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Reaction kinetics and mechanism of acid-catalyzed anomerization of 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-L-ribofuranose

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ABSTRACT

The mechanism of the acid-catalyzed anomerization of 1-*O*-acetyl-2,3,5-*O*-benzoyl-α- and -β-L-ribofuranoses in different acetic acid–acetic anhydride mixtures was investigated. The progress of the reactions was followed by NMR spectroscopy and the rate constants for the reactions were determined by the use of a kinetic model. The site of anomeric activation was clarified by the use of ^{13}C-labeled acetic acid and acetic anhydride, respectively, proving that the anomerization takes place by exocyclic C–O cleavage, thus ruling out anomerization via acyclic intermediates. The role of the acetyl cation as the catalytically active species was further verified.

1. Introduction

Nucleoside mimics form an emerging class of drugs for antiviral and anticancer therapies and hence the interest in the use of L-nucleosides as chemotherapeutic agents is growing.[1] The somewhat unexpected discovery that some of the non-natural L-nucleosides possess better binding properties to enzymes than the natural D-nucleosides has given rise to extensive research within the fields of nucleobase, as well as sugar modified L-nucleosides.[2] A great deal of research has been focused on optimizing yields and stereospecificities in the glycosylation steps of the nucleoside synthesis. A number of protocols involving the use of 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-L-ribofuranose (**2**) or the corresponding sugar halide as the sugar component in glycosylation have been described. The best known of these are the Wittenburg procedure[3] and the silyl-Hilbert–Johnson reaction[4] utilizing the sugar bromide or, alternatively, the latter was performed by using acylated ribose in the presence of a Friedel–Crafts catalyst (Vorbrüggen conditions).[5]

We are currently investigating in detail the synthesis of ester-protected L-ribofuranoses and we became interested in the fundamental mechanism of anomerization in 1-O-acetylated L-ribofuranoses under standard acetolysis conditions. Whereas extensive studies on both acid and base catalyzed anomerization and hydrolysis of various alkyl furanosides have been reported recently,[6] only a few investigations have targeted the corresponding reactions of acylated furanoses regardless of their wide use in synthetic nucleoside chemistry.[7] The mechanism of anomerization, as it relates to *fundamental carbohydrate chemistry*, has been the subject of much investigation. However, an ongoing debate exists on whether the anomerization proceeds via *endo*- or *exo*-cyclic activation. Lönnberg and Kulonpää have shown that the hydrolysis of β-D-ribofuranosides takes place either by opening of the five-membered ring or by formation of a cyclic oxo-carbenium ion, the path taken depending on the electronegativity of the aglycon group.[8] In the present investigation, we report kinetic data on the anomerization of 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-L-ribofuranose obtained by NMR spectroscopy and propose a mechanism for the anomerization and formation of the acyclic side products in various acetylation media, including different acetic acid/acetic anhydride mixtures as catalyzed by sulfuric acid or zinc chloride.

2. Results and discussion

The anomerization reactions of 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-α- (**1**) and β-L-ribofuranoses (**2**) were carried out at 25 °C in a mixture of acetic acid and acetic anhydride (5:4 v/v) containing 0.75% sulfuric acid and monitored by ^{1}H NMR spectroscopy. All compounds formed: **1**, **2** and the acyclic 1,1,4-tri-*O*-acetyl-2,3,5-tri-*O*-benzoyl-L-ribose hydrate **3** were characterized by ^{1}H and 2D NMR spectroscopic techniques. The structures of all compounds present in the anomerization reaction studies are shown in Figure 1 (for details, see Supplementary data). Pyranose forms were not detected in these experiments.

The NMR chemical shifts of the signals arising from the different compounds present in the reaction mixture clearly deviate from each other, thus allowing the determination of relative product concentrations by simple integration of the anomeric signals in the ^{1}H NMR spectra. As shown in Figure 2, the anomerization

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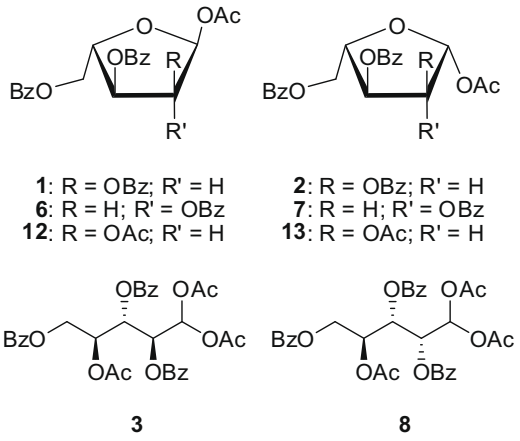


Figure 1. Structures of the compounds studied in the anomerization experiments.

reactions produce equilibrium mixtures of **1** and **2** containing 29% and 71% of the α and β anomers, respectively, regardless of whether pure **1** or **2** is used as starting material.

