

KINETICS AND MECHANISM OF BASE-CATALYSED ALDOLIZATION OF 1,3-DIMETHOXY-2-PROPANONE

Michal FEDOROŇKO, Mária PETRUŠOVÁ and Vladimír KOVÁČIK

*Chemical Institute, Chemical Research Center,
Slovak Academy of Sciences, 842 38 Bratislava*

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1,3-Dimethoxy-2-propanone (HA) in an aqueous alkaline solution undergoes specifically base-catalysed aldolization with the formation of a dimer, 4-hydroxy-1,3,5-trimethoxy-4-methoxy-methyl-2-pentanone (H_2A_2). The reaction is reversible and involves the formation or decomposition of an intermediate anion, HA_2^- , as the rate-determining step. The formation of a carb-anion ion, A^- , of the starting compound and of the HA_2^- anion are rapid, preceding, and generally base-catalysed reaction steps. The activation and thermodynamic parameters of the reversible reaction were determined from the dependences of the rate and equilibrium constants on the temperature.

In contrast to nonsubstituted trioses¹⁻³, the kinetics and mechanism of acid-base catalysed conversions of their O-methyl derivatives has been studied only recently^{4,5}. It was proved that 2-oxopropanal is formed as end product from both types of compounds in acid-catalysed reactions^{2,4}. Whereas 2-oxopropanal can be formed as intermediate product from nonsubstituted trioses even in alkaline medium², in the case of 2,3-di-O-methyl-D-glyceraldehyde the reaction ends with 2-methoxypropenal⁵. However, 1,3-dimethoxy-2-propanone in alkaline medium cannot undergo an analogous β -elimination reaction, hence its aldolization reaction could be expected. In this respect, it is interesting to study the kinetics and mechanism of the base-catalysed reaction of 1,3-dimethoxy-2-propanone and to compare the results with those for the analogous reactions of 1,3-dihydroxy-2-propanone³ and acetone^{1,6}.

EXPERIMENTAL

Apparatus. The reaction kinetics was measured in aqueous solutions containing NaOH (Titri-sol, Merck, Darmstadt) at defined temperatures maintained with an accuracy of $\pm 0.1^\circ\text{C}$ (Kombinations-Thermostat TB, Gerätewerk Medingen, GDR) by the polarographic method (LP 7 Polarograph, Laboratorní přístroje, Prague). Measurements of pH values and potentiometric titrations were done on an apparatus of the type Titrator TT 2 (Radiometer, Copenhagen). The kinetics of incorporation of heavy water (Merck, Darmstadt) into 1,3-dimethoxy-2-propanone was measured by mass spectrometry (Jeol JMS-D 100 Mass Spectrometer).

Chemicals. 1,3-Dimethoxy-2-propanone and 4-hydroxy-1,3,5-trimethoxy-2-pentanone were prepared by the method described by us⁷. Other chemicals were of reagent grade.

Methods. The kinetics of the base-catalysed decomposition of the dimer, H_2A_2 , in a concentration of $5 \cdot 10^{-3} \text{ mol dm}^{-3}$ was measured in 0.05–0.50M-NaOH at 15–50°C by the polarographic method. This was based on the fact that only the monomer, HA, gives a polarographic reduction wave in a buffer solution containing 0.25M-(NH_4) $_2$ SO $_4$ and 0.05M-NH $_3$. The derivative curve was recorded, the peaks being more suited for the measurement than the rather ill-defined limiting current. The concentration of HA and hence also H_2A_2 was determined by using a calibration curve valid in the range $2 \cdot 10^{-4}$ – $2 \cdot 10^{-3}$ M-HA in the mentioned buffer at 20°C in the presence of an equivalent of H_2A_2 . These conditions were the same as during the reaction. Samples of the reaction solution were taken at chosen time intervals and added into the buffer solution, whereby the reaction stopped. After deaerating with pure nitrogen, derivative polarograms were recorded beginning at –1.0 V (against saturated calomel electrode) at 20°C. Thus, time changes of the concentrations of both reaction components and their equilibrium concentrations were determined. The concentrations of the base solutions used to obtain the calibration curve and in the kinetic measurements were determined titrimetrically as follows. A solution of 0.1M-NH $_2$ OH.HCl, 0.1M-NH $_2$ OH and 0.015M-HA or H_2A_2 was allowed to react with hydroxylamine for 20 h at 30°C to yield the corresponding oximes. The concentration of free hydroxylamine was then determined by titration with 0.1M-HCl. The concentration of HA or H_2A_2 was found from the difference between the hydroxylamine concentration in the presence and in the absence of these compounds.

