hz.[3] If the assignment is true, this reaction is stereochemically attractive, because a similar reaction of **3** with sodium methoxide in methanol exclusively afforded the β-D-*gluco* adduct **5**.[3] In order to elucidate whether or not the ring oxygen atom (O-5) contributes to this stereochemical difference, we have performed a similar reaction of the corresponding 5a-carba sugar **4** with *p*-toluenethiol and found that the *gluco* isomer **10** obtained has mainly, at least, a non-chair conformation in solutions but a chair conformation in a solid state.[4]

Different from the case of sugar **3**, a reaction of the 5a-carba sugar **4** with *p*-toluenethiol in methanol in the presence of triethylamine gave two products, the *manno* isomer **2** and the *gluco* isomer **10**, in a 1.2:1 ratio in almost quantitative yield.[5] In these adducts more information is available from the coupling constants, because in 5a-carba sugars the ring oxygen atom is replaced by the methylene group. Thus, these products are unequivocally assigned to have the *manno* configuration with the $^4C_1$ conformation for **2** and the *gluco* configuration with the $^4S_2$ and/or $^{1,4}B$ conformation for **10**: $J_{1,2}$ 3.3, $J_{1,5'a}$ 11.2, $J_{1,5'e}$ 3.3, $J_{2,3}$ 3.3, $J_{2,5'e}$ 2.0, $J_{3,4}$ 10.9, $J_{4,5}$ 10.6, $J_{5,5'a}$ 13.2, $J_{5,5'e}$ 4.0 Hz for **2** and $J_{1,2}$ 4.0, $J_{1,5'\alpha}$ 6.3, $J_{1,5'\beta}$ 2.6, $J_{2,3}$ 3.3, $J_{3,4}$ 9.6, $J_{4,5}$ 10.9, $J_{5,5'\alpha}$ 7.9, $J_{5,5'\beta}$ 10.2 Hz for **10**. Assignment of H-5′β was confirmed by NOESY spectrum: correlation between H-5′β and H-6*a* was observed. The *gluco* structure for **10** was confirmed by transformation into the debenzylidenated compound **13**, the conformation of which changed to the $^4C_1$ form: $J_{1,2}$ 9.2, $J_{1,5'a}$ 9.9, $J_{1,5'e}$ 4.0, $J_{2,3}$ 10.6, $J_{3,4}$ 9.9, $J_{4,5}$ 9.9, $J_{5,5'a}$ 12.5, $J_{5,5'e}$ 4.6 Hz. Benzylidenation of **13** again afforded the non-chair compound **10**, indicating that no epimerization occurred during the transformation and that the non-chair structure is thermodynamically more stable than the chair one. X-Ray analysis showed that compound **10** has indeed the *gluco* configuration, but exists in the $^4C_1$ conformation (Fig. 1). Thus compound **10** takes mainly, at least, the non-chair form in solution ($CDCl_3$, benzene-d_6, and DMSO-d_6), but the $^4C_1$ conformation in the solid state.

During our work Pathak et al. reported the opposite results for methyl 2-benzylamino-4,6-*O*-benzylidene-2,3-dideoxy-3-*C*-phenylsulfonyl-β-D-glucopyranoside, which occupies the $^{1,4}B$ conformation in a solid state as judged from X-ray analysis[6] but the $^4C_1$ conformation in solution from NMR data.[7]

Keywords: β-D-glucopyranoside; boat form; sulfonyl sugars; X-ray analysis.

