The Transformation Mechanism of 3,4,6-Tri-*O*-acetyl-1,5-anhydro-2-deoxy-D-*arabino*-hex-1-enitol in Water

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Heating of 3,4,6-tri-*O*-acetyl-1,5-anhydro-2-deoxy-D-*arabino*-hex-1-enitol (per-*O*-acetyl-D-glucal) in water leads to a mixture of unsaturated compounds with cyclic as well as open-chain structures. The mixture obtained was analyzed by the CGC method. The experimental findings were employed to model the mechanism of the transformation studied. In addition, AM1 calculations were carried out in order to describe the elementary processes suggested. Full geometry optimizations performed for species found in the mixture made it possible to evaluate the thermodynamic characteristics of particular reactions. Next, the calculations for transition states afforded appropriate kinetic barriers. All computations were carried out for a gaseous phase as well as an aqueous solution. Both experimental and theoretical results conform well with the mechanism proposed.

The glycals [1,5-anhydro-2-deoxypent(hex)-1-enitols], cyclic compounds having a double bond between C-1 and C-2, are vinyl ethers and consequently can take part in a wide variety of reactions. The widespread use of variously protected glycals in the syntheses of carbohydrate and noncarbohydrate products such as C-nucleosides,[1] ionofores,[2] leucotrienes,[3] heteroprotanoids,[4] and 2-deoxy-2-fluoro-[5] and 2-deoxy-2-aminosugars[6] has recently aroused considerable interest in equally simple and efficient procedures for their preparation.

In the presence of a nucleophile, acetylated glycals can undergo allylic rearrangement reaction to give 2,3-unsaturated products bearing the nucleophile at C-1. For water, the product, 4,6-di-*O*-acetyl-2,3-dideoxy-D-*erythro*-hex-2-enose (cyclic-4,6-di-*O*-acetylpseudoglucal), formed by heating of tri-*O*-acetyl-D-glucal at 100 °C, is well known.[7] It is evident that the reaction proceeds by the resonance-stabilized C-1 allylic carbonium ion, but the elementary processes of the mechanism have not been completely recognized.

The present study was directed toward the CGC analysis of the mixture obtained in the heated aqueous solution of per-*O*-acetyl-D-glucal as well as the theoretical description of the transformation mechanism. For the latter purpose, i.e., the estimation of the thermodynamic and activation barriers of the elementary reactions, we employed the AM1 method including solvation effects (COSMO methodology).

This paper can be considered as a continuation of our studies on the transformation mechanism of glycals in water the results of which for 3,4-di-*O*-acetyl-1,5-anhydro-2-deoxy-D-*threo*-pent-1-enitol have recently been published.[8]

Experimental Section

General Methods. All reactions were monitored by CGC (DB 23 fused silica column 60 m × 0.258 mm i.d.). All compounds of the reaction mixture are well known.[9−13] Two of them were isolated and identified by ^{1}H-NMR spectra (recorded at 350 MHz). The rest of them were identified as fully *O*-acetylated derivatives by CGC−MS analyses, the HPLC−UV method (Nucleosil ODS column 10 cm × 4.6 mm i.d. and UV detector-230 nm), and diagnostic microreactions.

Reaction of Per-*O*-acetyl-D-glucal in Water. Per-*O*-acetyl-D-glucal (0.5 mg) and 0.5 mL of water were heated at 373 K in reacti-vials for 10 and 30 min, respectively. A portion (10 μL) of each reaction mixture was concentrated to dryness under a nitrogen stream. The residue was conventionally *O*-acetylated with acetic anhydride−sodium acetate at 373 K for 1 h.

(*E*)-4,6-Di-*O*-acetyl-2,3-dideoxyhex-2-enose (Preparative Scale). Per-*O*-acetyl-D-glucal (0.5 g) was stirred according to the Gonzalez[13] method in a mixture of 5 mM sulfuric acid aqueous solution and dioxane in the presence of $HgSO_4$ and yielded 0.3 g of product having the same ^{1}H-NMR spectrum as that given by Gonzalez. Additionally, the presence of a double bond C=C was confirmed with microdiagnostic reactions.

