ORGANIC LETTERS

2004
Vol. 6, No. 4
505−508

Hydrolysis of α- and β-Glycosides. New Experimental Data and Modeling of Reaction Pathways

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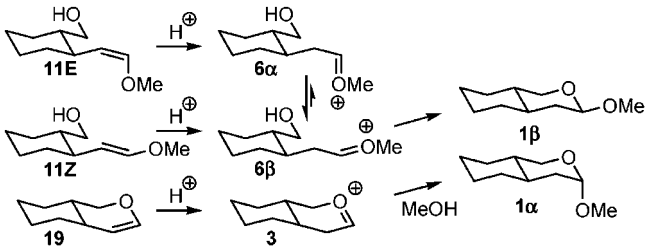
Received November 12, 2003

ABSTRACT



The cyclization of oxocarbenium ion conformers 6α and 6β (from 11E and 11Z) gave only the β-glycoside 1β, and the addition of methanol to the oxocarbenium ion 3 yielded mainly the α-glycoside 1α with both experiments being carried out under kinetically controlled conditions. RHF/6.31G* calculations reproduce well these experimental results and show that the endocyclic and the exocyclic C–O bond cleavage processes can compete in the hydrolysis of 1β, whereas 1α gets hydrolyzed by exocyclic C–O bond cleavage only.

The enzyme catalyzed hydrolysis of glycosides is an important biochemical transformation.[1] Two possible mechanisms for lysozyme hydrolysis of β-glycosides have been studied according to the C−O bond-breaking mode. From X-ray studies, Philips and co-workers suggested that the β-glycoside **1β** (Scheme 1) is first forced to distort into a twist-boat or sofa conformation **2β** during its binding process with the enzyme.[2] According to Deslongchamps,[3] this change of conformation is necessary for the cleavage of the exocyclic C−O bond, which takes place by specific acid catalysis[4] and with the assistance of an antiperiplanar lone pair of electrons of the ring oxygen.[3,5] The resulting cyclic oxocarbenium ion **3** then reacts with water to form the hydrolytic product **4**. On the other hand, Karplus[6] has proposed that conformational distortion is not necessary because it is the endocyclic C−O bond of **1β** that breaks down. In this pathway, the reaction takes place via the chair conformation **5β** and the cleavage is facilitated by stereoelectronic assistance of an antiperiplanar lone pair of electrons from the exocyclic oxygen. Many kinetic studies of glycopyranosides and THP acetals favor the first mechanism;[3−7] however, the 2nd mechanism cannot be ruled out.[8] The trapping experiments of Franck[9] on the acid-catalyzed cleavage of alkyl β-THP acetal derivatives and other glycoside cleavage experiments demonstrated that both pathways exist.[10] For α-glycosides, the known data support the stereoelectronically controlled exocyclic C−O

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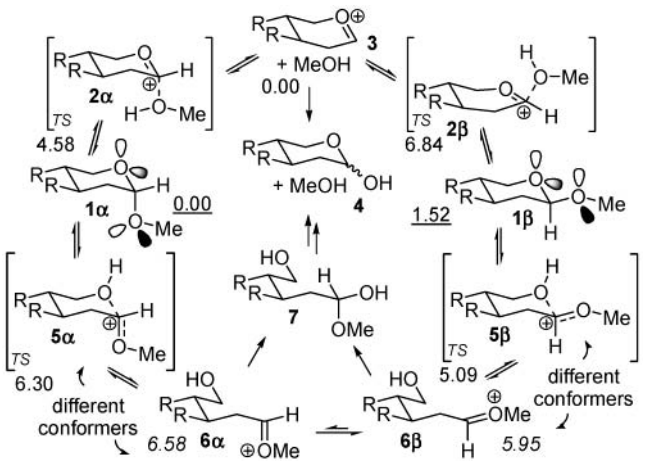
10.1021/ol036220+ CCC: $27.50
Published on Web 01/24/2004

bond breaking via their ground-state chair conformation (**1α** to **2α** to **3** to **4**).[3,5,11]

