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# Hydrogen atom transfer experiments provide chemical evidence for the conformational differences between *C*- and *O*-glycosides

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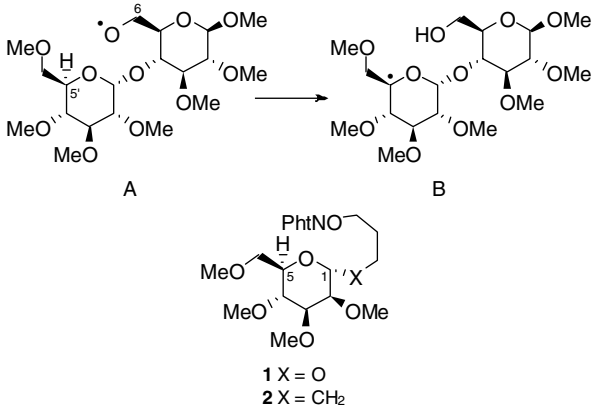
**Abstract**—The regioselectivity of the hydrogen atom transfer (HAT) reaction promoted by alkoxyl radicals generated from 3-hydroxypropyl α-D-mannopyranoside derivative (*O*-glycoside) and 2,6-anhydro-D-*glycero*-D-*manno*-decitol derivative (*C*-glycoside) is studied. The *O*-glycoside model abstracts preferentially the hydrogen atom at C-5 (1,8-HAT) while the *C*-glycoside abstracts the hydrogen atom at C-1 (1,6-HAT) but no abstraction at C-5 could be detected. These results are explained by the stereoelectronic control exerted by the *exo*-anomeric effect in the *O*-glycoside.


Intramolecular hydrogen atom transfer (HAT) is a radical-mediated process, which has interesting applications in synthetic organic chemistry since it can be profitably employed for the selective functionalization of molecular positions considered to be unreactive under other, more classical conditions.[1] The reaction, when promoted by alkoxyl radicals, occurs most frequently through a chair-like six-membered transition state (TS),[2] although some exceptional cases of 1,6-HAT reactions that proceed via a seven-membered TS are known.[3]

In a recent paper from this laboratory, a rare 1,8-HAT, promoted by alkoxyl radicals, between two glucopyranose units in a α-D-Glc*p*-(1→4)-β-D-Glc*p* disaccharide model was described (Scheme 1).[4] The alkoxyl radical A, generated from the alcohol at C-6 under oxidative or reductive conditions, abstracts the hydrogen atom at C-5′ through a nine-membered transition state in a highly efficient and regioselective manner to give *C*-radical B. The reaction is supposedly favored by the *exo*-anomeric effect, and consequently, the glycosidic bond adopts a preferred syn conformation ($\Phi_H = -30.0°$, $\Psi_H = -32.0°$) with the alkoxyl radical positioned at a suitable distance (≈3 Å) from the hydrogen atom to be abstracted.[5]




**Scheme 1.** HAT between glucopyranose units in a disaccharide model.

On the other hand, the chemistry of *C*-glycosides has recently attracted considerable interest from the point of view of carbohydrate mimetics and in view of the increased detection of the *C*-glycosidic bond in natural products.[6]

Due to the numerous biochemical applications of *C*-glycosides, especially as enzyme inhibitors, the comparison of the conformational behavior of *C*-glycosides with the naturally occurring *O*-counterparts is an interesting research topic.[7] The conformational studies have so far been carried out by using physical methods, particularly NMR spectroscopy (NOE analysis and coupling

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constants data) in combination with molecular mechanics and ab initio calculations.[7a]

With our results on the 1,8-HAT reaction in mind, we sought to develop a radical process, which could provide chemical evidence for the conformational differences between *C*- and *O*-glycosides. As far as we know, studies of this type have not been reported to date.