Di-*O*-acetyl-3-hydroxy-2-(hydroxymethyl)-2*H*-pyran (Preparative Scale). A solution of per-*O*-acetyl-D-glucal (0.5 g) in acetic acid (3.5 mL) was kept for 1.5 h at 150 °C, poured into a mixture of water and ice, and extracted three times with chloroform; the extracts were combined, successively washed with aqueous sodium hydrogen carbonate solution and water, dried, and finally evaporated to an oil (yield, 0.40 g). The column chromatography separation gave 0.15 g of product with R_f = 0.35 (solvent 10:1, CCl_4−acetone). Its 99% purity was confirmed by CGC analyses. The MS analyses using FD technique shows its molecular ion to be *m*/*z* 212. Its H^1-NMR spectrum [two acetyl groups (δ = 2.01 and 2.05) and six protons bonded to skeleton carbon atoms H-1 (δ = 6.05); unresolved H-2 and H-3 (δ = 6.18); H-5 (δ = 7.40); two protons H-6 (δ = 4.43); for numbers see Figure 1) is analogous with the ^{1}H-NMR spectrum for a byproduct of the reaction of per-*O*-acetyl-D-glucal in aqueous mercuric salt solution proposed by Gonzalez.[13] The presence of two double bonds was confirmed by rapid consumption of bromine.

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Table 1. Relative Yields of the Compounds after the Rearrangement Reaction of *Per-O*-acetyl-D-glucal in Aqueous Solutions at 373 K

		GC peak area (%)	
per-*O*-acetyl derivative[a]	t_R (min)	10 min	30 min
5	6.3	4	21
3	12.3	76	3
4	12.4	3	
α-**6**; β-**6**[b]	15.2; 15.4	10	19
8	16.4	7	57

[a] For numbers see Figure 1. [b] α or β relates to the anomeric form of the compound.

Identification. Heating per-*O*-acetyl-D-glucal in water at 373 K leads to the formation of the mixture of the compounds (Table 1). The gas chromatogram of the mixture obtained after heating the title compound in water at 373 K shows six well-separated peaks. In order to assign the CGC peak to a specific compound we proposed identification on the microscale. Identification of all components is presented in order of elution in CGC.

2,3-Di-*O*-acetyl-3-hydroxy-2-(hydroxymethyl)-2*H*-pyran (5, Scheme 1). The compound was identified by coinjection with the standard.[30]

4,6-Di-*O*-acetyl-D-allal (4). The compound was identified by CGC−MS analyses. Only four isomers of D-glucal are known, i.e., D-allal, D-galactal, D-idal, and D-glucal itself. The compound formed in the reaction mixture has a different retention time in CGC from those of D-galactal and D-glucal, thus it could be D-idal or D-allal. According to the proposed mechanism we suggest it to be 4-*O*-acetyl-D-allal.

4,6-Di-*O*-acetyl-2,3-dideoxy-α- and -β-D-*erythro*-hex-2-enopyranose (6). The identity of the isomers of **6** as per-*O*-acetyl derivatives was confirmed by H^1-NMR spectroscopy [three acetyl groups ($\delta = 2.10$); H-1 and H-3 ($\delta = 5.95$); H-2 ($\delta = 5.80$); H-4 ($\delta = 6.35$); H-5 ($\delta = 5.50$); two protons H-6 ($\delta = 4.25$)] and diagnostic microreactions.

(*Z*)- and (*E*)-4,6-Di-*O*-acetyl-2,3-dideoxy-D-hex-2-enose (*cis*- and *trans*-Chain Pseudoglucals 7 and 8). HPLC-UV studies carried out on the reaction mixture obtained immediately after heating of per-*O*-acetyl-D-glucal in water reveal the existence of the *E* and *Z* isomers in the system studied (maximum at 216 and 204 nm, respectively).

The structures of both isomers after the reduction of original unsaturated aldehydes with $NaBH_4$ as well as the H_2/Pd system were confirmed by the coinjection with authentic sample in CGC (4,6-di-*O*-acetyl-2,3-dihydro-2,3-dideoxy-D-glucose was prepared in the manner described by Fischer[14] and next reduced).

General Procedure of Diagnostic Microreactions.[15] Addition of Bromine. Five mg of the sample was dissolved in 0.2 mL of chloroform, and 30 μL of bromine was added. After 3 h of conditioning at room temperature the volatile components were removed under a nitrogen stream.

Selective Reduction with $NaBH_4$ in Water. Five mg of the sample was dissolved in 0.5 mL of water, and 5 mg of $NaBH_4$ was added. After 2 h of conditioning at room temperature 10 μL of acetic acid was added, and the mixture then concentrated to dryness under a nitrogen stream. Next, 0.5 mL of methanol was added, and the sample was again concentrated to dryness.

Exhaustive Reduction with Pd/H_2. Five mg of the sample was dissolved in 2 mL of absolute ethanol, and 10 mg of catalyst (5% Pd/C) was added. The mixture was reduced for 10 h with hydrogen, at room temperature. The catalyst was then removed and the residue concentrated to dryness under a nitrogen stream.