We have carried out a molecular modeling study of the various endocyclic and exocyclic cleavage pathways of the bicyclic tetrahydropyranyl acetals **1α** and **1*β*** (Scheme 1) and

Scheme 1[a]



[a] Plain numbers are relative energies (kcal/mol) of charged species **2**, **3**, **5**, and **6α**, and **6*β***; underlined numbers are relative energies of acetals **1α** and **1*β***. R = H (calculations). R = $(CH_2)_4$ (experimental). Italic numbers are for cations **6α** and **6*β*** in extended conformations (no interactions between cation and alcohol).

validated the theoretical results with suitable experiments to provide new valuable information on the hydrolysis of α- and *β*-glycosides. We calculated the energies of the four possible transition structures **2α**, **2*β***, **5α**, and **5*β*** and two intermediates **3** and **6** in the hydrolysis of the glycoside models **1α** and **1*β***. No true transition structures could be found (RHF/6.31G*) for the exocyclic pathways (structures **2α** and **2*β***). The potential energy surface corresponding to the endocyclic cleavages is also very flat, but the calculations indicate the presence of transition structures **5α** and **5*β***, having endocyclic C−O bond distances around 1.8−2.0 Å. Consequently, all the transition structures discussed in this work have their breaking C−O bond set at a distance of 1.9 Å, even those belonging to the exocyclic cleavage paths. Although our theoretical calculations do not include solvent and entropy effects, they are in good qualitative agreement with experimental data obtained in solution.[12]

For the hydrolysis of acetal **1α** to **4**, both the exocyclic (via **2α**) and the endocyclic (via **5α**) C−O bond cleavages take place via a chairlike transition structure conformation with stereoelectronic assistance (one electron lone pair antiperiplanar to the leaving group). Modeling analysis indicates that the transition structure **2α** for the exocyclic process is 1.72 kcal/mol lower than that of the endocyclic process (**5α**). In addition, there is an entropy effect favoring the exocyclic process (formation of two molecules: the oxocarbenium ion **3** and methanol). It is therefore expected that the transition structure for the exocyclic cleavage process for α-glycosides should be highly favored in agreement with the published experimental results.[3,5,7]

For the hydrolysis of acetal **1*β*** to **4**, calculations indicate that the transition structure **2*β*** for the exocyclic C−O bond cleavage takes place via a sofa conformation with an endocyclic oxygen lone pair periplanar to the C−O bond (syn or anti) to be cleaved.[13] For the endocyclic C−O bond cleavage, calculations show that the transition structure geometry **5*β*** remains close to the chair ground state conformation. This is the result of the participation of the exocyclic oxygen lone pair antiperiplanar to the leaving group. The enthalpy difference between the two transition structures **2*β*** and **5*β*** is 1.75 kcal/mol, now favoring the endocyclic C−O bond cleavage process. On the other hand, entropy disfavors the opening of a ring over the exocyclic C−O bond cleavage, which leads to the formation of two molecules. Since enthalpy favors one process and entropy the other, both processes could take place concurrently in accord with published experimental observations.[9]

The present calculations are in full agreement with the fact that the relative rate of hydrolysis of the α-anomer in a conformationally rigid model is faster than that of the *β*-anomer (rate ratio = 3/2):[14] The transition structure **2α** for the exocyclic C−O bond is less energetic (4.58 kcal/mol) than the *β*-isomer, **2*β*** (6.84 kcal/mol); it is also slightly lower in energy than the other competing endocyclic C−O bond cleavage of the *β*-isomer (**5*β***, 5.09 kcal/mol). The calculations show also that there is a slight energy difference (0.63 kcal/mol) between the 2 conformers **6*β*** and **6α** of the corresponding hydroxy-oxocarbenium ion **6**. The relative energy difference of these ions is enhanced in the corresponding transition structures **5*β*** and **5α**, respectively (1.21 kcal/mol favoring **5*β***). During the endocyclic hydrolysis of **1*β***, the hydroxy-oxocarbenium ion **6*β*** could undergo a rotation and recyclize via conformer **6α**, to give the more stable anomer **1α**. However, experimental results show that the isomerization of the *β*-anomer into the α-anomer does not take place concurrently with hydrolysis.[15] This suggests that either the exocyclic cleavage via **2*β*** is in fact much more favored for entropy reasons than the endocyclic cleavage via **5*β***, or the recyclization barrier **5α** is too high. Accordingly, if one can find a method to generate, in an essentially irreversible manner, the hydroxy-oxocarbenium ion **6**, it will exist preferentially in conformation **6*β***, which, in the absence of water, is expected to cyclize to give mostly the anomer