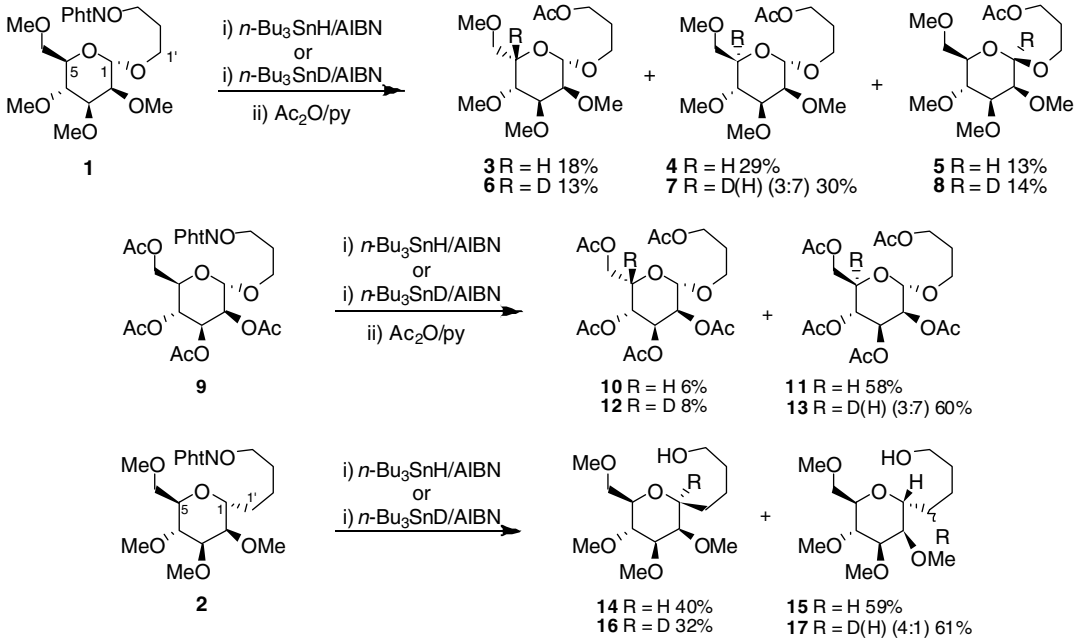
To probe the entropic barrier resulting from flexibility around glycosidic bonds in going from the more flexible *C*-glycosides to *O*-glycosides it was necessary to synthesize a relatively simple model system. In designing 3-hydroxypropyl α-D-mannopyranoside derivative **1** and 2,6-anhydro-D-*glycero*-D-*manno*-decitol derivative **2** as models for the HAT reaction, we were guided by a number of considerations. Firstly, a α-D-*manno* configuration of the sugar would ideally permit hydrogen abstraction from almost all positions of the pyranose ring (specifically from C-1, C-2, C-3, and C-5). Secondly, none of the three staggered conformations around $\Phi_H$ angle for the $^4C_1$ chair (*exo–syn*, *exo–anti*, and non-*exo*) should undergo substantial steric interaction between the axial substituent at C-2 and aglycon. The influence of this interaction on the conformational equilibrium seems to be especially important in the absence of additional stereoelectronic effects, as in the case of *C*-glycosides.[7a] Thirdly, the aglycon should be a simple *n*-alkyl alcohol tether of five atoms, with the least possible conformational constraints, to avoid, as much as possible, destabilizing steric interactions in the HAT transition state.

In addition we have also synthesized tetraacetate **9**; the presence of such electron withdrawing groups (EWG) should deactivate the molecular hydrogen atoms for the abstraction by the electrophilic alkoxyl radicals.[8]

The alkoxyl radicals were generated under reductive conditions by treatment of the *O*-phthalimido derivatives with *n*-$Bu_3SnH$/AIBN and *n*-$Bu_3SnD$/AIBN in benzene solutions.[9] In order to acquire additional insight into the HAT reaction mechanism, the alkoxyl radicals in the case of the *C*-glycosides were also prepared under oxidative conditions, by visible light irradiation of the alcohol with hypervalent iodine reagents in the presence of iodine.

The synthesis of *O*-phthalimido derivatives was readily achieved from the corresponding alcohol and *N*-hydroxyphthalimide under Mitsunobu conditions in accordance with a previously described protocol.[10]

The results of the reductive HAT reaction for the *O*-glycosides are outlined in Scheme 2.[11] Under reductive conditions phthalimide **1** was transformed into three compounds that were characterized after acetylation to facilitate their chromatographic separation:[12] β-L-gulopyranoside derivative **3** formed by the hydrogen abstraction process and inversion of the configuration at C-5 (18%), β-D-mannopyranoside derivative **5** which, evidently arises from hydrogen abstraction, inversion of the radical at C-1, and axial quenching by the stannane (13%),[13] and compound **4** with the starting α-D-mannopyranoside configuration (29%). This last compound may be formed by three different mechanisms: abstraction and retention of configuration at C-5 or at C-1 or simply by a failed in the hydrogen abstraction process and a reduction of the *O*-radical prior to the abstraction reaction, or by a combination of these. Repetition of the reduction of phthalimide **1** with *n*-$Bu_3SnD$ shed more light on the mechanism. Analysis of the isotopic distribution in compounds **6** and **8** showed a complete substitution by deuterium at C-5 and C-1, respectively.[14] On the other hand, only 30% of deuterium labeling was




**Scheme 2.** Hydrogen atom transfer in α-*O*- and *C*-glycosides under reductive conditions. PhtN = phthalimide.

found at C-5 in compound **7**; no appreciable labeling at C-1 could be observed under the detection limits of the $^{1}H$ and $^{13}C$ NMR spectroscopy. We therefore conclude that in compound **7** all the deuterium comes only from abstraction–retention at C-5 and that the reduction of the *O*-radical is responsible for the unlabeled molecules.

