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Intramolecular 1,8-Hydrogen Abstraction Between Glucopyranose Units in a Disaccharide Model Promoted by Alkoxy Radicals**

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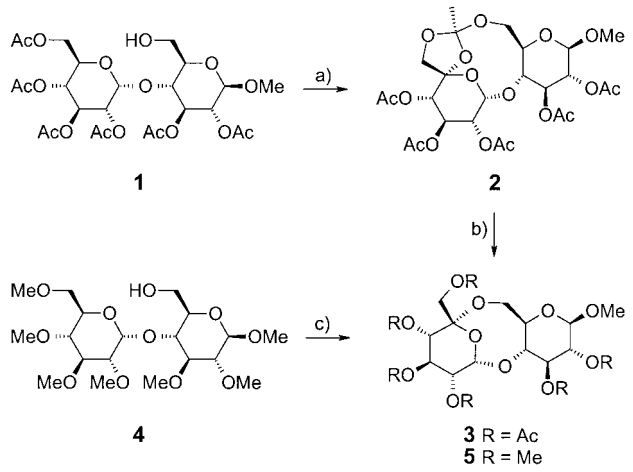
The use of radical reactions in carbohydrate chemistry has recently attracted considerable attention in the synthetic community.[1] Among free radical reactions intramolecular hydrogen abstraction (IHA) has been comparatively less studied in these systems.[2] Although 1,*n*-hydrogen transfer has been observed from C_{sp^3}–H to alkyl and aryl C radicals for $n = 4-7$,[3] 1,5-hydrogen transfer is by far the most common IHA reaction when promoted by alkoxy radicals.[4] In some cases, 1,6-hydrogen transfer from unactivated carbon atoms to alkoxy radicals has been observed, usually in low yield.[5] Only when the hydrogen atom to be removed is bonded to an oxygen-substituted carbon atom the yield of this last process could be considered to be of synthetic interest.[6] IHA reactions through eight- or higher membered transition states are practically unknown; entropic effects are probably responsible for the failure of these processes.[7]

With this in mind, we reasoned that an IHA reaction through an eight- or even higher membered transition state might be possible in a model with a restricted conformational mobility to avoid the entropic penalty. Two other conditions should be fulfilled: a low-energy transition state and a distance of around 3 Å between the O radical and the hydrogen atom to be abstracted.[8] It soon became evident that the Glc-α1 →4-Glc unit in compound **1** (see Scheme 1)[9, 10] has a preferred *syn* conformation of the glycosidic bond ($\Phi = -34.2^\circ$, $\Psi = -28.3^\circ$) and a $C_6O\cdots HC_{5'}$ distance of 2.5 Å in accord with previously reported X-ray crystallographic[11] and molecular mechanics[12] analyses of β-D-maltose octaacetate and methyl β-D-maltoside, respectively. A study of the transition state of the C_6-O$\cdots$H-$C_{5'}$ IHA reaction gave a similar situation for the glycosidic torsion angles ($\Phi = -32.7^\circ$, $\Psi = -37.3^\circ$) and a distance of 3.14 Å between the O radical and H-$C_{5'}$.[13]

In order to substantiate our assumption the C_6 alkoxy radical was generated by reaction of the D-maltose derivative **1**[14] with (diacetoxyiodo)benzene and iodine under irradiation with two 100 W tungsten filament lamps (Scheme 1). The reaction, which proceeds presumably through an alkyl



Scheme 1. IHA under oxidative conditions. a) DIB (1.5 equiv), iodine (0.7 equiv), CH_2Cl_2, *hν*, 25 °C, 90 min, 62 %; b) $CDCl_3$, RT, 60 h, 100 %; c) DIB (1.7 equiv), iodine (0.5 equiv), CH_2Cl_2, 25 °C, 90 min, 56 %. DIB = (diacetoxyiodo)benzene.

hypoiodite intermediate,[15] gave orthoacetate **2** in 62 % yield. Compound **2** is a moderately stable crystalline solid with an unprecedented 1,3,5,7-tetraoxecane ring system whose structure was elucidated by extensive NMR studies including COSY, TOCSY, DEPT, and HMQC experiments and confirmed by X-ray crystallographic analysis.[16] The orthoacetate group is hydrolyzed under very mild acidic conditions with concomitant ring contraction to give the 1,3,5-trioxocane derivative **3** in excellent yield. The trioxocane ring adopts a constrained, highly stable boat–chair conformation.[17] The reaction of the DIB/I_2 system with D-manoside **4**[18] gave directly the $C_{5'}$-functionalized disaccharide **5** through a nine-membered transition state (Scheme 1).

