Carbohydrate Research 346 (2011) 2004–2006

Contents lists available at ScienceDirect

Carbohydrate Research

journal homepage: www.elsevier.com/locate/carres

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A kinetic study on the reductive opening of the diphenylmethylene acetal in methyl 2,3-*O*-diphenylmethylene-α-L-rhamnopyranoside

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ARTICLE INFO

Article history:
Available online 3 May 2011

Dedicated to Professor András Lipták on the occasion of his 75th birthday

Keywords:
Diphenylmethylene acetal
Reductive opening
Chloroalane
Kinetics

ABSTRACT

Reductive opening of the diphenylmethyl acetal in methyl 2,3-*O*-diphenylmethylene-α-L-rhamnopyranoside has been investigated by kinetic studies, and the results have been compared to those recently obtained by quantum chemical calculations. In contrast to the previous theoretical calculations which related only to the presumably rate limiting step of the reductive opening, the reaction system $LiAlH_4$, $AlCl_3$, and the title compound consists of at least four simultaneous reactions. Nevertheless, reasonable agreement can be found between the activation Gibbs free energy obtained from kinetic measurements and the theoretically calculated ones in spite of the experimental errors and the approximate nature of theoretical calculations.

Reductive opening of cyclic acetals is very important in synthetic carbohydrate chemistry, facilitating selective protection of polyol systems. Good examples are the 4,6-*O*-benzylidene acetals of hexopyranosides,[1,2] which can be opened selectively under specific conditions from both sides yielding 4-*O*- or 6-*O*- ethers.[3,4] Reagents applied for reductive opening usually consist of an electrophile (a Lewis or a protic acid) and a hydride donor. Mixtures of lithium aluminium hydride (LAH) and $AlCl_3$[5] are widely used for this purpose, since in an equilibrium reaction various alanes can form, depending on the ratio of LAH and $AlCl_3$, differing in their acidity and hydride-donating ability.[6] Very few kinetic experiments[7,8] and theoretical work[9] can be found in the literature, however, for the ring opening of cyclic acetal derivatives, and these papers deal mainly with benzylidene acetals and borane reagents.

Comparing to the 4,6-*O*-benzylidene acetals, partial hydrogenolysis of 2,3-*O*-diphenylmethylene acetals requires milder conditions.[10] Thus reductive opening of methyl 2,3-*O*-diphenylmethylene-α-L-rhamnopyranoside derivatives was studied by Hajkó et al. applying LAH and $AlCl_3$ in a 1:1 ratio (i.e., chloroalane) in Et_2O/CH_2Cl_2 1:1.[11] While at the 4-unsubstituted derivative (**1**) only the 2-*O*-diphenylmethyl product was formed, at the 4-OMe or the 4-deoxy cases the reaction resulted in a mixture of 2-*O*- and 3-*O*-benzyl ethers, where the latter ones were the major products. In the 4-unsubstituted case a schematic reaction mechanism was proposed in which first a 4-*O*-chloroalane derivative (**2**) forms, followed by the opening of the dioxolane ring, and finally **3** is hydrolyzed by the addition of water (Scheme 1).

From the quick H_2 formation at the initial phase of the reaction the conclusion can be drawn that **1**→**2** reaction step is substantially faster than the **2**→**3** one, therefore, the **2**→**3** transformation can be regarded as the rate limiting step. Recently, a theoretical study has been presented on the presumed (**2**→**3**) rate limiting step of the reductive opening reaction shown in Scheme 1.[12] Based on the quantum chemical calculations, a modified reaction mechanism was proposed for the dioxolane ring opening. It was found that aluminium spontaneously coordinates to the O3 atom forming a strong, almost fully developed single bond (**a**), which leads to weakening of the O3–$C_{acetalic}$ bond. There follows a single step reaction which is, however, rather asynchronous. First the C–O bond practically vanishes (**b**), and only then begins the C–H bond formation (**c**). Zero point corrected activation energies were found to be around 125–130 kJ/mol with DFT methods, consistently, while HF, MP2, and ONIOM calculations resulted in somewhat higher transition state energies.