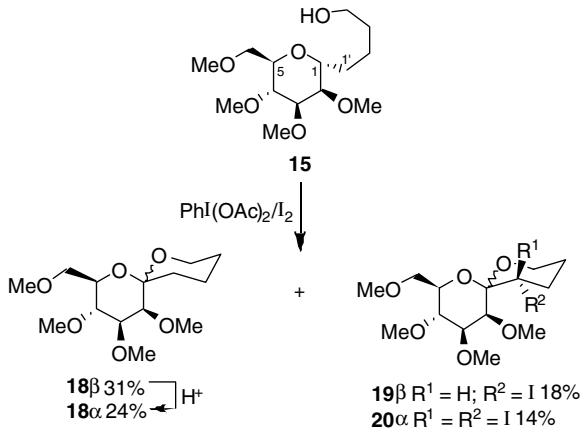
Several other conclusions can be drawn from the results presented above. For this *O*-glycoside the abstraction at C-5, through an apparently less stable nine-membered TS competes favorably with the abstraction at C-1 through a seven-membered TS (C-5:C-1 abstraction ratio of 6:4). Interestingly, the abstraction at C-5 proceeded with an inversion–retention ratio of 6:4, while a complete inversion of configuration was observed during the abstraction at C-1.

As expected, the HAT reaction was less effective with tetraacetyl phthalimide **9** (26% yield), while 42% of undeuterated compound **13** was obtained as the result of failure of the hydrogen abstraction process. On the other hand, the reaction was much more regioselective, the abstraction now occurring exclusively at C-5 with an inversion–retention ratio of approx. 1:2 (Scheme 2). We should point out that no abstraction at C-1 could be detected by NMR analysis of the crude reaction mixture.

The results obtained for the reductive HAT reaction of *C*-glycoside **2** are illustrated in Scheme 2. NMR spectral analysis of compounds **14** and **15** and of their deuterated counterparts **16** and **17** revealed that the reaction proceeded by hydrogen abstraction at C-1 and C-1′, but no abstraction at C-5 could be detected. As may be expected, the abstraction at C-1′ is, in this *C*-glycoside, a competitive reaction since it presumably proceeds via a six-membered TS. The inversion of configuration at C-1 observed in compound **14** is in good agreement with the previously reported stabilization of the α-radical by the so-called radical anomeric effect.[15]

We have also studied the oxidative HAT reaction of α-alcohol **15** in order to clarify the 1,5- versus 1,6-competitive abstraction observed in the reductive process of the *C*-α-glycoside. The alkoxyl radical was generated by reaction of alcohol **15** with (diacetoxyiodo)benzene and iodine under irradiation with visible light (Scheme 3).

Four compounds were isolated and characterized from the reaction mixture: the diastereoisomeric spiroacetals **18α** and **18β** and two iodinated compounds **19β** and **20α**. The stereochemistries at C-1 were determined by NOE experiments and by acid-catalyzed isomerization of kinetic **18β** spiro to thermodynamic **18α**, which may exist in a minimum energy conformation with two stabilizing anomeric effects. Reductive removals of the iodine atoms with *n*-$Bu_3SnH$/AIBN confirmed the proposed C-1 stereochemistry of **19β** and **20α**. In the $^{1}H$ NMR spectrum of **19β**, the coupling pattern of H-1′ (dd, 12.9 and 4.5 Hz) was consistent with the equatorial configuration of the iodine atom. The iodine compounds were plausibly formed by a single or double abstraction at C-1′ through a six-membered TS and subsequent radical quenching by iodine atoms from the reaction medium before the abstraction and spirocyclization at C-1 could take place. In reality, the qualitative results of the reductive and oxidative experiments are similar, in both cases the abstraction occurs only at C-1 or C-1′ but not at C-5. The differences appear to center around the possibility of multiple abstractions by the alkoxyl radical in the oxidative process, which ultimately leads to more complex final products.




**Scheme 3.** HAT in α-*C*-glycosides under oxidative conditions.

From the experimental results shown above it seems to indicate that the stereoelectronic control exerted by the *exo*-anomeric effect in the *O*-glycosides gives rise to two minimum energy conformations, which can abstract hydrogen from C-5 and C-1. The *C*-glycosides, in the absence of this effect, adopt a more flexible conformation. The HAT reaction is now controlled by the energy of the TS and the abstraction occurs exclusively at C-1. In this work we have also developed a simple methodology to generate the 5-glycopyranosyl radicals with moderate efficiency, which may prove to be highly suitable for reactivity studies. While numerous studies related to 1-glycopyranosyl radicals have been reported, the preparation and reactivity of its homologous 5-glycopyranosyl radicals have received comparatively very little attention.[16] In the few cases studied, most of them related with the D-glucuronic to L-iduronic acid isomerization, the additions are notably non-stereoselective in contrast with 1-glycopyranosyl radicals. Therefore, our ongoing work in this area is aimed at further studying the reactivity of 5-glycopyranosyl radicals generated by using this method.

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## Supplementary data

Experimental procedures and analytical data for all new compounds are provided. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.05.166.

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