ACID-CATALYZED HYDROLYSIS OF 2-METHOXYPROPENAL

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ABSTRACT

2-Methoxypropenal in acid media undergoes general acid-catalyzed hydrolysis with formation of 2-oxopropanal. The kinetics of this reaction were studied, the rate constants established, and a reaction mechanism is suggested. Hydrolysis of 2-methoxypropenal is governed by a mechanism of the vinyl ether type, and the presence of the aldehyde group causes a decrease in the reaction rate. The analogy of the acid-catalyzed hydrolysis of 2-methoxypropenal to that of a vinyl ether was shown by the solvent isotope-effect, $k_D/k_H = 0.41$, and the value of the Brönsted exponent, $\alpha = 0.60$. The activation parameters found and quantum-chemical calculations of charge distribution in 2-methoxypropenal and other model compounds were also utilized to explain the mechanism of the acid-catalyzed hydrolysis of the title compound.

INTRODUCTION

It has been proved that methoxyacetaldehyde undergoes acid-catalyzed hydrolysis with formation of glycolaldehyde, which is present, under appropriate conditions, in equilibrium with its enediol[1]. Acid-catalyzed hydrolysis of trioses, either free[2] or as *O*-methylated derivatives[3], always gives 2-oxopropanal. Higher monosaccharides and their *O*-methylated derivatives behave analogously[4-6].

The rate-determining step of the acid-catalyzed reactions of these compounds is their enolization[1-3], and this is followed by successive, rapid changes. As aliphatic ethers are very stable in acid media, we assume that the hydrolysis of methoxyacetaldehyde[1] and 2-methoxypropenal, (the intermediate in the acid-catalyzed reaction of 2,3-di-*O*-methyl-D-glyceraldehyde[3]) proceeds by the vinyl ether type of mechanism[7-13]. As the molecule of 2-methoxypropenal may be considered as either a derivative of vinyl ether or of propenal[14], it was necessary to discover which of the two characters predominates and determines the chemical reactivity. Therefore, we studied the kinetics and mechanism of acid-catalyzed reactions of 2-methoxypropenal. The knowledge obtained will also be applicable to analogous intermediates of unsubstituted monosaccharides which, because of their instability[5,6], cannot be prepared and studied separately.

EXPERIMENTAL

Instruments and apparatus. — The kinetics of formation of 2-oxopropanal from 2-methoxypropenal was studied in aqueous solutions of hydrochloric acid and chloroacetate buffers at defined temperatures, maintained with a precision of ± 0.1. The reaction was monitored spectrophotometrically (Specord UV VIS, Zeiss Jena) and polarographically (Polariter, Type PO4g, Copenhagen). The 2-oxopropanal formed was converted by condensation with *o*-phenylenediamine into 2-methylquinoxaline, which was identified by using a JEOL JMS-D 100 mass spectrometer as described in previous work[3]. Quantum-chemical calculations were performed with a Siemens 4004 computer.

Chemicals. — 2-Methoxypropenal was prepared by base-catalyzed β-elimination of 2,3-di-*O*-methyl-DL-glyceraldehyde[15]; DCl (VEB Berlin Chemie) and D_2O (Koch-Light Laboratories. Ltd.) were also employed. The other chemicals used were of analytical grade.

Procedures. — Hydrolysis of 0.2mM 2-methoxypropenal was conducted in 0.01–0.1M aqueous solutions of hydrochloric acid at 25 and in 0.05M hydrochloric acid over the temperature range 20–40. The effect of different H_2O D_2O ratios on the rate of hydrolysis of 0.2mM 2-methoxypropenal in 0.1M hydrochloric acid at 25 was also examined. The hydrolysis was monitored spectrophotometrically from the decrease of the absorption band of 2-methoxypropenal at $\lambda_{max} = 248$ nm. The effect of buffer concentration on rate of hydrolysis of 2-methoxypropenal was monitored in 0.5M chloroacetic acid–0.1M sodium chloroacetate at the ionic strength $I = 0.1$ mol.dm^{-3} at 25 and at further lower concentrations of buffer, keeping the ratio (5:1) of its components constant and the ionic strength I at 0.1 mol.dm^{-3} by addition of the necessary amount of sodium chloride. As the buffer solutions used absorb in the same region as 2-methoxypropenal, hydrolysis in this case was monitored polarographically by recording the polarographic waves from 0.6 V versus a saturated calomel electrode.