Exchange of deuterium. The kinetics of the base-catalysed incorporation of deuterium into the molecule of 1,3-dimethoxy-2-propanone was studied in a similar way. At chosen time intervals, 5 ml samples were taken from 50 ml of a solution of $2 \cdot 10^{-3}$ M-HA and $2 \cdot 10^{-3}$ M-NaOD in D $_2$ O at 25°C, they were neutralized with an equivalent quantity of HCl, and HA was extracted with chloroform. After evaporation to a small volume, HA was analysed GC mass spectrometrically.

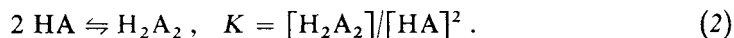
RESULTS

Orientation experiments have shown that the reaction $2 HA \rightleftharpoons H_2A_2$ is of pseudo-second order with respect to HA and pseudo-first order with respect to the dimer at constant concentration of NaOH acting as catalyst. The rate constant for the decomposition of H_2A_2 was calculated from the equation⁸

$$k_{-2} = \frac{x_e}{t(2a - x_e)} \ln \frac{ax_e + x(a - x_e)}{a(x_e - x)}, \quad (1)$$

where $a = [H_2A_2]_0$, $x = [H_2A_2]_0 - [H_2A_2]$, and $x_e = [H_2A_2]_0 - [H_2A_2]_e$ are respectively the starting concentration of H_2A_2 and the reacted amounts of H_2A_2 at a time t and t_∞ . The same values of k_{-2} were obtained by using a first-order kinetic equation during the initial stage of the reaction (*i.e.* far from the equilibrium). In contrast, no reliable value of k_2 for the formation of the dimer H_2A_2 from the monomer could be obtained either from a kinetic equation analogous to Eq. (1) (ref.⁸) or from a simple kinetic equation corresponding to a second-order reaction. Therefore, the values of k_2 for the aldolization of HA were calculated from the experimental values of k_{-2} for the back reaction and from the equilibrium constant defined

as



(A similar method was used in the case of aldolization of acetone^{1,6}).

The activation parameters for aldolization of HA and decomposition of H₂A₂ were determined as in our earlier work⁹. The thermodynamic equilibrium quantities were determined from the temperature dependence of the equilibrium constant ($\ln K = -\Delta G/RT$), the differences between the activation energies and enthalpies of the forward and back reactions ($\Delta H = E_2 - E_{-2}$ and $\Delta H = \Delta H_2^+ - \Delta H_{-2}^+$) and from the familiar equation $\Delta G = \Delta H - T\Delta S$.

It turned out that the rate and equilibrium constants for the formation and decomposition of H₂A₂ found in 0.1M-NaOH at 25°C are independent of the starting concentration of H₂A₂ in the range $5 \cdot 10^{-3} - 5 \cdot 10^{-2} \text{ mol dm}^{-3}$. On the other hand, an increase in the starting concentration causes the equilibrium concentration $[\text{H}_2\text{A}_2]_e$ to rise much more than that of the monomer $[\text{HA}]_e$ as follows from the equation for the equilibrium constant (2). This circumstance was made use of in the preparation of higher forms of the aldolization products of the studied compound⁷.

The influence of the NaOH catalyst concentration on the rate constants k_2 and k_{-2} is apparent from the data in Table I. Both rate constants are proportional to the catalyst concentration. The use of the mean values of the catalytic rate constants ($k_2(\text{OH}^-)$, $k_{-2}(\text{OH}^-)$) in the whole range of the sodium hydroxide concentrations used is problematical (see Discussion). The calculated values of k_2 are based on the value of $K = 9.1 \text{ dm}^3 \text{ mol}^{-1}$ at 25°C (Table II).