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Computational Methods

The AM1[16] calculations for per-*O*-acetyl-D-glucal and products of its transformation in water at 373 K were carried out using MOPAC93[17] and MOPAC6[18] packages. The choice of AM1 from among the four methods included in the packages was motivated by several reasons. First, the errors in basic molecular characteristics (geometries, heat of formations, dipole moments, etc.) are smaller for AM1 and PM3 approaches than for the MNDO.[18] On the other hand, the accuracy of AM1 and PM3 methods is, in general, very similar.[18] Secondly, the proton affinities calculated by the AM1 method conform better with the experimental values, as compared with PM3 and MNDO results (in some cases the proton transfer reaction is discussed in this work).[19] It should also be remembered that AM1 has been successfully applied to a very wide range of chemical reactions and other chemical problems, while PM3 has not been so widely tested.[20]

The molecular mechanics force field incorporated into the SPARTAN v. 3.0 program package[21] was used for conformational analysis.

Unconstrained geometry optimizations of the molecules studied were performed using the EF[22] optimization procedure. The final gradient norm of the energy gradient was always less than 0.1 kcal mol^{-1}.

Three consecutive steps were taken for the location of the transition state on the reaction path. First, the "saddle" calculations[23,24] led to the approximation of the saddle point structure. Next, the gradient minimization by the TS procedure[22] for this structure was carried out. Finally, force calculations were performed, always affording one and only one negative force constant. Force calculations were also carried out to evaluate changes in thermodynamic functions together with temperature (in harmonic approximation).[25]

In order to study solvent effects, the conductor-like screening model (COSMO)[26] incorporated into the MOPAC93 program package was applied both for minimum structures and saddle point configurations. The dielectric constant of water was taken as 55.3 (at 373 K). It should be noted that such formalism provides only an electrostatic contribution to the free enthalpy of solvation. To determine the reliability of the COSMO approach additional calculations were carried out using the alternative AM1/SM2[27] method. Data collected in Table 2 illustrate conformity between results obtained from both approaches. However, the AM1/SM2 calculations turned out to be much more time consuming than alternative COSMO computations which prompted us to choose the latter.

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Table 2. Thermodynamic Characteristics (ΔH_r, Enthalpy of Reaction, ΔS_r, Entropy of Reaction, ΔG_r, Free Enthalpy of Reaction, and *K*, Equilibrium Constant) of the Reactions Considered in the Transformation Process of Per-*O*-acetyl-D-glucal at 373 K

		gaseous phase				aqueous phase			
reaction no.	reaction	ΔH_r[a]	ΔS_r[b]	ΔG_r[c]	*K*	ΔH_r[a]	ΔS_r[b]	ΔG_r[c]	*K*
1	**1** → **2** + CH_3COO^-	638.59	268.47	538.45	3.92×10^{-76}	89.21	223.10	6.00	1.45×10^{-1}
2	**2** + $2H_2O$ → **3** + H_3O^+	133.59	−192.38	205.35	1.74×10^{-29}	−37.40	−161.87	22.98	6.05×10^{-4}
3	**2** + $2H_2O$ → **4** + H_3O^+	129.02	−207.77	206.52	1.20×10^{-29}	−35.61	−167.62	26.91	1.70×10^{-4}
4	**2** + $2H_2O$ → $\mathbf{6}_\alpha$ + H_3O^+	−97.68	−193.26	−25.59	3.84×10^{3}	−72.90	−164.72	−11.46	4.03×10
5	**2** + $2H_2O$ → $\mathbf{6}_\beta$ + H_3O^+	−98.51	−194.39	−26.00	3.38×10^{3}	−73.03	−165.18	−11.42	3.98×10
6	$\mathbf{6}_\beta$ → **7**	42.64	−8.66	45.87	3.77×10^{-7}	43.19	−4.52	44.88	5.19×10^{-7}
7	$\mathbf{6}_\beta^+$ → $\mathbf{7}^+$	0.63	25.03	−8.71	1.66×10	−23.74	1.51	−24.30	2.53×10^{3}
						−23.77[d]	10.59[d]	−26.91[d]	5.21×10^{4} [d]
								−31.55[e]	3.39×10^{5} [e]
8	**7** → **8**	−6.15	29.38	−17.11	2.49×10^{2}	−15.86	30.04	−27.06	6.16×10^{3}
9	$\mathbf{7}^+$ → $\mathbf{8}^+$	13.73	5.14	11.81	2.22×10^{-2}	−7.78	22.39	−16.13	1.82×10^{2}
10	**2** + H_2O → **5** + H_3O^+	184.64	−20.55	192.30	1.17×10^{-27}	−6.74	11.22	−10.93	3.39×10

[a] kJ mol^{-1}. [b] J mol^{-1} K^{-1}. [c] kJ mol^{-1}. [d] COSMO results for 298 K. [e] AM1/SM2 results for 298 K.