Isolation and characterization of products. — *A.* 2-Methoxypropenal (10mM, 10 mL) was allowed to react in 0.1M hydrochloric acid for 2 h at room temperature. The solution was made neutral with solid potassium hydrogencarbonate, and then an equivalent amount of *o*-phenylenediamine was added and the reaction was allowed to proceed for 30 min. The aqueous solution was distilled at normal pressure, and the 2-methylquinoxaline formed passed over into the distillate and was extracted with ether. The ether solution was dried with calcium chloride, evaporated, and the residue analyzed by mass spectrometry.

B. Experiments as in *A* were conducted in DCl and D_2O.

C. Experiments were performed as in *B*, however, instead of starting with 2-methoxypropenal, the expected end-product, namely, 2-oxopropanal, was used.

Determination of the activation parameters. — The energy of activation (E_a) was calculated by least-squares analysis of the plot of $\log k_{H_2O}$ against $1/T$ and the enthalpy of activation ($\Delta H^{\ddagger}$) by analysis of the plot of $\log(k_{H_2O}/T)$ against $1/T$. The

activation free energy ($\Delta G^{\ddagger}$) and entropy ($\Delta S^{\ddagger}$) were calculated from the relationships $\Delta G^{\ddagger} = -2.303 RT \log(k_{H_3O^+} hN/RT)$ and $\Delta S^{\ddagger} = (\Delta H^{\ddagger} - \Delta G^{\ddagger})/T$, where $k_{H_3O^+}$ is the catalytic rate-constant for hydrolysis of 2-methoxypropenal at 25°.

Quantum-chemical calculations. — Electron structures, energies, and geometries of the compound studied, its expected intermediates, and further model compounds were calculated by a semiempirical MNDO[16,17] quantum-chemical method including optimization of bond angles, bond lengths, and dihedral angles by the Davidon–Fletcher–Powell algorithm[18,19].

RESULTS

Kinetics of hydrolysis of 2-methoxypropenal in aqueous solutions of hydrochloric acid. — It has been proved experimentally that acid-catalyzed hydrolysis of 2-methoxypropenal, affording 2-oxopropanal, is a first-order reaction with respect to the acid used. Under pseudo-first-order conditions, the observed rate-constants (k_{obs}) for hydrolysis of 2-methoxypropenal increase linearly with the concentration of hydrochloric acid (Fig. 1). From the slope of this dependence, the catalytic rate-constant $k_{H_3O^+} = 7.5 \times 10^{-3}$ dm^3.mol^{-1}.s^{-1} at 25° was obtained. It was further found that the hydrolysis of 2-methoxypropenal is catalyzed not only by hydronium ions but also by undissociated acids. General acid-catalysis of hydrolysis of 2-methoxypropenal was confirmed in chloroacetate buffers of various concentrations, maintaining constant the ratio of the components and the ionic strength ($I = 0.1$ mol.dm^{-3}). The effect of a slight increase in pH of the buffers upon dilution was eliminated by relating the observed rate-constants and the corresponding concentrations of chloroacetic acid to unit activity of hydronium ions (Fig. 2). The slope of this dependence gave the value of the catalytic rate-constant for undissociated chloro-
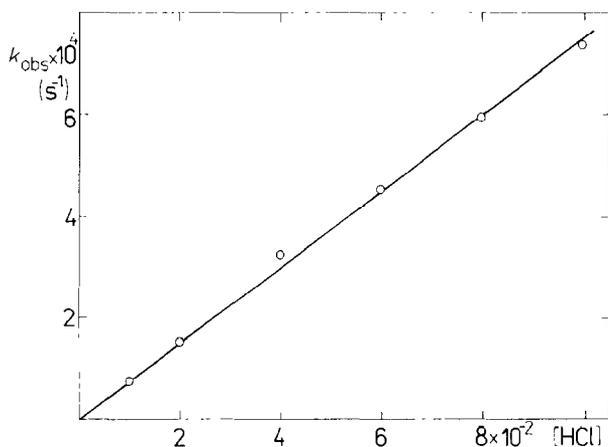