Low concentrations of the acyclic ribose hydrate **3** were detected as well, the observation being consistent with earlier reports on endocyclic cleavage in furanosides.[8] The anomerization of acetylated glucopyranosides has been proposed to proceed, under similar conditions, via a ring-opening/ring-closing process where the ring oxygen is acetylated in the acyclic form.[9] However, in the present study, when pure **3** was treated under similar acetylation conditions as employed for **1** and **2** using the acetylation mixture containing 0.75 vol % sulfuric acid, none of the furanoses **1** and **2** were detected. This observation is, in fact, in agreement with the 1965 results of Painter who claimed that no ring closing of the fully acylated acyclic intermediate took place which would require the C4 ester to act as a nucleophile.[10] The fact that no ring closing of the fully acylated ribose hydrate **3** takes place suggests that the formation of this product is not in equilibrium with the furanoses but rather serves as a molecular exit. When the anomerization reactions were repeated for **1** and **2** with 7.5 vol % of sulfuric acid a constant accumulation of compound **3** was observed showing 10 mol % of **3** after 96 h. In order to verify whether the anomerization takes place via endocyclic or exocyclic cleavage, the reactions were repeated using acetic acid-1-^{13}C and acetic anhydride-1,1′-$^{13}C_2$. The reactions were followed by quantitative ^{13}C NMR

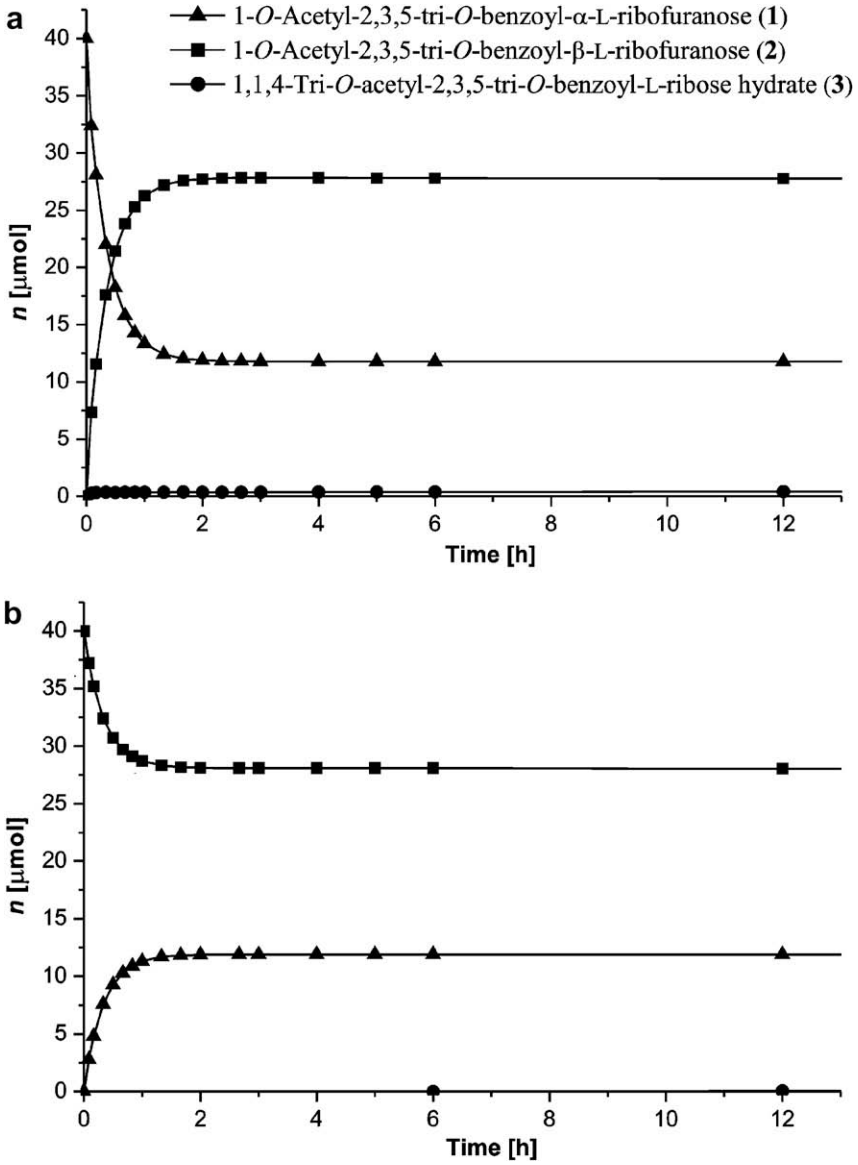


Figure 2. Time-dependent product distributions in the anomerization of (a) compound **1**, and (b) compound **2** in a 5:4 (v/v) AcOH–Ac_2O mixture catalyzed by 0.75% of H_2SO_4.

spectroscopy. By carrying out the reaction from **1**, a slow decrease in the concentration of starting material and in the concurrent formation of the ^{13}C-labeled α and β anomers **4** and **5** was observed as presented in Supplementary data (Fig. S4). When, on the other hand, compound **2** was used as the starting material, an immediate exchange of the acetoxy group was observed followed by subsequent anomerization of the ^{13}C-labeled β-anomer **5** to provide the equilibrium mixture of **4** and **5** (Fig. 3a).