In order to further support the reaction mechanism proposed earlier,[12] we have performed kinetic measurements to determine the activation Gibbs free energy of the reaction experimentally. Methyl 2,3-*O*-diphenylmethylene-α-L-rhamnopyranoside (**1**)[13,14]

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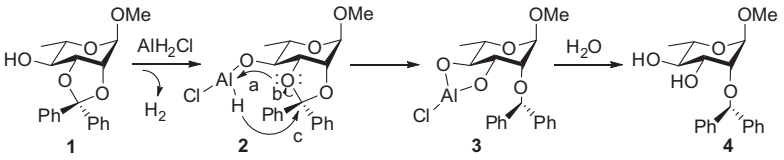
doi:10.1016/j.carres.2011.04.041



Scheme 1. Previous assumption for the mechanism of the reductive opening of **1**.[11]

was prepared from methyl α-L-rhamnopyranoside (**5**) and freshly prepared benzophenone dimethyl acetal[15] in the presence of (±)10-camphorsulfonic acid in MeCN (Scheme 2). Methyl 2-*O*-diphenylmethyl-α-L-rhamnopyranoside (**4**) was synthesized according to the literature[13] with LAH/$AlCl_3$ 1:1 in Et_2O/CH_2Cl_2 1:1 to use as a standard for the HPLC measurements.

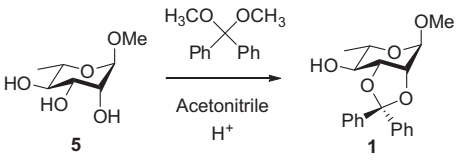
For each (**1**→**4**) reaction in the kinetic experiments we used methyl 2,3-*O*-diphenylmethylene-α-L-rhamnopyranoside (**1**), 2 equiv LAH and 2 equiv $AlCl_3$, and the reactions were carried out at 10, 15, 20, and 25 °C. LAH was added to the sugar solution, and after 1 min the reaction was started with the addition of $AlCl_3$ (in order to exclude the impact of the first fast step, i.e., the LAH + -free OH reaction) (Scheme 3). Samples taken at certain times were analyzed by HPLC.

Based on the previous assumptions[11] and the theoretical results[12] the rate determining step of the reaction should follow first order kinetics. However, our kinetic data contain considerable experimental errors, which can mainly arise from two factors. The first one is one of the side reactions, namely the hydrolysis of the acetal ring, since it seems to be very sensitive to the LAH/$AlCl_3$ ratio which is also affected by a very small amount of water may be present in the system. The second one is the ratio of Et_2O and CH_2Cl_2. Even a slight change of this ratio surprisingly seems to alter the rate of LAH–$AlCl_3$ induced reductive opening reactions in a significant manner.[16] Further errors can arise i.a. from the relatively circuitous simple preparation process for the HPLC measurements. As a consequence of these facts the order of the reaction could not be determined with high certainty. Nevertheless, the experimental data do not contradict the first order kinetics.

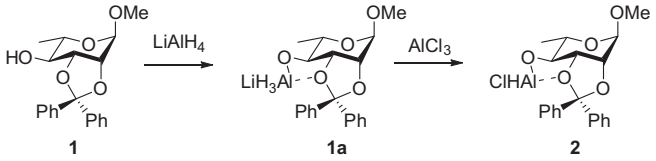
Accordingly, rate constants for the consumption of **1** for forming **4** were determined supposing first order kinetics. An example can be seen in Figure 1. Primary kinetic data are listed in Table S1 in the Supplementary data.

ΔH, ΔS, and ΔG values have been determined from these rate constants using the Eyring–Polányi equation (Fig. 2).[17–19] Activation Gibbs free energy was found to be 94.09 kJ/mol.