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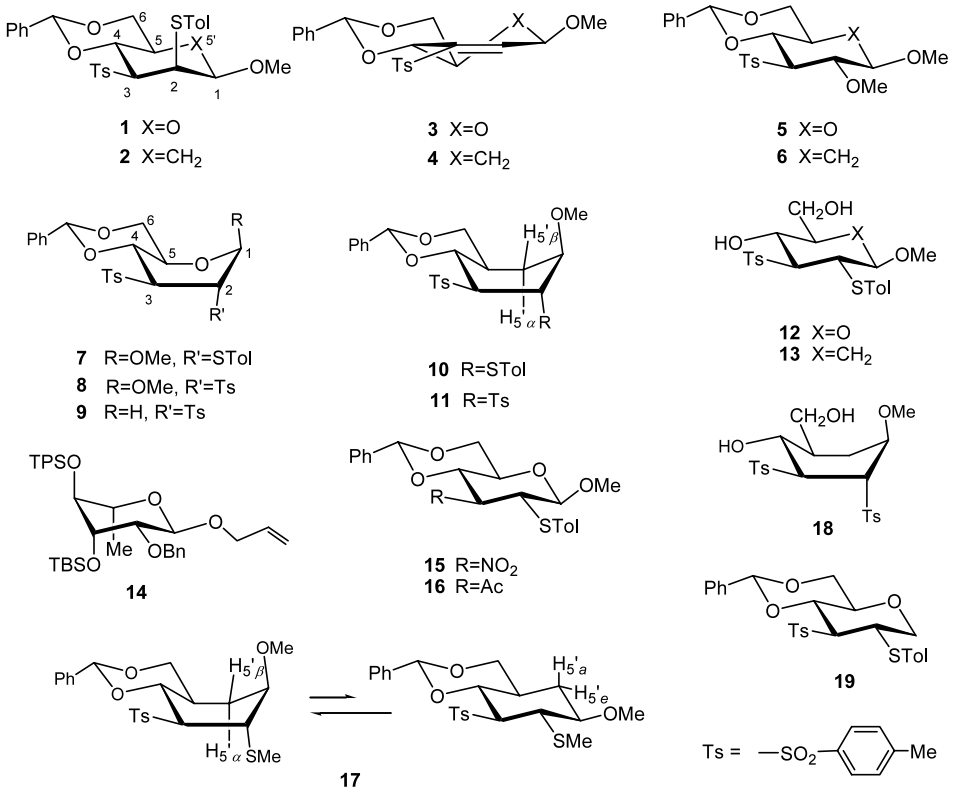


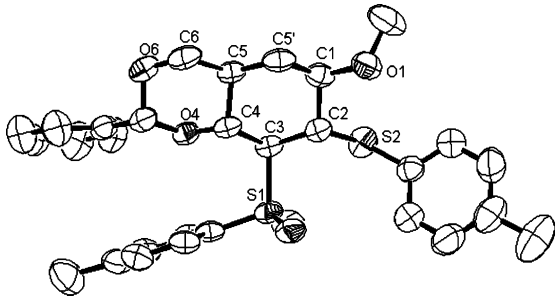


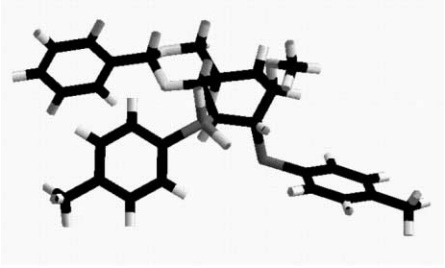
Figure 1. X-Ray data of **10** written with ORTEP3.

From these results it is enough possible that the adduct **1** assigned previously to have the *manno* structure with the $^4C_1$ conformation is the *gluco* isomer **7** having a non-chair conformation. The *gluco* structure is proved by NMR spectroscopy of the debenzylidenated product **12**, which also occupied the $^4C_1$ conformation ($J_{1,2}$ 8.0, $J_{2,3}$ 11.6, $J_{3,4}$ 9.3 Hz).