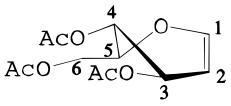


Figure 1. Numbering of the ring atoms in the per-*O*-acetyl-D-glucal molecule.

The procedures described above afforded full thermodynamic characteristics of the systems under consideration. Namely, the values of heat of formation (ΔH_f) and entropy (*S*) for particular reactants, provided by MOPAC, were used to calculate the free enthalpy of reaction (ΔG_r) according to formula $\Delta G_r = \Delta H_r - T\Delta S_r$, where ΔH_r is the enthalpy of reaction defined as the difference between the sum of heats of formation of products and that of heats of formations of substrates (multiplied by relevant stoichiometric coefficients); the ΔS_r term is defined in the manner described for ΔH_r but the heat of formation in the previous definition is replaced by entropy.

One should note that the same ideal gas expressions for the translational and rotational terms in thermal correction for both gaseous and aqueous phase were used. In the past this approximation turned out to be accurate enough.[28] The only difference is in the vibrational terms and results from different frequencies for compounds in both phases.

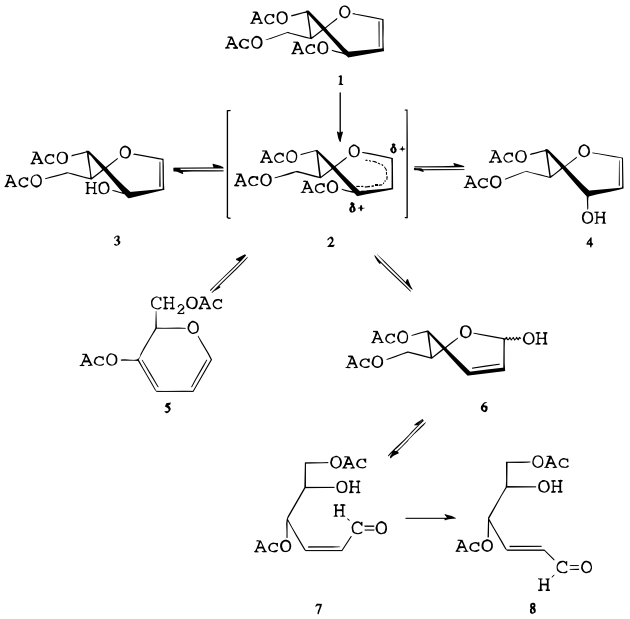
All computations were carried out using an HP Apollo 9000 m 735 workstation or PC/486 computers.

Results and Discussion

The Proposed Mechanism (Scheme 1). The first step of the reaction studied could be the heterolytic dissociation of the *O*-acetyl group bonded to C-3 (for atom numbering, see Figure 1), leading to the formation of the allylic carbocation **2** (see Scheme 1). A strong argument for the splitting of this particular bond involves the stabilization of the allyl-like cation structure **2** (calculated AM1 heats of the formation of carbocations in aqueous solution after splitting 3-C−O and 4-C−O bonds are equal to −332.7 and −203.2 kJ/mol, respectively).

The carbocation can further be transformed in two ways, namely, by proton elimination or by the nucleophilic attack of a water molecule on the C-1 or C-3 atoms. The former reaction should yield the 2,3-di-*O*-acetyl-3-hydroxy-2-(hydroxymethyl)-2*H*-pyran (**5**) as one of the final products.

Scheme 1. Proposed Mechanisms of Transformation in the Course of the Per-*O*-acetyl-D-glucal Rearrangement Reaction



Nucleophilic attack of a water molecule and subsequent proton elimination could occur at the C-1 or C-3 atoms of the carbocation. In the latter case D-glucal and the expected D-allal (derivatives **3** and **4**) should be formed, which could next be transformed in the reverse reaction into the original carbocation. On the other hand, the addition of water to C-1 and subsequent proton elimination leads to the formation of α or β anomers of cyclic pseudoglucal **6**. The relative amounts of the reaction products formed by the nucleophilic attack of water on C-1 or C-3 depends primarily on the charge distribution over the crucial carbon atoms (C-1 and C-3). Net atomic charges on C-1 and C-3, calculated using the diagonal elements of total semiempirical density matrix, equal to 0.35 and 0.02 for the aqueous phase, respectively, conform qualitatively to the relative yields of products formed after nucleophilic attack on these atoms (19%, 3%, Table 1).