In this experiment, however, the reaction steps from the full reaction cannot be separated, that is, it includes the reaction of alkoxy-aluminium hydride (**1a**) with $AlCl_3$ (Scheme 3), the multiple equilibrium reaction between the excess of LAH and $AlCl_3$, the presumable rate limiting **2**→**3** reaction itself and the hydrolysis of the acetal ring resulting in **5**. In other words, not only the formation of **2**, but also the side reactions are included in the reaction rate calculated from the experiments. Nevertheless, the ~100 kJ/mol seems to be the upper limit of the activation free energy of the rate determining step.



Scheme 2. Preparation of **1** with transacetalization.



Scheme 3. Formation of alkoxy-aluminium hydride **1a** and the chloroalane derivative **2** in two steps caused by the subsequent addition of LAH and $AlCl_3$.

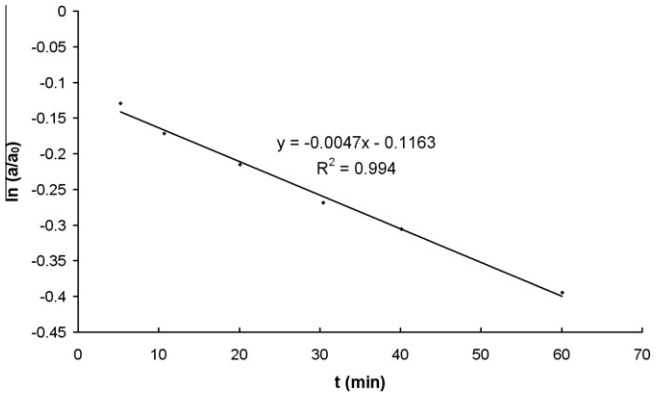


Figure 1. Rate constant determination for entry 1 at 10 °C (see Table S1).

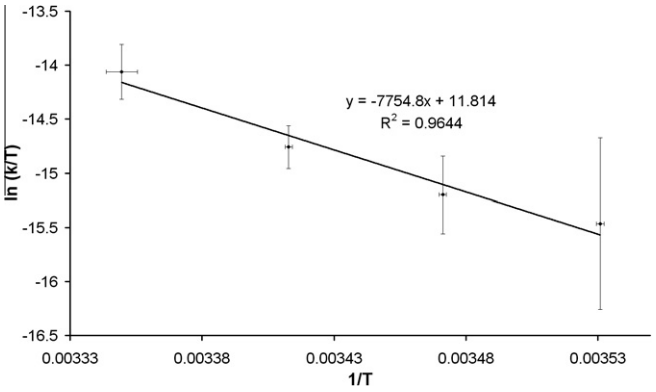


Figure 2. Temperature dependence of the rate constants. ΔH = 64.47 kJ/mol, ΔS = −99.32 J/mol K, ΔG = 94.09 kJ/mol at 298.15 K.

Comparing the theoretically[12] and the experimentally determined activation parameters, it should be noted, that by calculations the activation energies corrected by zero point vibrational energy (ZPVE) were calculated while some kind of overall activation free energy was obtained from the experiments.

Accepting the calculated 'overall' experimental activation free energy as an activation (Gibbs) free energy for the reaction we modeled (even though this value is suffering from experimental errors) it is still substantially lower than any of the previously computed zero point ZPVE corrected activation energies.[12] It should be

noted, that comparison of the calculated ZPVE-corrected energy differences (as activation energy) to the activation free energy is theoretically incorrect. However, at gas phase model, since the reaction mechanism was predicted to be an intermolecular bond rearrangement neither substantial entropy effect nor substantial volume changes are expected and the calculated ZPVE-corrected energy differences should be close to the theoretical free energy differences as it was pointed out in our previous paper.[12] It is true even though the harmonic approximation of the low frequency vibrations can cause large uncertainty in the calculated free energy, which can be an additional source of differences between the theoretical and experimental values.