The determination of the dependence of the equilibrium and rate constants on the temperature and the calculation of the activation and thermodynamic parameters is based on kinetic and thermodynamic measurements of the studied reaction in the temperature range 15–50°C. The data are summarized in Table II from which it can be seen that the decomposition of H₂A₂ is much more accelerated by increasing temperature than its formation. This results in a decrease of the equilibrium constant K with the temperature. The obtained thermodynamic values are $\Delta H = -23.4 \text{ kJ} \cdot \text{mol}^{-1}$ for the enthalpy and $\Delta S = -60.2 \text{ J K}^{-1} \text{ mol}^{-1}$ for the entropy.

The dependences of the catalytic rate constants for the formation ($k_2(\text{OH}^-)$) and decomposition ($k_{-2}(\text{OH}^-)$) of H₂A₂ on the temperature give the activation parameters which, by difference, give the thermodynamic quantities for the reaction under study (Table III). These are practically identical with those calculated from the dependence of K on the temperature.

The results of the study of the kinetics of base-catalysed incorporation of deuterium into HA are shown in Fig. 1, illustrating the dependence of the concentration of non-deuterated HA molecules on the time and the courses of the exchange of 1–4 hydrogen atoms. The incorporation rate of the first deuterium atom (*i.e.* decrease of the

TABLE I

Rate and catalytic constants for the formation and decomposition of 4-hydroxy-1,3,5-trimethoxy-4-methoxymethyl-2-pentanone in aqueous NaOH at 25°C

[NaOH] mol dm ⁻³	$k_2 \cdot 10^3$ dm ³ mol ⁻¹ s ⁻¹	$k_{-2} \cdot 10^3$ s ⁻¹	$k_2(\text{OH}^-) \cdot 10^2$ dm ⁶ mol ⁻² s ⁻¹	$k_{-2}(\text{OH}^-) \cdot 10^2$ dm ³ mol ⁻¹ s ⁻¹
0.05	5.65	0.62	11.29	1.25
0.10	11.21	1.24	11.21	1.24
0.20	23.58	2.61	11.79	1.30
0.30	29.59	3.27	9.86	1.09
0.40	39.55	4.37	9.89	1.09
0.50	49.50	5.47	9.90	1.09
<i>Average</i>			$10.66 \cdot 10^{-2}$	$1.18 \cdot 10^{-2}$

TABLE II

Temperature dependence of rate and equilibrium constants for the formation and decomposition of 4-hydroxy-1,3,5-trimethoxymethyl-2-pentanone in aqueous 0.1M-NaOH

<i>t</i> °C	$k_2 \cdot 10^3$ dm ³ mol ⁻¹ s ⁻¹	$k_{-2} \cdot 10^3$ s ⁻¹	<i>K</i> dm ³ mol ⁻¹	ΔG kJ mol ⁻¹
15	4.88	0.42	11.6	-5.9
20	8.32	0.81	10.3	-5.7
25	11.18	1.24	9.1	-5.5
30	17.70	2.26	7.8	-5.2
35	22.86	3.34	6.8	-4.9
40	30.96	5.31	5.8	-4.6
45	42.00	8.70	4.8	-4.2
50	54.70	14.10	3.9	-3.6

TABLE III

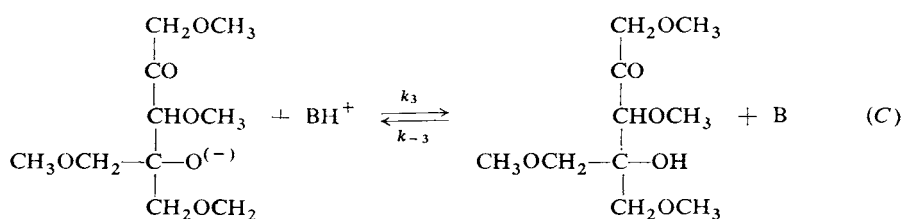
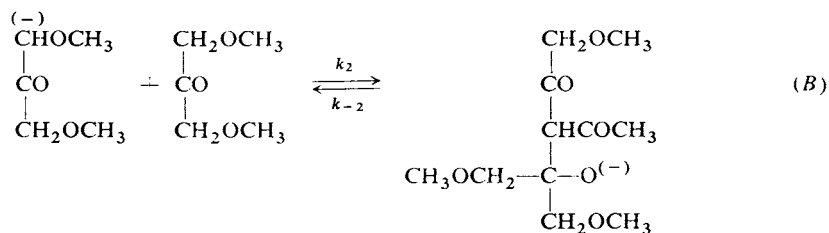
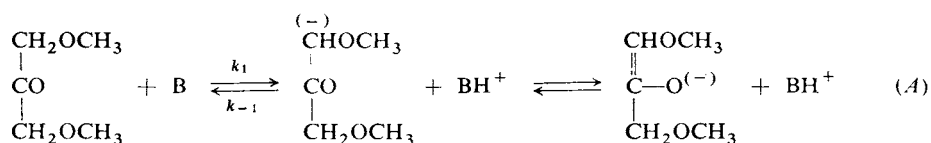
Activation and thermodynamic parameters for base-catalysed formation and decomposition of 4-hydroxy-1,3,5-trimethoxy-4-hydroxymethyl-2-pentanone at 25°C. ΔG , ΔH , and *E* expressed in kJ mol⁻¹, ΔS in J K⁻¹ mol⁻¹