Neither of the reactions showed any formation of the other unlabeled anomer, clearly suggesting anomerization via exocyclic cleavage. The difference in the reaction rates between **1** and **2** may be explained by the *trans*-1,2-configuration in the β-anomer, which evidently gives rise to neighboring group participation from the benzoyl group at C2 thus resulting in fast exchange of the 1-*O*-acetyl group[11]. In order to verify the role of neighboring group participation, we synthesized the analogous 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-α- (**6**) and β- (**7**) L-arabinofuranoses, the structures of which are shown in Figure 1. Similar experiments as carried out earlier for the ribose-based compounds were then repeated using **6** and **7** producing the expected reaction pattern: The acylated α-arabinofuranose **6** possessing 1,2-*trans* configuration underwent immediate cleavage and exchange of the anomeric acetyl group similar to the analogous β-ribofuranose to form ^{13}C-labeled 1-*O*-acetyl α-L-arabinofuranose (**9**) which then anomerized to give the corresponding β-anomer **10** (Fig. 3b). In an analogous fashion, the β-arabinofuranose **7** followed a reaction pattern similar to that observed for **1** to give a mixture of the labeled compounds **9** and **10** in 74% and 26% proportions, respectively, results provided in Supplementary data (Figure S5). Due to minor overlapping of the ^{13}C NMR methyl carbon signals of the acetyl groups, the accuracy of the analytical results in the arabinose study was not as high as that in the ribose case. When the reaction time was prolonged some formation of the corresponding acylated acyclic L-arabinose hydrate (**8**) was observed.

Earlier, Lindberg has studied the action of strong acids on acetylated glucosides.[9] He proposed that the source of catalytic activity in a solution of sulfuric acid in acetic acid/acetic anhydride is the acetyl cation formed upon reaction of the anhydride with sulfuric acid. We aimed to verify this hypothesis by comparison of our results obtained from the sulfuric acid-catalyzed reactions with those of anomerization experiments catalyzed by zinc chloride in acetic acid–acetic anhydride. Acetic anhydride and zinc chloride are used in Friedel–Crafts acylation reactions where the Lewis acid supposedly reacts with the anhydride to form the active acetyl cation. The anomerization solution was prepared by dissolving 13% by weight of zinc chloride in a mixture of acetic acid and acetic anhydride (3:7, v/v). The reactions were monitored by ^{1}H and ^{13}C NMR spectroscopy in order to clarify the mechanism. The anomerization of **1** and **2** under these conditions followed the same pattern as observed for the sulfuric acid-catalyzed reactions. It appears that

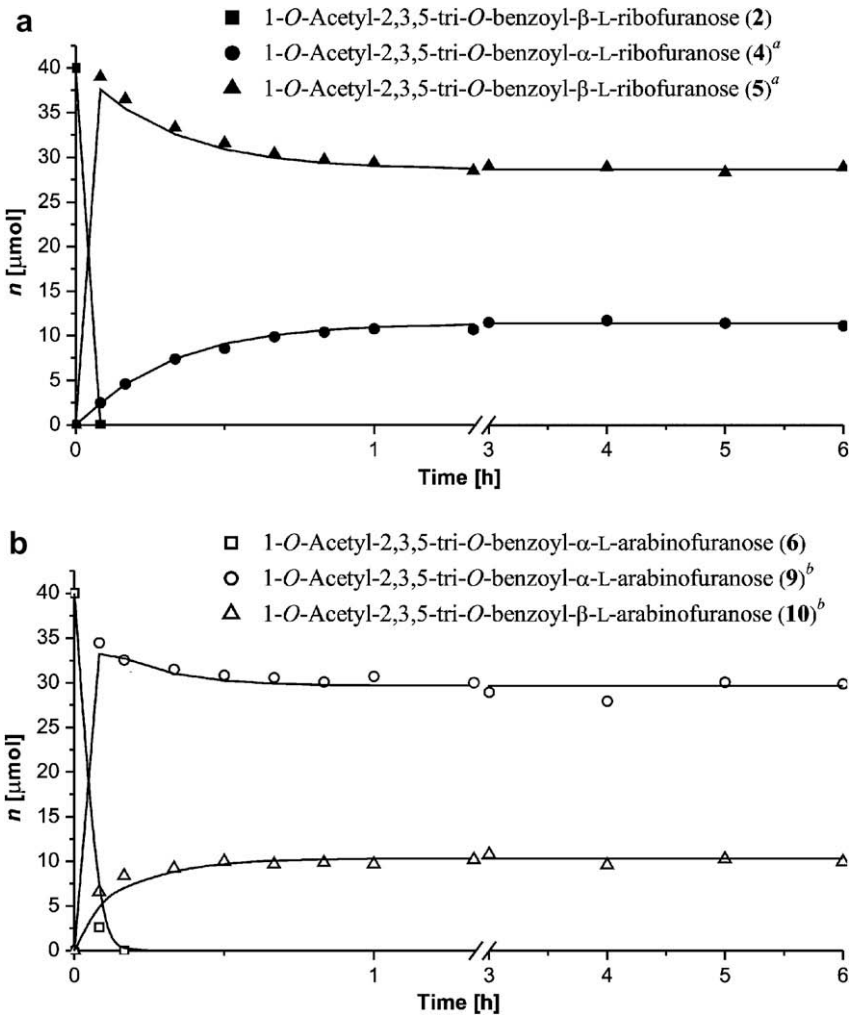


Figure 3. Anomerization and acetyl exchange of (a) acylated β-L-ribofuranose (**2**) and (b) acylated α-L-arabinofuranose (**6**) as studied by ^{13}C NMR spectroscopy. Experimental and modeled results are presented as symbols and as solid lines, respectively. (a) Carbonyl carbon labeled in acetyl group. (b) Methyl carbon labeled in acetyl group.