Nevertheless, one of the main reasons of the discrepancy mentioned above probably resides in the fact that no solvent molecules were included in the theoretical calculations. In solvent phase the polar solvent molecules with non-bonding electron pairs can solvate more effectively the transition state than the reactant due to the increased hard character of aluminium at transition state geometry compared to the reactant geometry. (In the latter case the hydride anion is partially left the aluminium.) This more prevalent solvation effect results in both decreased activation energy and loss of entropy (due to the more ordered solute–solvent interaction) at transition state compared to the hypothetical gas phase reaction.

Another important reason can be that the previously calculated rate limiting reaction is strongly asynchronous, since the C–O bond breaking precedes the C–H bond formation and the transition state corresponds dominantly to a hydride anion transfer. For such systems the contribution of tunneling effect is usually non negligible.[20]

In conclusion, reaction kinetics studies on the reductive opening of methyl 2,3-*O*-diphenylmethylene-α-L-rhamnopyranoside can be satisfactorily featured by a first order kinetics model which is in a good accordance with the theoretical reaction mechanism published recently.[12] The moderate discrepancy between the published theoretical and the experimental activation Gibbs free energy as well as entropy values presented here can be rationalized based on the assumption of direct interaction between the solute and solvent molecules (with non-bonding electron pairs) at the transition state.

1. Experimental

1.1. General methods

Optical rotations were measured at room temperature with a Perkin–Elmer 241 automatic polarimeter. Melting points were determined on a Kofler hot-stage apparatus and are uncorrected. TLC was performed on Kieselgel 60 F_{254} (Merck) with detection by 5% sulfuric acid in ethanol. Column chromatography was performed on Silica Gel 60 (Merck 0.062–0.200 mm). The organic solutions were dried over $MgSO_4$ and concentrated in vacuum. The ^1H (400.13 and 500.13 MHz) and ^{13}C NMR (100.61 and 125.76 MHz) spectra were recorded with Bruker DRX-400 and Bruker DRX-500 spectrometers for solutions in $CDCl_3$. Internal references: TMS (0.00 ppm for ^1H), $CDCl_3$ (77.00 ppm for ^{13}C). HPLC separation conditions: Waters Symmetry C18 column 3.5 μm 4.6 × 150 mm, MeOH–water 80:20 eluent, flow rate: 0.6 ml/min, detection: 220 nm.

1.2. Kinetic details

For each (**1**→**4**) reaction in the kinetic experiments we used 200 mg methyl 2,3-*O*-diphenylmethylene-α-L-rhamnopyranoside (**1**), 44 mg (2 equiv) LAH, 156 mg (2 equiv) $AlCl_3$, 20 cm^3 Et_2O and 20 cm^3 CH_2Cl_2. Reactions were carried out in a double-walled reaction vessel at 10, 15, 20, and 25 °C under Ar atmosphere. Before starting the reaction 2 cm^3 sample was taken from the sugar solution. LAH was added and after 1 min the reaction was started with the addition of $AlCl_3$ (in order to exclude the impact of the first fast step, i.e., the LAH + free OH reaction). Further samples were taken at 2, 5, 10, 20, 30, 40, and 60 min. Since the high volatility of the solvents used would result in a poor reproducible sample volume, they were corrected by the mass of each sample. The 2–2 cm^3 samples taken at certain times were quenched with a mixture of MeOH and water, and the reaction solvents were evaporated by the aid of Ar. Volumes were filled up to 10 cm^3 with MeOH–water 80:20, filtered with 0.45 μm syringe filter, and analyzed by HPLC.

Acknowledgments

This work was financially supported by the Hungarian Scientific Research Fund (OTKA K-62802) and the TÁMOP 4.2.1/B-09/1/KONV-2010-0007 project. The project is co-financed by the European Union and the European Social Fund.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.carres.2011.04.041.

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