ΔG_2^\ddagger	ΔG_{-2}^\ddagger	ΔH_2^\ddagger	ΔH_{-2}^\ddagger	<i>E</i> ₂	<i>E</i> ₋₂	ΔS_2^\ddagger	ΔS_{-2}^\ddagger
76.0	81.4	49.7	73.1	52.3	75.5	-88.1	-26.8
$\Delta G = -5.4$		$\Delta H = -23.4$		$\Delta H = -23.2$		$\Delta S = -61.3$	

nondeuterated monomer) satisfies the pseudo-first order kinetic equation; the corresponding rate constant was determined as $k_1(\text{OH}^-) = 1.23 \text{ dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$ at 25°C .

DISCUSSION

In spite of the great importance of aldolization reactions in synthesis of organic compounds¹⁰ there is a lack of quantitative data about the kinetics and mechanism of these acid-base catalysed reactions. The theory is mostly based on the study of the simplest carbonyl compounds, acetaldehyde, and acetone¹. Aldolization is important also in the formation and decomposition of saccharides^{1,3,11}, for which reason the present work has been undertaken. The model compound HA has the advantage that neither isomerization nor β -elimination takes place in its base-catalysed reactions, in contrast to nonsubstituted trioses² and O-methyl derivative of D-glyceraldehyde⁵. Our experimental results indicate that 1,3-dimethoxy-2-propanone in aqueous alkaline solutions undergoes aldolization with the formation of the dimer, 4-hydroxy-1,3,5-trimethoxy-4-methoxymethyl-2-pentanone which decomposes back to the monomer. The equilibrium reactions are



Here, B denotes a general base and BH^+ its conjugated acid. With a solution of NaOH, B is OH^- ion and BH^+ is water.

A comparison of the catalytic rate constant for incorporation of deuterium into 1,3-dimethoxy-2-propanone ($k_1(\text{OH}^-) = 1.23 \text{ dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$) with the aldolization constant ($k_2(\text{OH}^-) = 0.11 \text{ dm}^6 \text{ mol}^{-2} \text{ s}^{-1}$) clearly shows that the addition of the intermediate anion product A^- to the neutral HA molecule (B) is relatively slow, *i.e.* the rate-determining step. This is preceded by a mobile equilibrium reaction (A) yielding the A^- anion. As with acetaldehyde¹², also in this case the dehydration of the hydrated form of the starting compound¹³ (HA) is probably without influence on the rate of its aldolization. Similarly, in the decomposition of the dimer (H_2A_2), the formation of the HA_2^- anion from the neutral H_2A_2 molecule (C) is considered as a rapid reaction preceding the rate-determining step, namely β -elimination splitting off of the A^- anion from the intermediate HA_2^- anion (B). These conclusions are in accord with the data¹⁴ for decomposition of diacetone alcohol, which was proved by the change of the activation volume of the reaction to proceed by the E1cB mechanism. The pronounced reversibility of the studied reaction is due to the inability of the aldolization product H_2A_2 to become stabilized by forming cyclic hemiacetals, which is possible in the case of nonsubstituted 1,3-dihydroxy-2-propanone¹⁵. It follows that both the first (A) and third (C) reaction steps are generally base-catalysed, whereas the formation and decomposition of the HA_2^- anion in the second step (B) is only specifically base-catalysed. By analogy with the rate and equilibrium constants for base-catalysed keto-enol tautomerism of acetone¹⁶, we assume that also in the present case the preceding equilibrium in the first reaction step is markedly shifted toward the starting compound, and in the third step toward the HA_2^- anion. The latter circumstance may cause a decrease of the rate constant for the β -elimination decomposition of the HA_2^- anion as observed in the analogous