The IHA reaction between the two glucopyranose units can also be realized under reductive conditions. In our experience, one of the best methods to generate alkoxy radicals under reductive conditions is by reaction of *N*-hydroxyphthalimide

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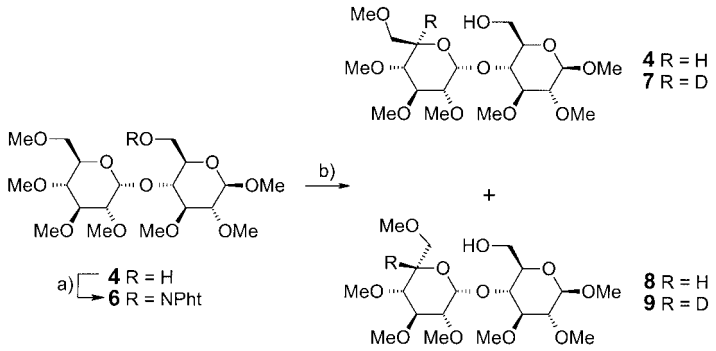
derivatives with the nBu$_3$SnH/AIBN system.[19] We prepared the phthalimide derivative **6** by treatment of alcohol **4** with *N*-hydroxyphthalimide under Mitsunobu conditions[20] (Scheme 2). Reduction of compound **6** with nBu$_3$SnH/AIBN afforded an easily separable mixture of the starting maltose

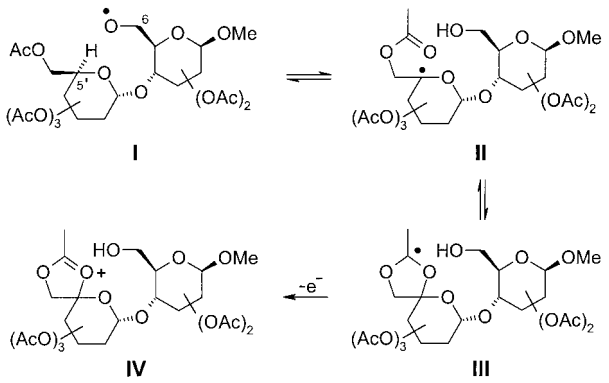


Scheme 2. IHA under reductive conditions. a) DEAD (4 equiv), *N*-hydroxyphthalimide (4 equiv), PPh_3 (4 equiv), THF, 0 °C, 30 min, 82 %; b) nBu$_3$SnH or nBu$_3$SnD (9 equiv), AIBN (0.16 equiv), C_6H_6, reflux, 1 h, 86 – 78 %. DEAD = diethyl azodicarboxylate, AIBN = azobisisobutyronitril.

derivative **4** and a new disaccharide **8** with inversion of configuration at $C_{5'}$. It is worth noting that by using this simple protocol the second D-glucosyl moiety in the maltose derivative **4** has been transformed into a rare β-L-idosyl monosaccharide unit. As can be easily observed by NMR spectroscopy, epimerization of the $C_{5'}$ side chain triggers inversion of the pyranose ring chair conformation. The conformation changes from $^4C_1$ in the α-D-glucosyl unit to $^1C_4$ in the β-L-idosyl moiety, which leaves the $C_{2'}$, $C_{3'}$, and $C_{4'}$ substituents in axial positions.[21]

To unambiguously verify the structure of **8** and clarify the reaction mechanism, we used nBu$_3$SnD as reductant and obtained compound **9** with exclusive and quantitative incorporation of deuterium at the $C_{5'}$ position. In addition, the maltose derivatives **7** and **4** were obtained in a ratio of 57:43, compound **4** being formed by reduction of the alkoxy radical before the IHA reaction could take place. The deuterium position was determined NMR spectroscopically not only by the D-$C_{5'}$ coupling but also by the small yet significant displacement of the signals of the adjacent $C_{4'}$ and $C_{6'}$ carbon atoms in the ^{13}C NMR spectra.[22] These results have also allowed us to estimate a 60 % yield for the hydrogen abstraction reaction.