The main product in the exhaustively *O*-acetylated reaction mixture turned out to be the (*E*)-chain pseudoglucal; therefore, we suggest that the α and β anomers of cyclic pseudoglucal could be transformed into the isomeric (*Z*)-chain pseudoglucal in the ring opening

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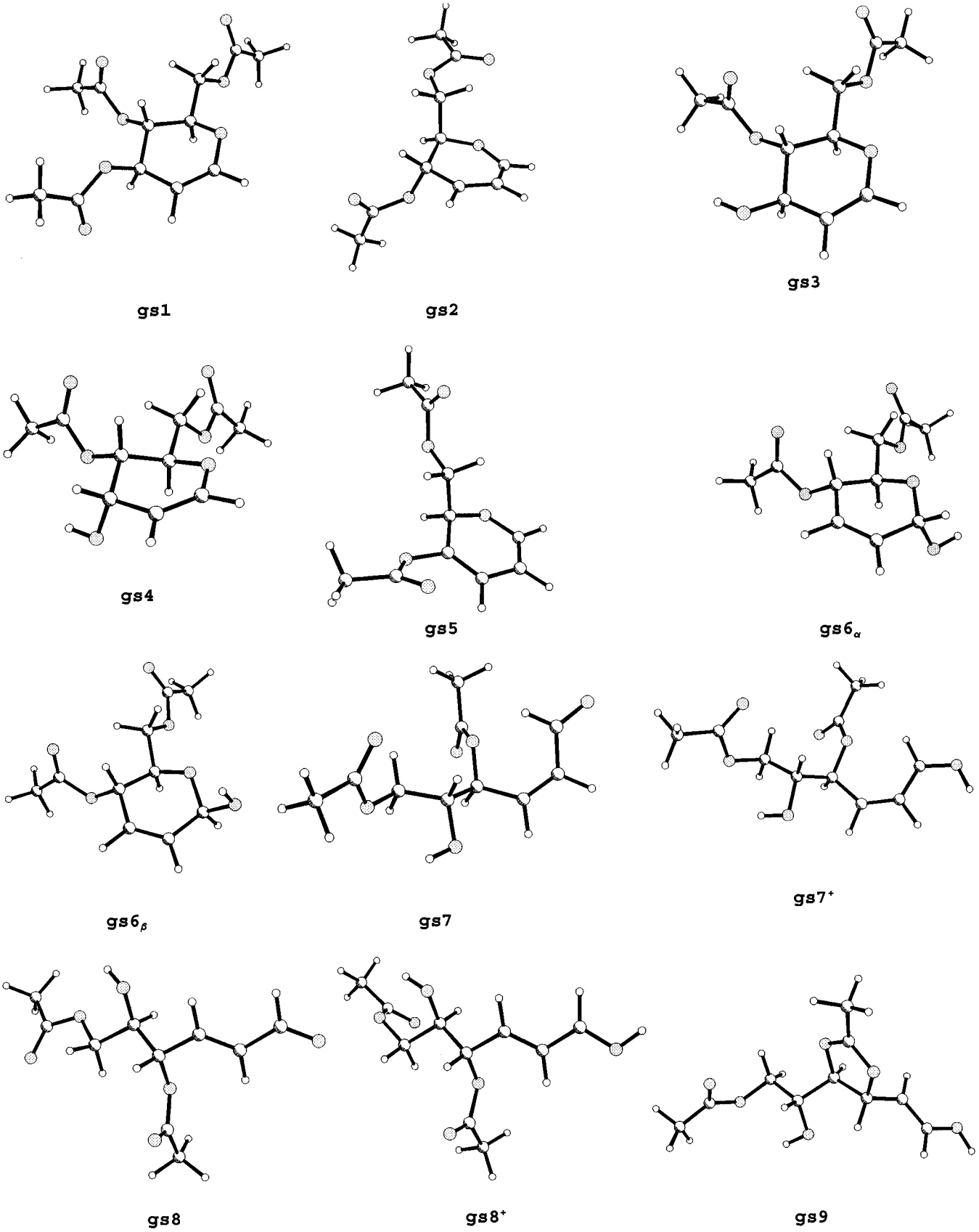

Figure 2. Minimum structures of the compounds considered in the per-*O*-acetyl-D-glucal rearrangement process. The carbon atoms are presented by shadowed, the oxygen atoms by dotted and the hydrogen atoms by empty circles: gsx, gs = ground state, *x* = 1−8 corresponds to the compounds **1**−**8** in Scheme 1, gs9 = acetoxonium ion.

reaction, and the (*Z*)−(*E*) isomerization is a process which closes the main reaction sequence.