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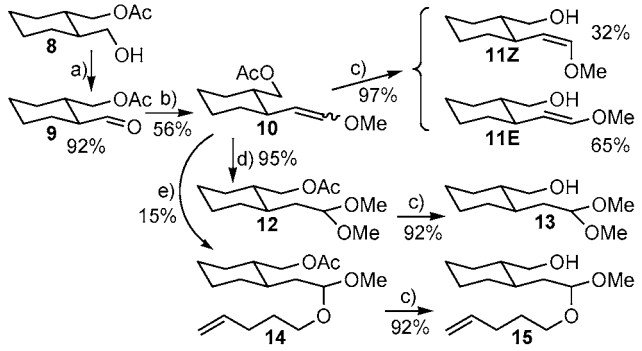
1β. On the contrary, the anomer **1α** would be preferentially obtained by adding methanol to the oxocarbenium ion **3**, as suggested by the 2.26 kcal/mol energy difference between the transition structures **2α** and **2β**.

Stimulated by these data, we have examined **three** different methods to generate an oxocarbenium ion such as **6** to study its preferred mode of cyclization. Hydroxy-enol ethers **11E** and **11Z** (Scheme 2) can be used for that purpose,

Scheme 2[a]



[a] Reagents and conditions: (a) (i) Swern; (ii) Et_3N. (b) Ph_3P^+MOM, LDA. (c) NaOH. (d) MeOH, Ph_3P-HBr. (e) $CH_2{=}CH(CH_2)_3OH$, Ph_3P-HBr.

since it is known that such compounds undergo hydrolysis with rate-limiting protonation of the C=C bond to produce the oxocarbenium ions **6α** and **6β**.[16] The same ion **6** can be generated from the acid-catalyzed treatment of the hydroxy-dimethoxy acetal precursor **13** or from the NBS oxidation of the hydroxy mixed acetal **15**.[17]

The starting materials **11E**, **11Z**, **13**, and **15** were prepared in the following manner: Swern oxidation of **8**[18] yielded the aldehyde **9**, which gave a 3:2 mixture of *E* and *Z* enol ether **10** (Wittig). Basic hydrolysis of **10** provided the pure enol ethers **11E** and **11Z**. Addition of methanol under acidic conditions to compound **10** gave dimethoxy acetal **12**, which produced the desired alcohol **13** after basic hydrolysis. From **10**, a similar procedure with *n*-pentenyl alcohol, instead of methanol, gave a diastereoisomeric mixture of hydroxyl mixed acetals **15** via **14**. Treatment of either hydroxy enol ether **11E** or **11Z** with TFA (catalytic) in benzene at room temperature gave exclusively the methoxy bicyclic acetal **1β** after 2 min (Scheme 3).[14b] The corresponding more stable acetal **1α** started appearing slowly after 4 min. Cyclization of hydroxy dimethoxy acetal **13** under similar conditions gave a 2:1 mixture of the anomers **1β** and **1α** after 2 min. The NBS-catalyzed cyclization of the mixed acetal **15** in deuterated acetonitrile produced a 2.6:1 mixture of **1β** and **1α**. We also examined the addition of methanol to the