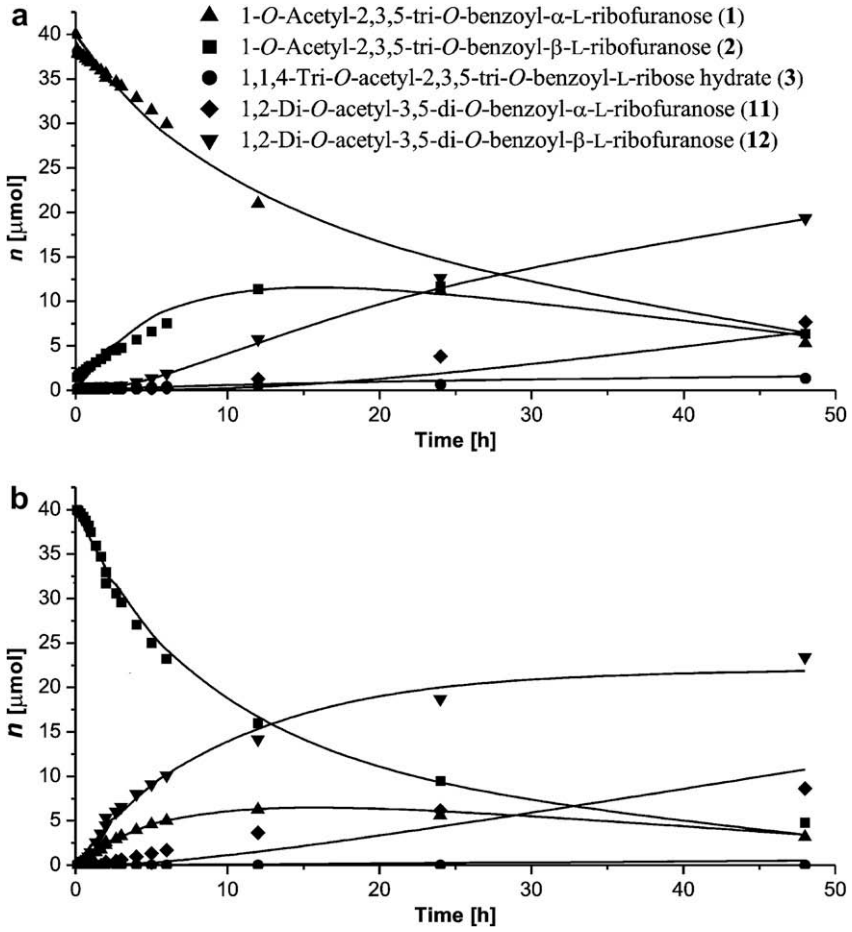


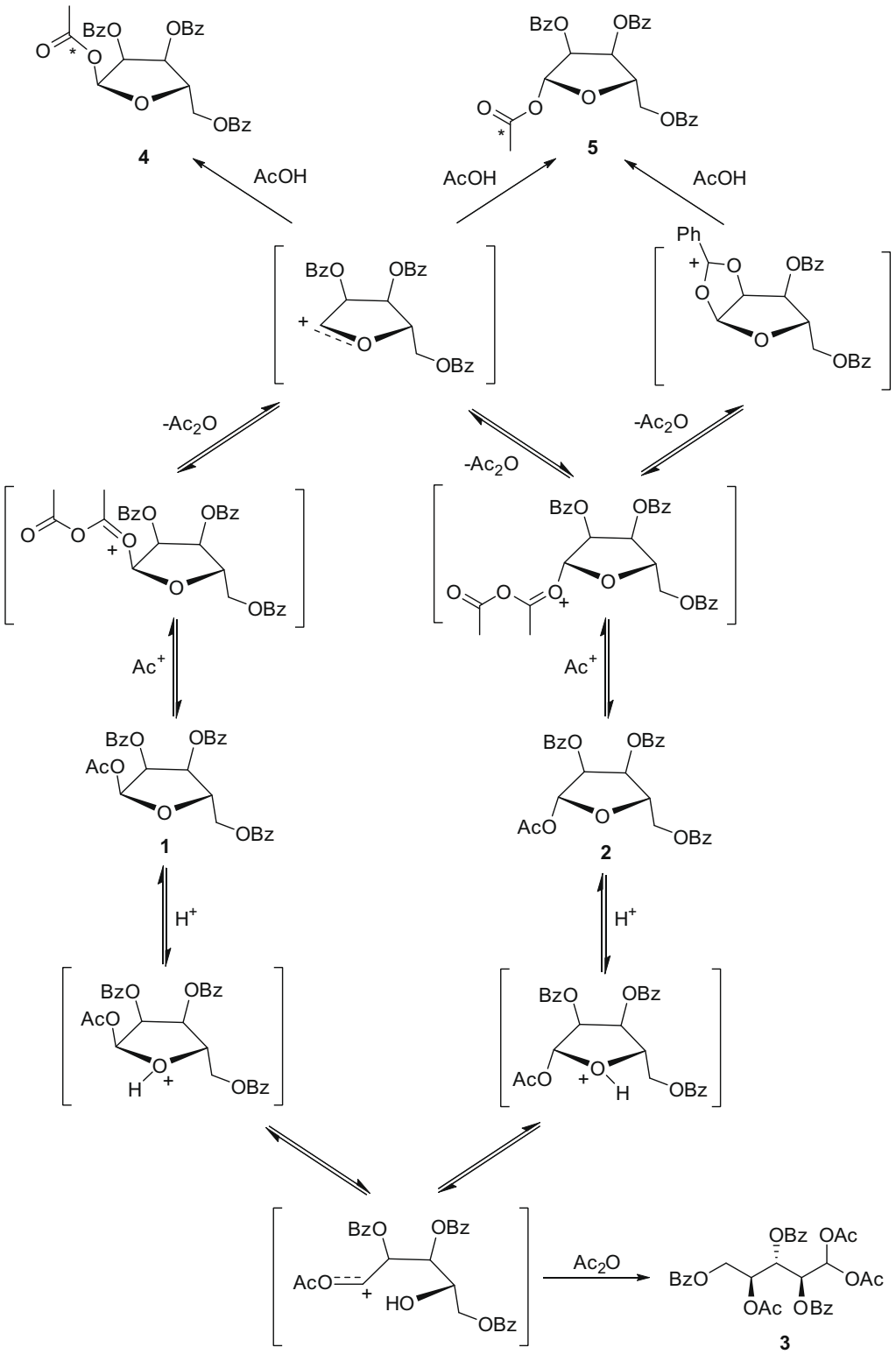
Figure 4. Time-dependent product distribution in the anomerization experiments of (a) **1** and (b) **2** in 0.75 vol % solution of H_2SO_4 in AcOH. Experimental and modeled results are presented as symbols and as solid lines, respectively.