The mechanism depicted in Scheme 3 has been proposed for the formation of the orthoacetate derivative **2**. Initially the C_6 alkoxy radical **I** abstracts specifically the hydrogen atom at $C_{5'}$ to give an alkyl radical **II** which adds intramolecularly to the carbonyl oxygen giving the 1,3-dioxan-2-yl radical **III**. This radical is oxidized with an excess of reagent to the oxycarbenium ion **IV**, which is subsequently trapped by the primary hydroxy group at C_6 to give the orthoacetate **2**. This intuitive stepwise ring closure through a dioxanyl radical has been excluded from a related β-(acyloxy)alkyl rearrangement in favor of an ion pair mechanism.[23] In our case, a tight ion pair intermediate which eventually could collapse to the



Scheme 3. Proposed mechanism for the IHA according to Scheme 1.

oxycarbenium **IV** under the oxidative reaction conditions used cannot be ruled out. In the case of hepta-*O*-methylmaltose derivative **4** the $C_{5'}$ radical initially formed is rapidly oxidized to a carbenium ion, which is stabilized as an oxycarbenium ion by the adjacent oxygen atom of the pyranose ring. This ion adds, exclusively through its *si* face, to the primary hydroxy group to afford the 1,3,5-trioxocane **5**.

In this paper we have demonstrated the possibility to modify specifically one sugar unit in a D-Glc-α1 $\rightarrow$4-D-Glc disaccharide. The disaccharide L-ido-β1 $\rightarrow$4-D-Glc (**8**) obtained may be of interest in the chemistry of heparin analogs since the L-iduronic-β1 $\rightarrow$4-D-Glc unit is present as a repetitive fragment in this polysaccharide.[24] We believe that the very mild IHA reaction presented here can be extended to other α1 $\rightarrow$4 disaccharides and presumably to other systems that fulfill the aforementioned conditions. Although the yields are moderate the obtained compounds are difficult to prepare by other methods; there synthesis requires in general relatively complex processes. Of particular interest is that the reactions can be realized under oxidative and under reductive conditions since this gives some synthetic control over the fate of the $C_{5'}$ radical.

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A New Catalyst for the Selective Oxidation of Butane and Propane**

Mark E. Davis,* Christopher J. Dillon, Joseph H. Holles, and Jay Labinger

The abundance and low cost of light alkanes has motivated the search for new catalytic materials that can accomplish selective oxidation processes. The conversion of *n*-butane to maleic anhydride over V-P-O catalysts with molecular oxygen is commercially well established.[1] Other reactions of current interest are the production of acetic acid from ethane and acrylic acid from propane. Polyoxometalates are among the numerous catalytic materials that have been extensively investigated for each of the aforementioned reactions. Typically different polyoxometalate compositions have been used for each alkane. These compounds (and other mixed-metal oxides) have not been found to perform as well as V-P-O catalysts for the conversion of *n*-butane to maleic anhydride,[2] or as well as mixed-metal oxides containing Mo-V-Nb-Te[3a,b] or Mo-V-Nb-Sb[4] for conversion of propane to acrylic acid.

We have discovered a new catalyst system that achieves selective oxidation of both *n*-butane and propane. Li et al. reported that a solid obtained by treating molybdophosphoric acid, $H_3PMo_{12}O_{40}$ (henceforth denoted as PMo_{12}) with pyridine followed by activation in nitrogen at 420 °C exhibits catalytic activity for oxidation of propane to acrylic acid.[5] Ueda and Suzuki also showed that molybdovanadophosphoric acid (denoted as $PMo_{11}V$) similarly treated gives a less active and selective catalyst.[6] Our catalysts are obtained from PMo_{12} and $PMo_{11}V$ (prepared by known methods[7]), exchanged sequentially with niobium oxalate (giving $NbPMo_{12}$ and $NbPMo_{11}V$) and pyridine (giving $NbPMo_{12}$pyr and $NbPMo_{11}V$pyr) in aqueous media, followed by heating to 420 °C in flowing helium. The elemental compositions of the solids thus obtained are typically $Nb_{0.1-0.25}PMo_{12}(pyr)_{3-4}$ or $Nb_{0.1-0.25}PMo_{11}V(pyr)_{3-4}$ within experimental error.

Table 1 reports the catalytic performance of various materials for *n*-butane oxidation under hydrocarbon-rich conditions ($C_4/O_2 = 2/1$). All the solids prepared from precursors containing *both* pyridine and niobium are very active and selective. Note particularly the high space time yield (STY) for $NbPMo_{12}$pyr and $NbPMo_{11}V$pyr achieved by increasing the total flow rate by a factor of eight (15 mL min^{-1} to 120 mL min^{-1}; see entries 6 and 7, and 13 and 14, respectively, in Table 1). In contrast, the polyoxometalates that have not been exposed to pyridine do not exhibit significant activity (entries 1, 2, 8, and 9, Table 1), while samples treated with pyridine but without niobium do not give the highest activities

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