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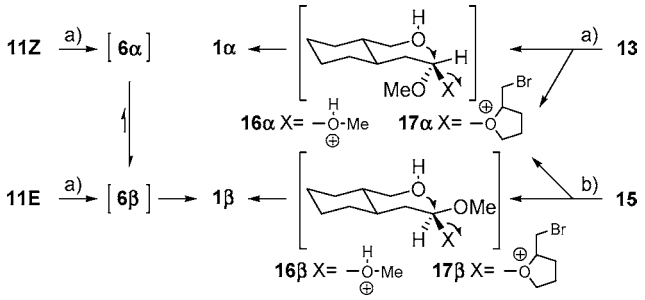
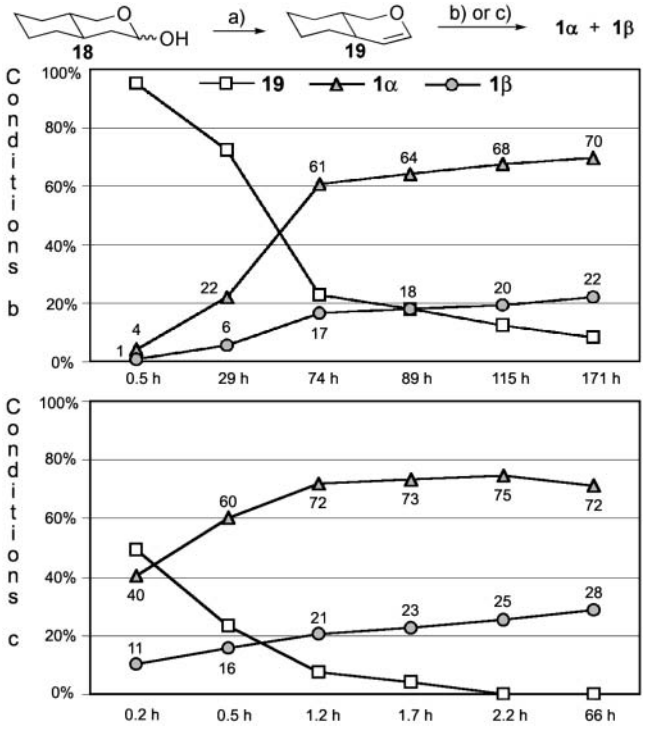
Scheme 3[a]



[a] Reagents and conditions: (a) TFA. (b) NBS. **13** yields **16** and **15** yields **17**.

oxocarbenium ion **3**, prepared in situ by acidic treatment of the bicyclic enol ether **19**, that had been obtained by dehydration of the corresponding lactol **18** (Scheme 4).[14b]

Scheme 4[a]



[a] Reagents and conditions: (a) PTSA. (b) **19** (0.1 mmol), AcOH (0.4 mmol), $CH(OMe)_3$ (0.2 mL), MeOH (2 mL). (c) **19** (0.1 mmol), TFA (0.1 mmol), $CH(OMe)_3$ (0.2 mL), MeOH (2 mL).

Treatment of **19** with either acetic acid or trifluoroacetic acid in methanol and in the presence of trimethyl orthoformate (acting as a trap for water) yielded mainly the most stable anomer **1α**. The reaction is much faster with TFA, since only 24% of starting material **19** remains after 0.5 h, and none after 2.2 h. In the case of acetic acid, there is as much as 95% of enol ether **19** after 0.5 h, and still 8% left after 171 h. On the other hand, the **1α**/**1β** ratios are constant

and similar all along in both experiments (80/20 to 72/28 bracket). This confirms that under the experimental conditions used, both compounds **1α** and **1*β*** equilibrate extremely slowly. The average **1α**/**1*β*** experimental ratio of 76/24 is therefore kinetic; it differs substantially from the thermodynamic ratio of 68/32 established for **1α** and **1*β***.[12b]