the change from Brønsted to Lewis acid does not influence the mechanism of anomerization, providing further evidence for the role of the acetyl cation as the catalytically active species, in accordance with the Lindberg hypothesis. The only observable difference between the results from the two sets of experiments (Lewis vs Brønsted acid) is that in the reactions catalyzed by zinc chloride a smaller amount of the acyclic product was formed. Nevertheless, these observations disagree with the results of Montgomery and coworkers,[12] who reported that the treatment of methyl 2,3,4-tri-*O*-acetyl-β-D-arabinopyranoside under similar conditions only gave acyclic acetyl methyl acetals without any formation of furanoses or pyranoses. To further shed light on the mechanism of anomerization in ribofuranoses **1** and **2**, we removed the acetic acid from the zinc chloride-catalyzed system and repeated the experiments. Again, the anomerization of both **1** and **2** followed the earlier observed route to reach the equilibrium. However, in this case, we did not detect any formation of compound **3** at all. This observation further supports the suggestion that the anomerizations of **1** and **2**, and the formation of the acyclic ribose hydrate **3**, follow different mechanistical pathways. In addition, a set of experiments catalyzed by sulfuric acid in acetic acid in the absence of added acetic anhydride were carried out in order to verify whether the removal of the source of the catalytically active acetyl cation would influence the reaction mechanism. For these experiments, a 0.75 vol % solution of sulfuric acid in acetic acid was prepared. The course of the reaction changed dramatically upon removing the acetic anhydride from the system: By use of the β-anomer **2** as starting material, a slow anomerization to the α-anomer **1** was still observed, but the main reaction consisted of the formation of two new compounds 1,2-di-*O*-acetyl-3,5-di-*O*-benzoyl-α- (**11**) and β- (**12**) L-ribofuranoses, characterized by a set of 2D NMR experiments. When starting the reaction from the α-anomer **1**, anomerization to form the β-anomer **2** was first observed, followed by the subsequent formation of compounds **11** and **12** (Fig. 4).

Due to severe overlap of the ^{13}C NMR signals from the acetyl groups in compounds **11** and **12** and the anomeric acetyl group of compound **2**, much information on the exchange of the anomeric acetoxy groups could not be extracted from the experiments with ^{13}C-labeled reagents. The only confident conclusion from these ^{13}C NMR experiments was that no immediate exchange of the unlabeled acetyl group of compound **2** with a labeled one, as seen in the earlier experiments, takes place.