Theoretical Arguments Supporting the Mechanism of the Transformation Studied. Quantum chemistry calculations, carried out even on a semiempirical level, should provide further insight into the rearrangement reaction. Thus, thermodynamic and kinetic barriers for each elementary process proposed were

Table 3. Kinetic Characteristics ($\Delta H^{\ddagger}$, Enthalpy of Activation, $\Delta S^{\ddagger}$, Entropy of Activation, $\Delta G^{\ddagger}$, Free Enthalpy of Activation, and *k*, Kinetic Constant) of Elementary Processes Postulated for Transformation of Per-*O*-acetyl-D-glucal in Water at 373 K Calculated by AM1 in Water Phase

		gaseous phase				aqueous phase			
reaction no.	reaction	$\Delta H^{\ddagger a}$	$\Delta S^{\ddagger b}$	$\Delta G^{\ddagger c}$	k^d	$\Delta H^{\ddagger a}$	$\Delta S^{\ddagger b}$	$\Delta G^{\ddagger c}$	k^d
1	**2** + $H_2O \rightarrow$ **6**$_\alpha^+$	3.26	−28.79	14.00	2.31×10^{11}	2.09	−2.51	3.03	7.96×10^{12}
2	**6**$_\alpha^+$ + $H_2O \rightarrow$ **6**$_\alpha$ + H_3O^+	21.51	−20.42	29.13	1.76×10^{9}	25.74	−3.60	27.08	3.41×10^{9}
3	**6**$_\beta \rightarrow$ **7**	240.30	−2.26	248.14	3.75×10^{-22}	219.04	−5.73	221.18	2.24×10^{-18}
4	**6**$_\beta^+ \rightarrow$ **7**$^+$	19.96	3.52	18.65	5.17×10^{10}	6.01	0.13	5.96	3.09×10^{12}
5	**7** → **8**	147.94	2.34	147.07	5.35×10^{-8}	153.88	12.05	149.39	2.53×10^{-8}
6	**7**$^+ \rightarrow$ **8**$^+$	122.08	−0.54	122.28	1.59×10^{-4}	118.77	13.52	113.73	2.50×10^{-3}
7	**7**$^+ \rightarrow$ **9**	18.04	4.90	16.21	1.14×10^{11}	45.07	10.55	41.13	3.67×10^{7}
8	**2** + $H_2O \rightarrow$ **5** + H_3O^+	91.96	−28.42	102.21	1.03×10^{-1}	90.98	25.40	81.51	8.13×10

[a] kJ mol^{-1}. [b] J mol^{-1} K^{-1}. [c] kJ mol^{-1}. [d] Calculated on the basis of transition state theory[23] (s^{-1}) or (s^{-1} dm^3 mol^{-1}).

calculated. In order to obtain the characteristics mentioned above, conformational analyses were performed first, which assured the lowest conformation of molecules involved in the elementary reactions. The AM1-optimized structures for starting geometries generated in the molecular mechanics force field are displayed in Figure 2, whereas thermodynamic characteristics for both gaseous and aqueous phase have ben compiled in Table 2.

The values collected in Table 2 indicate the strong influence of the solvent on the overall thermodynamics. This effect is most obvious in the case of the initial elementary process (reaction 1). On the basis of ΔG_r and related equilibrium constant values one can come to the conclusion that the reaction is already completely inhibited just at the first step, in the gaseous phase. Thus, on the one hand the results obtained show that the compound is very stable in the gaseous phase (indeed, it could be distilled without decomposition under reduced pressure), and on the other hand, the need for water to initiate the process is revealed. Therefore, further discussion, considering thermodynamic characteristics, will be restricted to the aqueous phase exclusively.

Since no saddle point was found for reaction **1**, ΔG_r should fully determine the behavior of the title compound. For this particular reaction ΔG_r is only 6.0 kJ/mol and the value of equilibrium constant (Table 2) indicates that the compound should spontaneously dissociate to some extent in an aqueous solution at 373 K. It is worth mentioning here that most ΔG_r values are negative (reactions **4**, **5**, and **7**−**10**, excluding the characteristic for the formation of **3** and **4**, which can be considered as the side products). This indicates that possible equilibria are moved toward products, which supports the possibility of transformations in the manner suggested (see equilibrium constants in Table 2). Only for the ring opening (reaction **6**) is ΔG_r relatively high. The comparison of this characteristic with that of protonated cyclic pseudoglucals shows, however, that for the latter system ΔG_r adopts a relatively strong negative value (reaction **7**). Being in accordance with experimental findings, this result suggests that the presence of H_3O^+ ions is necessary for progress of the process.