Fig. 1. Dependence of the observed rate-constants for hydrolysis of 0.2mM 2-methoxypropenal on concentration of hydrochloric acid at 25°.
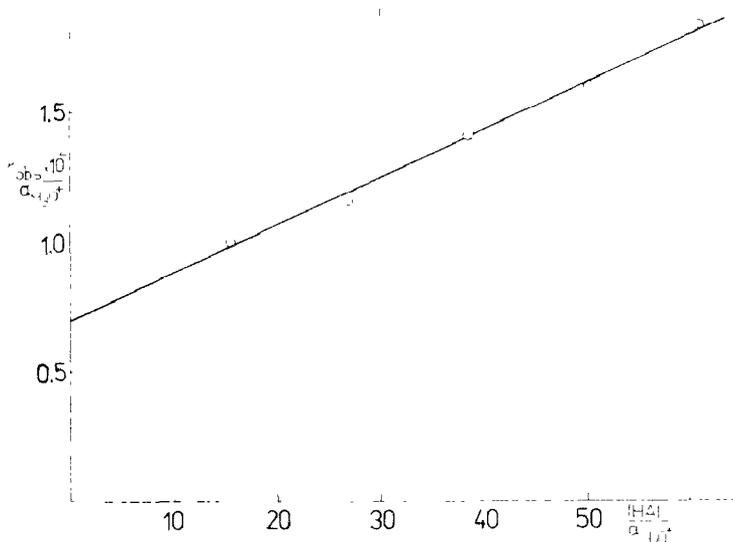
Fig. 2. Dependence of acid-catalyzed hydrolysis of mм 2-methoxypropenal on concentration of chloroacetate buffer at a constant (5 1) ratio of its components and ionic strength I 0.1 mol.dm ³ at 25 .

acetic acid ($k_{HA} = 1.9 \times 10^{-4}$ dm³.mol⁻¹.s⁻¹). The intercept obtained by extrapolation of concentration of chloroacetic acid to zero represents the rate constant for hydronium-ion catalyzed hydrolysis of 2-methoxypropenal. $k_{H_3O} = 70 \times 10^{-3}$ dm³.mol⁻¹.s⁻¹, a value in accord with that already determined.

Activation parameters. - From the observed rate-constants (k_{obs}) for hydrolysis of 2-methoxypropenal in 0.05м hydrochloric acid over the temperature range 20–40 , the appropriate catalytic rate-constants (k_{H_3O}) were calculated and used for calculation of all basic activation parameters of the reaction. The data are presented in Table I.

Deuterium solvent isotope-effects. —– The experimental data obtained suggest

TABLE I

CATALYTIC RATE-CONSTANTS AND ACTIVATION PARAMETERS FOR ACID-CATALYZED HYDROLYSIS OF 2-METHOXYPROPENAL

Temperature (C)	k_{H_3O} 10^3 (dm³.mol⁻¹.s⁻¹)	A $10^{-\cdot}$ (dm³.mol⁻¹ s⁻¹)	IG^2 (kJ.mol⁻¹)	IH^- (kJ.mol⁻¹)	E_a (kJ.mol⁻¹)	IS (J mol⁻¹.K⁻¹)
20	4.98					
25	7 42					
30	10.50	3.9	85.2	58 6	61.1	89.1
35	16.88					
40	25.00					

that the acid-catalyzed hydrolysis of 2-methoxypropenal is similar to that of vinyl ethers. It is known that solvent isotope-effects in these types of reaction provide important information concerning a proton-transfer transition-state[7,10,20]. In our case, therefore, we studied the hydrolysis of 2-methoxypropenal as catalyzed by hydrochloric acid in H_2O, D_2O, and their mixtures at 25°. The solvent composition and the appropriate, observed rate-constants are presented in Table II, and the variations of rate constants with content of deuterium in the solvent are shown in Fig. 3. Circles denote the observed values and lines are calculated from Eq. *1* (see refs. 7, 10, and 20):

$$k_n/k_H = \frac{(1-n+nl^{1-\alpha})^2\,(1-n+nl^{1+2\alpha}\,k_D/k_H)}{(1-n+nl)^3} \qquad (1),$$