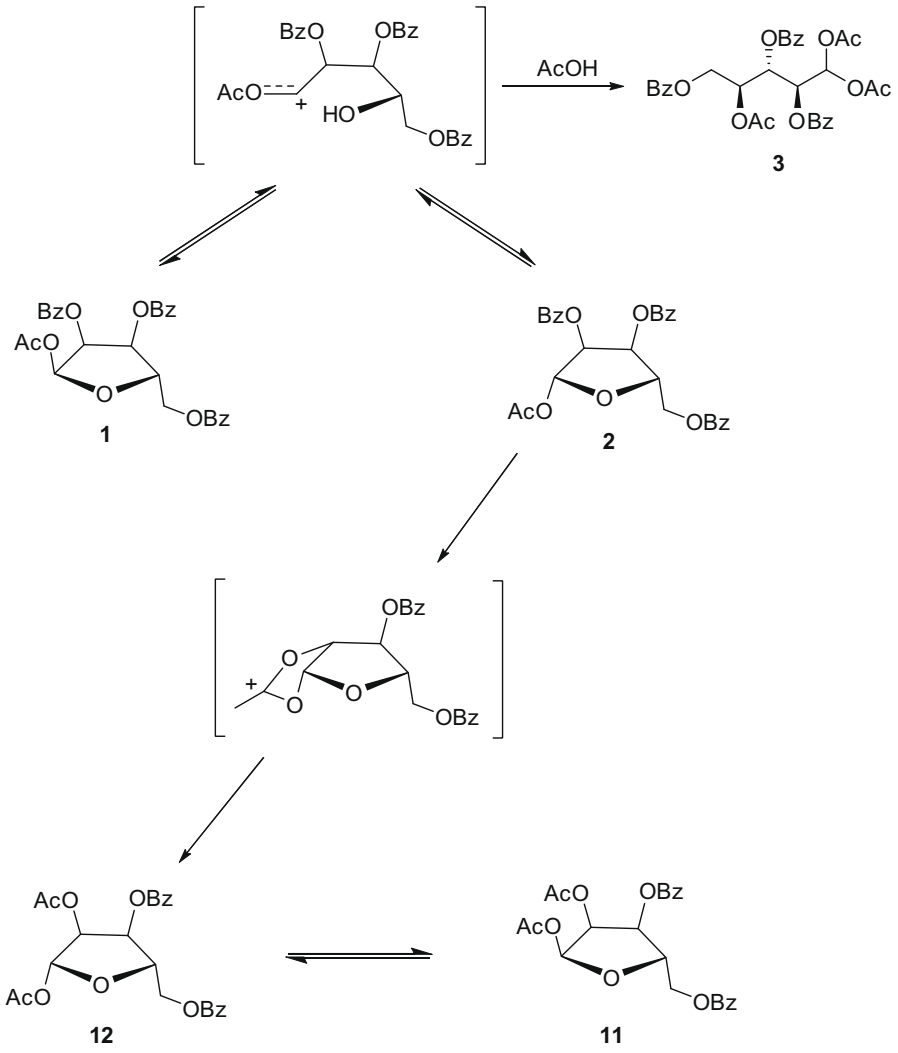
Based on these results, we propose a mechanism for the anomerization of 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-L-ribofuranose, where the acetyl cation formed in the acetylation media activates the anomeric acetyl group for *exo* C–O cleavage, as presented in Scheme 1.

The fact that no change in the overall reaction path is observed as long as acetic anhydride, the source of the acetyl cation, is present, is in good agreement with the earlier results of Lindberg.[9] Furthermore, the results from the ^{13}C-labeled experiments clearly rule out any anomerization via acyclic intermediates, as this would result in the formation of the opposite anomer while retaining the original unlabeled acetoxy group. The immediate exchange of the acetoxy groups of β-ribofuranose and α-arabinofuranose further evidences the formation of a *cis*-fused dioxonium ion intermediate



Scheme 1. Proposed mechanism for the acid-catalyzed anomerization of 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-α- (**1**) and β-L-ribofuranose (**2**).

via neighboring group participation. The retention of stereochemistry in the fast acetoxy exchange observed for the β-anomer **2** is not observed for the α-anomer **1** possessing a 1,2-*cis* configuration. Formation of the acyclic 1,1,4-tri-*O*-acetyl-2,3,5-tri-*O*-benzoyl-L-ribose hydrate (**3**), detected in the reactions catalyzed by sulfuric acid or carried out in the presence of a Brønsted acid, did not take place in acetic anhydride when the anomerization was catalyzed by zinc chloride. These observations indicate that the ring-opening reaction is catalyzed by protonation of the ring oxygen followed by subsequent acetylation to form **3**, which in turn is not in equilibrium with **1** and **2**. From the results obtained here, it can also be seen that the α-anomer **1** is more prone to form the acyclic hydrate **3** than the β-anomer **2**. The observed difference toward ring opening between the α- and β-anomers is in good agreement with the



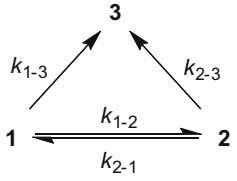
Scheme 2. Proposed mechanism for the formation of 1,2-di-*O*-acetyl-3,5-di-*O*-benzoyl-α-**12** and β-L-ribofuranose **13**.

previously published results, although the anomeric effects used to explain this type of differences are not as significant in furanoses as they are in pyranoses.[13] The formation of compounds **11** and **12** in the absence of acetic anhydride can be explained by acetyl group-assisted replacement of the benzoyl group at C2 (Scheme 2).