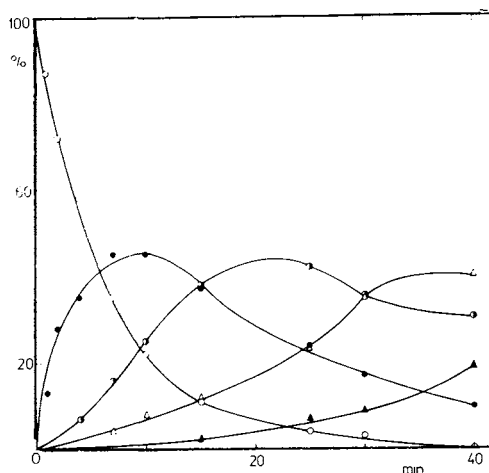


FIG. 1

Time dependence of incorporation of deuterium into $2 \cdot 10^{-3} \text{ M}$ 1,3-dimethoxy-2-propanone in the presence of $2 \cdot 10^{-3} \text{ M}$ NaOD in D_2O at 25°C . Number of D atoms: \circ none; \bullet 1; \bullet 2; \triangle 3; \blacktriangle 4

reaction of 2,3-dimethoxy-D-glyceraldehyde⁵. The corresponding values in Table I show a similar trend which is however of little significance.

The experimental values of the catalytic rate constants for incorporation of deuterium into 1,3-dimethoxy-2-propanone, $K_1(\text{OH}^-) = 1.23 \text{ dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$, and acetone¹⁷, $k_1(\text{OH}^-) = 0.23 \text{ dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$, suggest that the rate of splitting off of a proton increases by a factor of 5 on replacing the H atoms in acetone by methoxy groups. It is remarkable that the equilibrium constant for the formation and decomposition of diacetone alcohol at 25°C is smaller than 1 ($K = 3.9 \cdot 10^{-2} \text{ dm}^3 \text{ mol}^{-1}$ according to ref.^{1,6} or, more probably¹⁸, $K = 9.8 \cdot 10^{-3} \text{ dm}^3 \text{ mol}^{-1}$), whereas in our case (for H_2A_2) K is higher than 1, i.e. $K = 9.1 \text{ dm}^3 \text{ mol}^{-1}$ at 25°C. It follows that the rate of formation of diacetone alcohol is lower by a factor of about 0.01 than its decomposition, whereas the rate of formation of H_2A_2 is higher by a factor of about 10 than its decomposition. The difference between the reactivities of these compounds is due not only to the higher acidity of the protons in 1,3-dimethoxy-2-propanone molecule but also to increased reactivity of its anion which forms the intermediate addition product with the neutral molecule in the second (rate-controlling) step. The different reactivity of the CO groups of both compounds toward nucleophilic agents is manifested by different values of the equilibrium constants for hydration of acetone¹⁹, $K = 2 \cdot 10^{-3}$, and 1,3-dimethoxy-2-propanone¹³, $K = 0.373$, at 25°C. It should be noted that, after the equilibrium between HA and H_2A_2 had been attained, a slow decrease of the equilibrium concentrations with the time was observed, caused by the formation of higher aldolization products. This is especially pronounced at higher concentrations of HA and low temperatures and can be utilized for preparative purposes⁷.

The values of thermodynamic quantities (Table III) express the tendency of spontaneous aldolization of 1,3-dimethoxy-2-propanone (ΔG), its exothermic character (ΔH), and the increased degree of ordering of the product due mainly to the loss of the translation and rotation freedom of the HA molecule (ΔS). The backward reaction ($\text{H}_2\text{A}_2 \rightarrow \text{HA}$) can be characterized analogously.

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