TABLE II

HYDROLYSIS OF 0.2mM 2-METHOXYPROPENAL CATALYZED BY 0.1M HYDROCHLORIC ACID IN H_2O, D_2O, AND H_2O–D_2O MIXTURES AT 25°

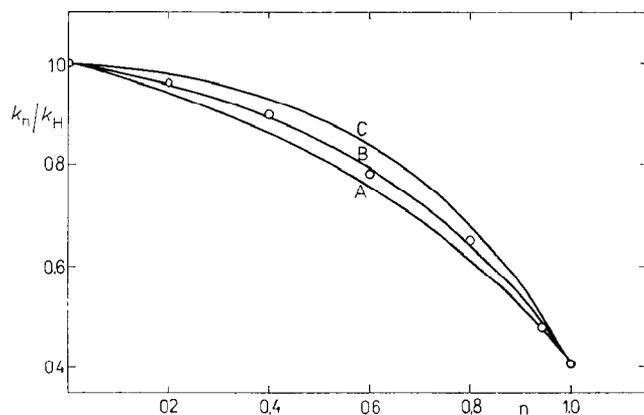| Solvent comp. (mL)		n	$k_n \times 10^4$ (s^{-1})	k_n/k_H
H_2O	D_2O			
5	0	0	7.57	1.00
4	1	0.2	7.31	0.96
3	2	0.4	6.84	0.90
2	3	0.6	5.91	0.78
1	4	0.8	4.99	0.65
0.3	4.7	0.94	3.70	0.48
0	5	1.0	3.10[a]	0.41[a]

[a]Approximation of values to 100% D_2O.

Fig. 3. Relationship between solvent isotopic composition, n, and solvent effect, k_n/k_H, on hydrolysis of 2-methoxypropenal catalyzed by 0.1M hydrochloric acid in H_2O–D_2O mixtures; circles denote the observed values and lines are calculated from Eq. *1* with α = 0.4 (*A*), 0.6 (*B*), and 0.8 (*C*).
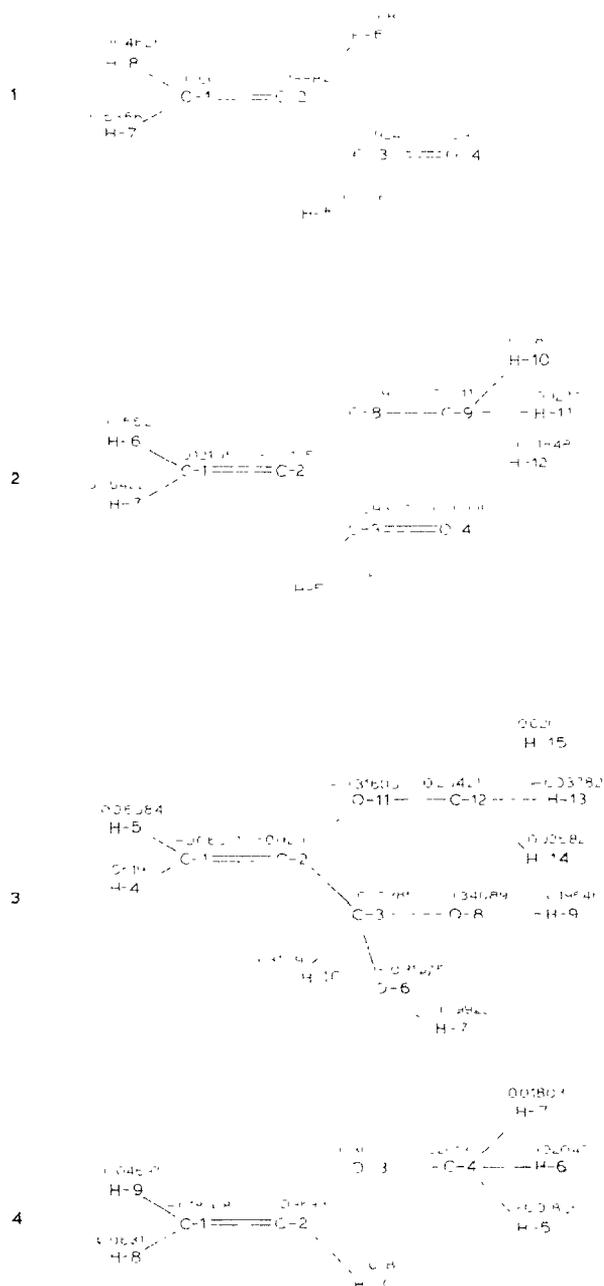
Fig. 4. Charge distribution in the most-stable conformations of propenal (1), 2-methoxypropenal (2), its hydrated form (3), and methyl vinyl ether (4).

where k_n is the observed rate-constant in a solvent of composition n and k_H is the observed rate-constant in pure H_2O; $k_D/k_H = 0.41$ is the ratio of rate constants obtained in D_2O and H_2O, n is the fraction of deuterium in the solvent and l is known to be 0.69 and is the fractional abundance of deuterium in lyonium ion (L_3O^+) relative to that in the solvent[20]. The quantity α, which represents a measure of the position occupied by the transition state in a proton-transfer reaction, was found to be 0.60 (average of three measurements).