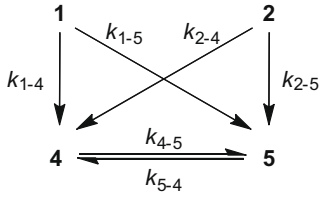
As evidenced by the experimental results, it is the β-anomer **2** that is converted to the diacetylated β-anomer **12** with subsequent anomerization to **11**. As the reaction proceeds with retention of stereochemistry at C2, it is reasonable to suggest that the 1-*O*-acetyl group at C1 participates in the replacement of the benzoyl group at C2. The cyclic oxonium ion formed is then attacked by acetic acid at C2 to form the 1,2-*trans*-diacetylated compound **12**.

Reaction schemes representing the smallest amount of reactions required to describe the anomerizations of **1** and **2** and the subsequent formation of the acyclic hydrate **3**, as well as the formation and anomerization of the labeled compounds **4** and **5** are depicted in Schemes 3 and 4, respectively.

Kinetic calculations of the anomerization reaction presented in Scheme 3 were based on the 7.5% sulfuric acid containing mixture of acetic acid and acetic anhydride (5:4 v/v). When lower concentrations of sulfuric acid were used, the amount of **3** formed in the reaction was so low that the accuracy of the integration of the proton spectra was not sufficient for kinetic calculations. Kinetic modeling showed that the reaction rate r_{2-3} is equal to zero which further supports that compound **3** is formed only from the α-anomer **1**. The equilibrium constant for the reaction between **1** and **2** was determined from the experimental data as $K_{2-1} = 0.43$ while



Scheme 3.



Scheme 4.

Table 1
First order rate constants for the reactions involved in the H_2SO_4 catalyzed anomerization of **1** and **2** carried out at 25 °C in different AcOH/Ac_2O mixtures

Reaction conditions[a] k (h^{-1})		Reaction conditions[b] k (h^{-1})		Reaction conditions[c] k (h^{-1})	
k_{1-2}	33.21 ± 1.33	k_{1-4}	0[d]	k_{1-2}	0.06 ± 0.0014
k_{2-1}	14.28 ± 0.57	k_{1-5}	2.26 ± 0.022	k_{2-1}	0.034 ± 0.0021
k_{1-3}	0.0037 ± 0.00006	k_{2-4}	0[d]	k_{1-3}	0.002 ± 0.00056
k_{2-3}	0[d]	k_{2-5}	89.4 ± 0.12	k_{2-3}	0[d]
		k_{4-5}	2.35 ± 0.0023	k_{2-12}	0.058 ± 0.0011
		k_{5-4}	0.94 ± 0.0014	k_{12-11}	0.012 ± 0.00059

[a] The reaction was carried out in AcOH/Ac_2O (5:4 v/v) containing 7.5% H_2SO_4.
[b] The reaction was carried out in ^{13}C-labeled AcOH/Ac_2O (5:4 v/v) containing 0.75% H_2SO_4.
[c] The reaction was carried out in AcOH containing 0.75% H_2SO_4.
[d] Rate constants set to 0 based on kinetic modeling.

the rate constants k_{1-2}, k_{2-1}, and k_{1-3} were estimated. The initial rates when starting from the α-anomer **1** or the β-anomer **2** are given in Supplementary data (Table S5). The rate constants obtained for the partial reactions involved have been listed in Table 1.

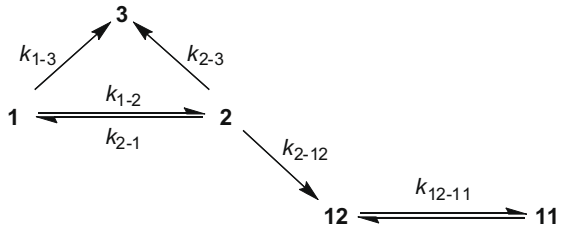
The experimental data combined with the kinetic modeling show that, in the acetyl exchange experiments performed with ^{13}C-labeled acetic acid and acetic anhydride, the reaction rates r_{1-4} and r_{2-4} are equal to zero (Scheme 4). This further indicates that regardless of whether the reaction is started from the α-anomer **1** or the β-anomer **2**, the starting material is always first converted into the labeled β-anomer **5** which subsequently anomerizes to reach the equilibrium between compounds **4** and **5**. The equilibrium constant for the reaction between **4** and **5** was determined from the experimental data as $K_{5-4} = 0.399$.

In the reactions where the anomerization was studied in the absence of acetic anhydride (Fig. 4), compound **3** was formed in small quantities when starting from **1**. When, on the other hand, **2** was used as the starting material, compound **3** was not detected at all. That r_{2-3} in Scheme 5 equals to zero was also shown by the kinetic modeling which is in good agreement with all other results on the formation of compound **3**. The equilibrium constant for the anomerization of **1** and **2** in the absence of acetic anhydride is given in Supplementary data (Table S6).

In the modeling, the reaction r_{12-11} was considered to be irreversible as no equilibrium between the compounds **11** and **12** was formed during the time period when the reaction was followed. For this reason we could not determine the equilibrium constant K_{12-11}, although the eventual equilibrium between compounds **11** and **12** would probably have been established if the reaction was allowed to continue for a longer time period.