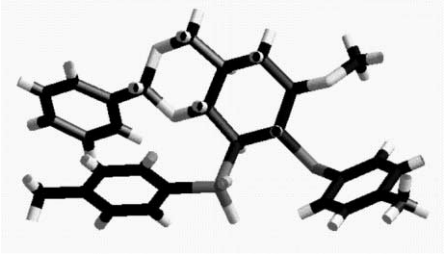
In spite of a strong tendency for a *gluco* isomer to have the $^4C_1$ conformation, why do compounds **7** and **10** exist in the non-chair conformation in solution? In this context it is noteworthy that bulky vicinal groups have a bias to take the *trans* form instead of the *gauche* form to reduce steric hindrance.[8] For example, the bulky *t*-butyldimethylsiloxy (OTB) and *t*-butyldiphenylsiloxy (OTPS) groups of **14** occupied the axial positions instead of the equatorial ones.[8b] If this is the case, *A* values[9] should be instructive. In fact the sulfonyl group (*A* value of SO_2Me[10] 2.50) is essential for occupying the non-chair conformation, because the corresponding 3-*C*-nitro **15** (*A* value of NO_2[10] 1.1) and 3-*C*-acetyl (*A* value of Ac[10] 1.02–1.52) derivatives **16** take up the $^4C_1$ conformation. The coupling constants of **17**, which has a methylthio group (*A* value 1.04)[10] instead of the *p*-tolylthio group (*A* value of SC_6H_5 1.10–1.24),[10] suggest that this compound is an equilibrium mixture of the non-chair and $^4C_1$ conformations in which the former seems to predominate. The corresponding 2-*O*-methyl (*A* value is 0.55–0.75)[10] derivatives **5** and **6** exclusively exist in the $^4C_1$ conformation. As expected from the *A* value the disulfonyl derivatives **8** and **11** derived by oxidation of **7** and **10**, respectively, exist in the non-chair form. As had been described the debenzylidenated derivative **13** have the $^4C_1$ form, however, the debenzylidenated compound **18** derived from the disulfonyl derivative **11** keeps the non-chair conformation.[11] Furthermore, 1,5-anhydro-2,3-di-*C*-*p*-tolylsulfonyl-D-glucitol **9** occupies the non-chair conformation, whereas the 1,5-anhydro-3-*C*-*p*-tolylsulfonyl-2-*C*-*p*-tolylthio-D-glucitol **19** exists in the $^4C_1$ conformation. The latter result shows that the anomeric methoxyl group of 2-*C*-*p*-tolylthio derivative **7** is required to shift the equilibrium to the non-chair form.

Energy difference between the non-chair and $^4C_1$ conformation for **10** should be small, because the stable conformers are different in solution and in the solid state. In a solid state, intermolecular interaction is believed to be operative. Furthermore compound **10** inevitably occupies the non-chair conformation regardless of solvent polarity. Therefore preferable conformation obtained by ab initio calculation, which is performed in an isolated molecule without solvent,

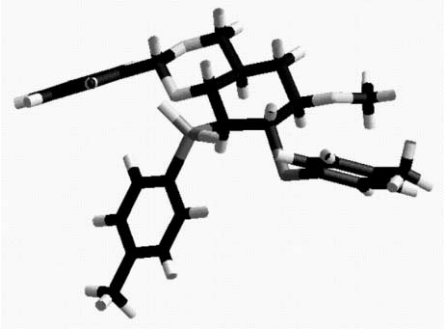
should be good agreement with the NMR data rather than X-ray data. Ab initio calculations (6-31G*)[12] of **10** afforded the following three interesting results. Firstly an intermediary structure between a $^{1,4}B$ and a $^{4}S_2$ conformation is generated during calculation starting from a $^{4}S_2$ and $^{1,4}B$ conformation, respectively. Secondly X-ray like structure calculated from the X-ray data is less stable than the most stable $^{4}C_1$ conformation found during the calculations by 4.1 kcal/mol; the two aromatic rings of the sulfonyl and benzylidene groups are not parallel in the latter, but parallel in the former, as being suitable for stacking intermolecularly. Thirdly the non-chair conformer calculated is more stable than the most stable $^{4}C_1$ conformer by 1.2 kcal/mol, being good agreement with the NMR data.



Most stable non-chair conformer of **10** calculated by 6-31G*



Calculated conformer of **10** by 6-31G* which is close to X-ray data



Most stable chair conformer of **10** calculated by 6-31G*

In conclusion methyl 3-*C*-*p*-tolylsulfonyl-β-D-glucopyranosides **7** and **8**, the corresponding 5a-carba analogs **10**, **11**, and **18** and 1,5-anhydro-2,3-disulfonyl derivative **9** exist mainly, at least, in the non-chair conformation in solutions probably due to steric hindrance. Ab initio calculation for **10** corroborated with the NMR data, but not with the X-ray data.

Acknowledgements

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