MNDO electron structure. — The results of quantum-chemical calculation of electron densities in 2-methoxypropenal (2), its hydrated form (3), methyl vinyl ether (4), and propenal (1) are illustrated schematically in Fig. 4 in the form of charges on the individual atoms. The charges Q_i presented characterize the MNDO electron distribution in structures of the molecules studied, obtained by optimization of all geometric parameters.
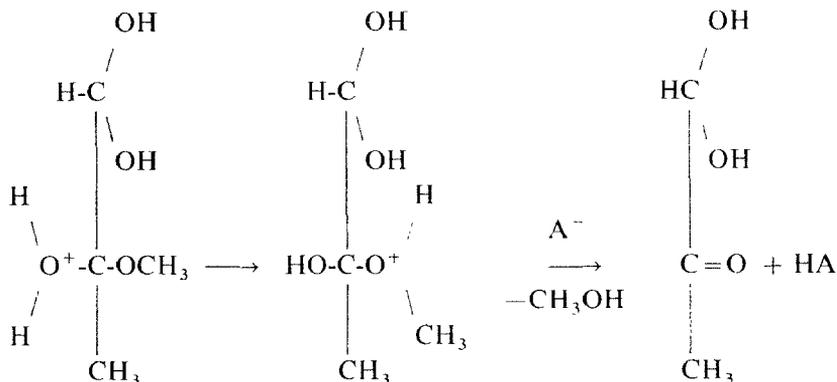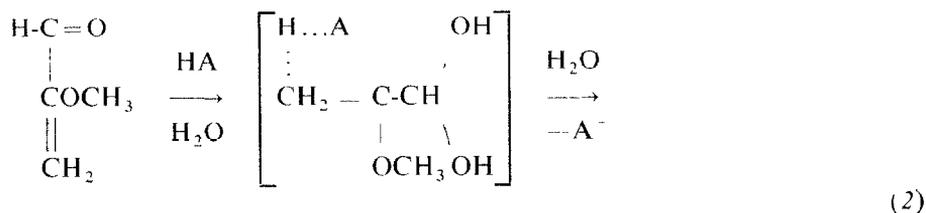
Analysis of products. — As already stated, acid-catalyzed hydrolysis of 2-methoxypropenal gave 2-oxopropanal, as confirmed by mass-spectral analysis of its product with o-phenylenediamine, namely 2-methylquinoxaline[21]. When the reaction was conducted employing deuterium chloride in D_2O, mass-spectral analysis proved the formation of 90% of 2-methylquinoxaline having molecular weight 145 and 10% having molecular weight of 144. Mass fragmentation confirmed that the 2-methylquinoxaline (molecular weight 145) had incorporated deuterium from the medium and it was present in the methyl group. This result indicates that, during the acid hydrolysis of 2-methoxypropenal, incorporation of deuterium into the methyl group of the 2-oxopropanal formed. As it is known that in strong acid, incorporation into 2-oxopropanal itself[22,23] may take place, a blank experiment also was conducted with the expected product. The extent of incorporation from the medium into the 2-oxopropanal molecule, under the conditions used, was found to be 5%.

DISCUSSION

In our previous work[3], we assumed that the formation of 2-oxopropanal in the acid-catalyzed reaction of 2,3-di-O-methyl-D-glyceraldehyde proceeded via the reactive intermediate 2-methoxypropenal. The present work provides experimental support of this assumption, and also proves that 2-methoxypropenal behaves more like vinyl ethers than propenal. This conclusion follows also from comparison of the electron-density distribution on the individual atoms in propenal (1), methyl vinyl ether (4), and 2-methoxypropenal (2) (Fig. 4). The distribution of electronic charge mainly on the alkenic, carbonyl, and methoxyl groups in these compounds is of key importance for chemical reactivity. Although propenal and methyl vinyl ether each contain two of these groups, the molecule of 2-methoxypropenal has all three groups present in close proximity (in the α-position) and therefore, they exert considerable mutual influence. It may be seen from Fig. 4 that the shift of electron density in the conjugated system in the molecule of propenal towards the oxygen atom of its aldehyde group (O-4) leads to concentration of positive charge on the alkenic

carbon atom (C-1). In the 2-methoxypropenal molecule, this polarization is hindered by the presence of the methoxyl group, which causes a substantial decrease of electronic charge on C-1 of its alkenic bond. By substituting the aldehyde group in the molecule of 2-methoxypropenal for a hydrogen atom, that is, when passing from 2-methoxypropenal to methyl vinyl ether, C-1 becomes even more electronegative From these facts it follows that, for electrophilic reactions, C-1 constitutes a more reactive center in the molecule of methyl vinyl ether than that in 2-methoxypropenal, whereas in the case of propenal, the reactivity is shifted to the vicinal carbon atom (C-2). Hydration of 2-methoxypropenal would probably cause considerable decrease of the aforementioned reactivity in comparison with that of the free form. The finding that, acid-catalyzed hydrolysis of 2-methoxypropenal leads to incorporation of one deuterium atom from the medium into the 2-oxopropanal formed is important in explaining the reaction mechanism.