3. Summary and conclusions

To summarize, new mechanistic and kinetic data on the anomerization of acylated L-ribofuranoses under different acetolysis conditions have been obtained thus contributing to the understanding of fundamental phenomena in carbohydrate chemistry. Our results show that the mechanism of anomerization is independent on the choice of type of acid employed (Brønsted vs Lewis acid), providing evidence for the role of the acetyl cation as the catalytically active species. Also, the dramatical change of reaction mechanism when acetic anhydride was removed from the system supports this hypothesis. Based on the experiments using ^{13}C-labeled acetic acid and acetic anhydride it can be deduced that the anomerization occurs via exocyclic C–O cleavage. The role of the neighboring benzoyl group at C2 in the cleavage, and the introduction of the anomeric acetyl group are significant as it becomes evident by inspecting Figure 3. The results herein contribute to the elucidation of fundamental reaction mechanisms in organic chemistry in general and in carbohydrate chemistry in particular, and may be utilized in further development of stereospecific glycosylation reactions in nucleoside synthesis.



Scheme 5.

4. Experimental

4.1. General experimental details

Synthesis of all starting compounds and detailed kinetic data are provided in Supplementary data. The anomerization experiments were carried out in sealed NMR tubes inside the magnet thermostated to 25 °C by a Bruker variable temperature unit. The NMR spectra were recorded using a Bruker Avance 600 MHz spectrometer equipped with a 5-mm inverse *z*-axis fg probe operating at 600.13 MHz for ^{1}H and at 150.92 MHz for ^{13}C. ^{1}H NMR spectra were acquired with single-pulse excitation, 45° flip angle, pulse recycle time of 3.6 s, and with spectral widths of 12 kHz consisting of 64 k data points. The quantitative ^{13}C NMR spectra were recorded with single-pulse excitation, 90° flip angle, pulse recycle time of 10 s, and with spectral widths of 3 kHz consisting of 64 k data points. Inverse-gated decoupling techniques were applied in order to avoid NOE.

The kinetics of the anomerization process was described with a first order reaction kinetics model. The reactor was described with a batch reactor model.

$$\frac{dc_i}{dt} = r_i$$

For the parameter estimation the following objective function was minimized:

$$Q = \sum_i \sum_t (c_{i,t,\mathrm{exp}} - c_{i,t,\mathrm{model}})^2 w_{i,t}$$

where $c_{i,t,\mathrm{exp}}$ and $c_{i,t,\mathrm{model}}$ are the experimentally recorded concentrations and the concentrations predicted by the model, respectively. The weight factor w was set to 1 for all experimental points. The software Modest was used to estimate the rate constants and to solve the reactor mass balances, the software minimizes the objective function with the Levenberg–Marquardt method, and solves the ODEs describing the reactor model by the backward difference method.[14] The fit of the model to experimental data of the reactions is presented in Figures 3 and 4 and in Supplementary data (Figs. S7–S14). As can be seen from the figures, the model can describe the experimental data very well. The estimated rate constants, kinetic models, and reactor component mass balances are listed in Tables S1–S4 (Supplementary data). The estimated kinetic constants are well identified (parameter sensitivity analysis plots in Supplementary data) and all the parameter errors are low.

4.2. General procedures for the anomerization reactions in AcOH–Ac_2O mixture with H_2SO_4

Compounds **1**–**3** and **6**–**7** (20 mg) were dissolved in 550 μl of CD_2Cl_2. To this solution was added 63 μl of a 5:4 (v/v) mixture of

AcOH and Ac_2O containing 0.75 or 7.5 vol % H_2SO_4. ^1H NMR spectra were recorded at different time intervals and the molar concentrations of the products were determined from the integral ratios.

4.3. General procedure for the anomerization in AcOH–Ac_2O catalyzed by $ZnCl_2$

Compounds **1** and **2** (20 mg) were dissolved in 550 μl of CD_2Cl_2. A solution of $ZnCl_2$ (20 mg) in AcOH (37 μl) and Ac_2O (85 μl) was prepared. The reaction was started by mixing the two solutions in the NMR tube. ^1H NMR spectra were recorded at different time intervals and the molar concentrations of the products were determined from the integral ratios.

4.4. General procedure for the anomerization in Ac_2O catalyzed by $ZnCl_2$

Compounds **1** and **2** (20 mg) were dissolved in 550 μl of CD_2Cl_2. To this solution was added a solution of $ZnCl_2$ (5 mg) in Ac_2O (100 μl). ^1H NMR spectra were recorded at different time intervals and the molar concentrations of the products were determined from the integral ratios.

4.5. General procedure for the anomerization in AcOH catalyzed by H_2SO_4

Compounds **1** and **2** (20 mg) were dissolved in 550 μl of CD_2Cl_2. Next, 63 μl of a 0.75 vol % solution of H_2SO_4 in AcOH was added to initiate the reaction. ^1H NMR spectra were recorded at different time intervals and the molar concentrations of the products were determined from the integral ratios.

4.6. General procedures for the quantitative ^{13}C experiments

For all reactions with compounds **1**–**3** acetic acid-1-^{13}C and acetic anhydride-1,1′-$^{13}C_2$ were used, while with compounds **6** and **7** acetic acid-2-^{13}C and acetic anhydride-2,2′-$^{13}C_2$ were used to obtain the best possible separation of the acetyl resonances for the determination of the reaction rates. The experiments were performed following the general procedures given above.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.carres.2009.02.031.

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