Further insight into the mechanism studied could be revealed by calculations of kinetic barriers for the steps postulated. Full activation parameters both in the gaseous phase and in aqueous solution for the reactions considered are given in Table 3, and the geometries of saddle point structures are presented in Figure 3. The comparison of the data obtained for the gaseous and aqueous phase reveals a distinctly lower influence of the surroundings on the kinetic characteristics than the thermodynamic ones. For the reasons mentioned previously further discussion will be restricted to characteristics obtained for the aqueous phase. Most of the barriers are easily passed as indicated by the $\Delta G_r^{\ddagger}$ values and by kinetic constants calculated for the aqueous phase on the basis of the theory of the transition state.[29] Only the free enthalpy of activation for the pseudoglucal ring opening reaction is extremely high (Table 3, reaction 3), suggesting that if this reaction were the bottle-neck step the final product (chain (*E*)-pseudoglucal) could not be observed experimentally (half-period equal to 8.1×10^{13} h). Considering the protonated (at the heterocyclic oxygen atom) molecule of cyclic pseudoglucal, however, the lowering of the activation barrier to 6.0 kJ/mol can be observed (Table 3, reaction 4), which supports proceeding of the process in the manner postulated. It has been proved experimentally that, in the course of the reaction, the neutral solution becomes acidic as the result of acetic acid formation. By comparison of the kinetic barriers collected in Table 3 it can be concluded that in solutions which are sufficiently acidic the bottle-neck step of the transformation studied should be the (*Z*)−(*E*) isomerization of chain pseudoglucal (Table 3). In the case of this reaction, the $\Delta G_r^{\ddagger}$ for the neutral compound and that protonated on the carbonyl oxygen atom are equal to 149.4 and 113.7 kJ/mol, respectively. Hence, half-peroids of the isomerization for neutral and protonated (*Z*)-chain pseudoglucal are equal to ca. 7.6×10^3 and 7.7×10^{-2} h, respectively. The lowering of the kinetic barrier after protonation could be explained in terms of the bond orders (see Table 4). One can observe that, due to protonation, the 1-C−C-2 bond assumes a double bond character in part, and simultaneously, the lowering of the 2-C═C-3 bond order can be observed which facilitates rotation around the latter bond.

Additional Remarks Concerning the Proposed Mechanism. It was found experimentally that in the acidic solution the rearrangement reaction leads mainly to compound **8**. This observation, however, is not explained by the proposed mechanism. Namely, if one compares the kinetic barriers for the (*Z*)−(*E*) isomerization and for the reaction leads to di-*O*-acetyl-3-hydroxy-3-(hydroxymethyl)-2*H*-pyran (reactions **6** and **8**, Table 3) the lack of the latter production in the reaction mixture is not understandable. The experimental findings thus indicate that the isomerization reaction (*Z*)−(*E*) should proceed with lower kinetic barrier than for the reaction **8** (in Table 3). Therefore we tried to find other than the rotation around 2-C−C-3 mechanism of (*Z*)−(*E*) isomerization. Namely, we calculated the kinetic barrier for **9**

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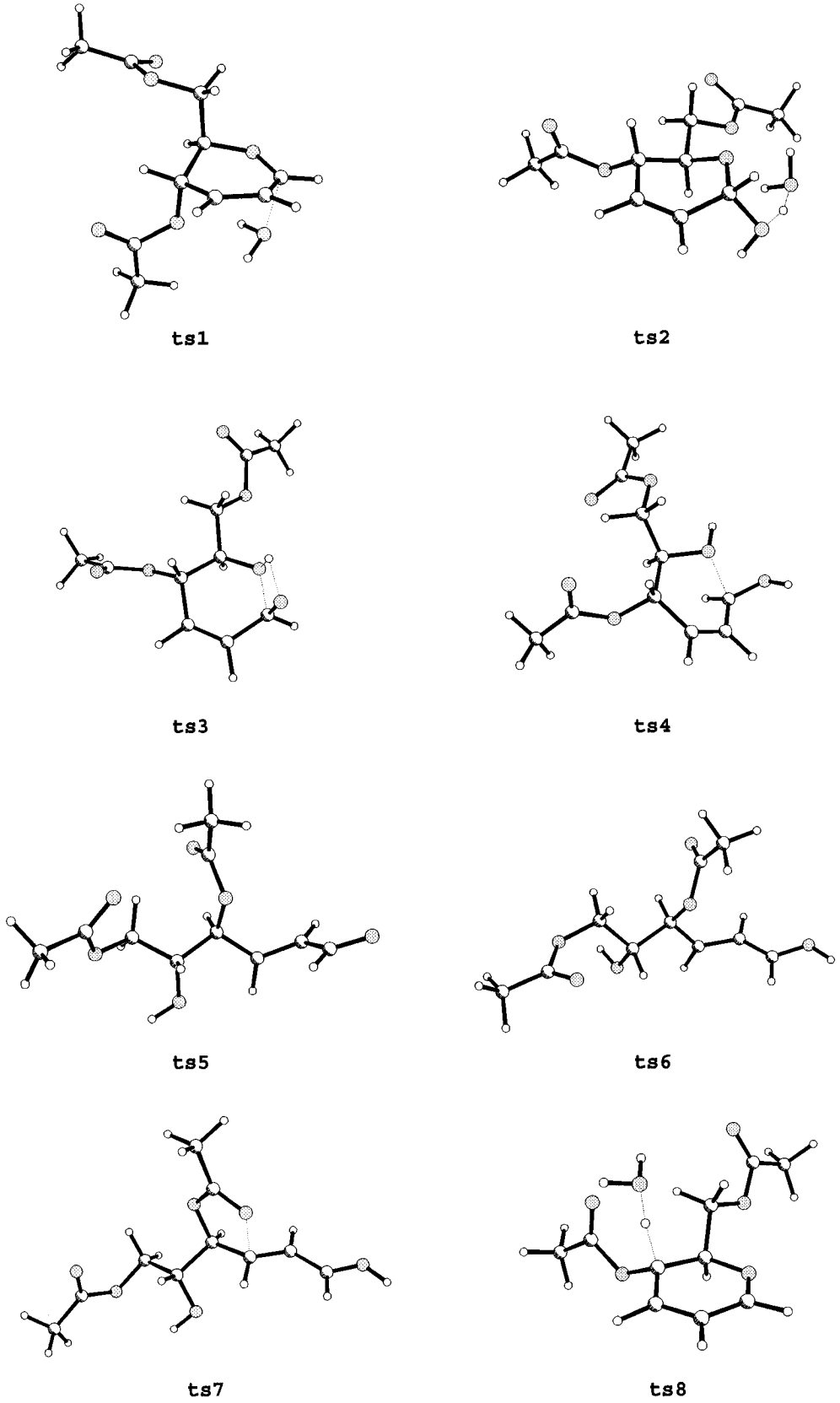