The experimental and calculated quantum-chemical data, together with the observations regarding the hydrolysis of vinyl ethers[7-11], enable us to suggest the following mechanism (2) for the acid-catalyzed hydrolysis of 2-methoxypropenal.

$$
\begin{array}{c}
H\text{-}C=O \\
| \\
COCH_3 \\
|| \\
CH_2
\end{array}
\quad
\begin{array}{c}
HA \\
\longrightarrow \\
H_2O
\end{array}
\quad
\left[
\begin{array}{c}
H...A \qquad OH \\
\vdots \qquad , \\
CH_2 - C\text{-}CH \\
| \quad \backslash \\
OCH_3\, OH
\end{array}
\right]
\quad
\begin{array}{c}
H_2O \\
\longrightarrow \\
-A^-
\end{array}
$$

$$(2)$$

$$
\begin{array}{c}
OH \\
/ \\
H\text{-}C \\
| \backslash \\
\phantom{H\text{-}C} OH \\
H \quad | \\
\backslash \quad | \\
O^+\text{-}C\text{-}OCH_3 \\
/ \quad | \\
H \quad | \\
 CH_3
\end{array}
\longrightarrow
\begin{array}{c}
OH \\
/ \\
H\text{-}C \\
| \backslash \\
\phantom{H\text{-}C} OH \\
H \\
| \\
HO\text{-}C\text{-}O^+ \\
| \quad \backslash \\
 CH_3 \\
 CH_3
\end{array}
\quad
\begin{array}{c}
A^- \\
\longrightarrow \\
-CH_3OH
\end{array}
\quad
\begin{array}{c}
OH \\
/ \\
HC \\
| \backslash \\
 OH \\
| \\
C=O + HA \\
| \\
CH_3
\end{array}
$$

As the hydrolysis of 2-methoxypropenal has been proved to be a general acid-catalyzed process, it is evident that the first step, corresponding to the transfer of a proton (deuteron) from a general acid to the substrate is the slowest, overall rate-determining step. Incorporation of deuterium into the methyl group of the 2-oxopropanal formed occurs in this step. On the basis of the charge distribution found in 2-methoxypropenal and its hydrated form, it is assumed that the more-reactive, free form is involved in the reaction. In the rate-determining step, proton transfer from

the acid catalyst to 2-methoxypropenal breaks down the original conjugated system in the molecule, facilitating the addition of a water molecule to the aldehyde group with formation of the transition complex already presented. The last assumption may be suggested on the basis of the rather low value found for the entropy of activation. An important parameter characterizing the transition state is the Brönsted exponent α, which is a measure of the extent to which the proton is transferred from the catalyst to the substrate in the transition state. In our case, the experimentally found value of $\alpha = 0.60$ indicates that the proton is approximately one-half transferred at the transition state, as was found with vinyl ethers[7,10]. Rapid addition of another molecule of water to the transition complex leads to the protonated hemiacetal of the hydrated form of 2-oxopropanal, which is unstable and easily rearranges to the final product. Addition of water to the alkenic bond of 2-methoxypropenal proceeds according to the Markovnikov rule[24] in contrast to the behavior with propenal, where the addition of water leads to 3-hydroxypropanal[14]. The results obtained confirms that the nature of the reaction is determined by the methoxyl and not by the carbonyl group in the molecule of 2-methoxypropenal. However, the influence of the carbonyl group cannot be neglected; it is manifested by the marked decrease of the rate of hydrolysis of 2-methoxypropenal as compared with that of vinyl ethers[7,9], and by its possible hydration during the reaction.

Useful knowledge also follows from comparison of the activation parameters characterizing the acid-catalyzed hydrolysis of 2-methoxypropenal with those for vinyl ethers. Whereas the activation energies for hydrolysis of 2-methoxypropenal are comparable with those for hydrolysis of vinyl ethers[7,9], the activation entropy is considerably more negative than with vinyl ethers. As already mentioned, the marked decrease of activation entropy is attributed to participation of water in formation of the transition complex.

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