Upon protonation, the enol ether **11E** should give directly the most favored oxocarbenium ion conformer **6*β*** (Scheme 3), which should then cyclized to give mostly the anomer **1*β***. whereas the enol ether **11Z** should first produce the less favored conformer **6α**, which can either cyclize directly to the corresponding anomer **1α** or else undergo a C−C rotation to produce the more stable **6*β*** conformer then the anomer **1*β***. Only the anomer **1*β*** was observed under kinetically controlled conditions. Therefore, these experimental results demonstrate that the cyclization takes place only via **6*β***. The late appearance of the anomer **1α** corresponds to the beginning of a thermodynamically controlled process, which can take place by the slow reopening of the anomer **1*β*** to produce **6*β***, which can then rotate to give **6α** then the more stable anomer **1α**. The formation of a mixture of anomers **1*β*** and **1α** from the mild acid treatment of dimethoxy acetal **13** must be the result of a different mechanism, because the equilibration between **1α** and **1*β*** is very slow under these conditions. Formation of an important quantity of the two isomers must be the result of a direct SN2 displacement of the protonated species **16α** and **16*β*** of dimethoxy acetal **13**. This type of SN2 pathway has been proposed in the hydrolysis of a diethyl acetal.[19] A similar conclusion can be reached for the NBS oxidation of the diastereoisomeric methoxy-*n*-pentenoxy acetal **15** where the isomers **1*β*** and **1α** would be produced from intermediate **17*β*** and **17α**, respectively. Therefore, the specific formation of anomer **1*β*** from the acid-catalyzed cyclization of hydroxy enol ether **11E** and **11Z** can be explained only via the intermediate formation of the more stable hydroxy-oxocarbenium ion **6*β***. These results can be taken as strong evidence that the cyclization of **6** produced the anomer **1*β*** as suggested by our calculations.

We have also briefly examined the acid cyclization of hydroxy-enol ethers **11Z** and **11E** in the presence of water (1 equiv) and using benzene as solvent with a catalytic amount of trifluoroacetic acid. After 10 min, a mixture of lactol **4** (6%), α-anomer **1α** (20%), and *β*-anomer **1*β*** (70%) was obtained. Thus, the experimental data indicate that, under such conditions, the intramolecular cyclization process was still favored, although a competing nucleophile (water) was present in the reaction medium. On the other hand, when the reaction was carried out with a substantial amount of water [TFA (cat) + D_2O (0.1 mL) + CD_3CN (0.4 mL)] only the hydrolysis product lactol was observed, indicating that water trapping of the oxocarbenium ion **6** was the major process.

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Addition of methanol to the oxocarbenium ion **3** occurs via a path almost perpendicular to the C−O═C−C plan according to kinetic stereoelectronic control, which follows the Bürgi−Dunitz angle of attack.[20] There are two possibilities to do so, either from the α face, via a chair transition structure **2α** and leading to the anomer **1α**, or via a more energetic boat/sofa transition structure **2*β***, leading to the anomer **1*β***. The calculated energy gap of 2.26 kcal/mol corresponds to a **1α**/**1*β*** ratio of 98/2. Although this ratio gives the right trend, it is however much higher than the experimental result of 76/24, with an energy difference of 0.70 kcal/mol. In fact, such a small difference suggests that the position of the transition state might be in fact much later than arbitrarily set in our calculations at 1.9 Å. Thus, at 2.1 Å, the theoretical energy difference becomes as small as 1.3 kcal/mol and implies that a late transition state picture gives a better description of the reaction path (**1α** to **2α** to **3**, **1*β*** to **2*β*** to **3**, and early transition states for the reverse reactions).[14a,21]

From this study and other available evidence, it seems quite clear that the α-glycosides undergo hydrolysis in their ground-state chairlike conformation via an exocyclic C−O bond cleavage while following the principle of kinetic stereoelectronic control (proper orbital alignment). *β*-Glycosides can be hydrolyzed either by an exocyclic C−O bond cleavage via a distorted twist-boat or sofa conformation or by an endocyclic C−O bond cleavage in the ground-state chairlike conformation. Both cleavages take place via late transition states and with stereoelectronic control. The exocyclic cleavage is favored by entropy and the endocyclic cleavage might be disfavored because the resulting hydroxy-oxocarbenium ion (like **6*β***) might undergo a fast cyclization to give back the *β*-glycoside rather than undergoing a reaction with water to produce the hydrolysis product. On that basis, the hydrolysis of *β*-glycosides can take place, in principle, via both the exocyclic and the endocyclic pathways,[22] the choice depending on the specific structure of the substrate and on the reaction conditions (acid catalyzed or enzymatic).[23]

Acknowledgment. We thank NSERC Canada and FQRNT Québec for financial support.

Supporting Information Available: Experimental procedures and full characterizations for compounds **9**−**15** and **19** and calculation details. This material is available free of charge via the Internet at http://pubs.acs.org.

OL036220+

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