Figure 3. Saddle point geometries for chosen elementary processes considered in the reaction mechanism. The carbon, oxygen, and hydrogen atoms are presented as in Figure 2. Dotted lines represent the bonds which are formed and broken in the course of the reaction: tsx, ts = transition state, $x = 1-8$ corresponds to the number of reactions in Table 3.

(Figure 2) formation. The ΔG_r for $\mathbf{7}^+ \rightarrow \mathbf{9}$ is equal to 18.29 kJ/mol ($K = 2.75 \times 10^{-3}$); thus, from the thermodynamic point of view **9** can play the role of a transient product (concentration of this entity will probably be high enough, as indicated by the equilibrium constant, to open this path for the reaction). It is worth mentioning here that for the cyclic acetoxonium cation **9** the 2-C−C-3 bond is of a single bond character (Table 4). On the other hand, the only stable conformations of **9** have the trans arrangement in the C(1)C(2)C(3)C(4) fragment (for atom

Table 4. Chosen Bond Orders for Neutral, Protonated (*Z*)-Chain Pseudoglucal and Acetoxonium Cation in Water Solution

bond	(*Z*)-chain neutral pseudoglucal	protonated (*Z*)-chain pseudoglucal	acetoxonium ion
1-O═C-1	1.81	1.46	1.11
1-C−C-2	0.98	1.13	1.76
2-C═C-3	1.89	1.73	1.01

numeration see Figure 1). The calculations also showed that without any activation barrier cation **9** changes into the (*E*)-chain pseudoglucal after deprotonation. Thus, **9** could be an ideal transient product for (*Z*)−(*E*) isomerization. The kinetic barrier for (*Z*)-protonated pseudoglucal $\mathbf{7}^+$ to **9** transformation is equal to 41.1 kJ/mol (Table 3). The barrier is more than two times lower than the characteristic for reaction **5**, which fully confirms that the (*Z*)−(*E*) isomerization could proceed via acetoxomium cation **9**.

Conclusions

The compilation of the experimental findings with the results of theoretical calculations concerning both thermodynamics and kinetics of the system studied enabled us to make the proposed mechanism of transformations more reliable. Some experimental observations, such as the catalytic role of hydrogen cations and the very important role of solvent were explained by the AM1/COSMO calculations.

The results obtained cannot be considered final in this matter. The COSMO methodology took into account only the electrostatic contribution to the free energy of solvation. This does not consider changes created in the solvent itself by introduction the solute molecule (i.e., the energy and entropy terms related to the creation of the solute cavity are ignored by this method, which, for example, could be taken into account in a supermolecular model). Moreover, the methodology used was not tested at higher temperatures. It is therefore difficult to say how accurate the results obtained are in the quantitative sense. Nevertheless, even the relatively simple approach presented in this paper affords insight into the reactivity and energetics in this important (both from the model as well as practical point of view) class of reactions.

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