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# BASE-CATALYZED β-ELIMINATION OF 2,3-DI-*O*-METHYL-D-GLYCERALDEHYDE

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ABSTRACT

2,3-Di-*O*-methyl-D-glyceraldehyde undergoes base-catalyzed β-elimination with formation of 2-methoxypropenal in two steps by the ElcB mechanism. The first step is a rapid, reversible, general base-catalyzed reaction giving an anionic intermediate of 2,3-di-*O*-methyl-D-glyceraldehyde. The second, slower step involves liberation of methoxide ion from the intermediate to give 2-methoxypropenal as the end-product. Reversibility of the first step was proved by incorporation of deuterium at C-2 of the starting compound. The order of the reaction decreases with increasing concentration of catalyst. A kinetic equation reflecting this fact was derived to determine the equilibrium constant of the first, reversible step and the rate constant of the second step. The mechanism of the reaction was elucidated on the basis of the kinetic rate-constants, deuterium solvent isotope-effect, and the activation parameters.

## INTRODUCTION

Acid–base catalyzed dehydration of saccharides, mainly monosaccharides and the analogous reaction of substituted derivatives, constitute important examples of β-elimination processes leading to the formation of various products[1]. In contrast to the β-elimination reactions of common organic compounds[2], reactions with saccharides are much more complex because of the involvement of different preceding, concurrent, and successive reactions. As demonstrated in our studies with glycolaldehyde, trioses, and their *O*-methylated derivatives[3–5] these are good models for more detailed kinetic studies and elucidation of the mechanisms of individual acid–base-catalyzed reactions of monosaccharides. As regards base-catalyzed β-elimination reactions, it has already been found that *O*-methyl derivatives of monosaccharides are especially suitable models because their degradation terminates at the stage of 2-methyl ethers[6]. The present paper deals with such a detailed study with 2,3-di-*O*-methyl-D-glyceraldehyde.

## EXPERIMENTAL

*Instruments and apparatus.* — The kinetics of racemization of 2,3-di-*O*-methyl-D-

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glyceraldehyde was monitored by circular dichroism (Dichrographe III, Jobin Yvon, Longjumeau, Paris), and the process of elimination of methanol from 2,3-di-*O*-methyl-D-glyceraldehyde by polarography (Type PO4g Polariter, Copenhagen), and by spectrophotometry (Specord UV VIS, Zeiss Jena). The reactions were monitored in aqueous solutions of sodium hydroxide and in buffers of sodium hydrogencarbonate–sodium carbonate and disodium hydrogenphosphate–trisodium phosphate at defined temperatures, with a precision of $\pm 0.1$ °. The products were analyzed by using a JEOL JMS-D 100 mass spectrometer as described in previous work[5]. Quantum-chemical calculations were performed with a Siemens 4004 computer. The linear dependences were calculated by the least-squares method by using a programmable calculator.

*Chemicals.* — 2,3-Di-*O*-methyl-D-glyceraldehyde was prepared as previously described[5-7]; NaOD (VEB Berlin Chemie) and $D_2O$ (Koch-Light Laboratories, Ltd.) were also employed. All other chemicals used were of analytical grade.

*Procedures.* — Racemization of 10mM 2,3-di-*O*-methyl-D-glyceraldehyde was performed in 2–10mM aqueous, carbonate-free solutions of sodium hydroxide at 25° and also in 5mM sodium hydroxide over the temperature range 20–40 °. The effect of buffer concentrations on the rate of racemization of the 10mM solution was investigated in 0.18M sodium carbonate–36mM sodium hydrogencarbonate of ionic strength $I = 0.58$ mol.dm$^{-3}$ at pH 10.52 and 25°, and also at lower concentrations of buffer that maintained the 5:1 ratio of the components and the ionic strength $I = 0.58$ mol.dm$^{-3}$ by adding the necessary amounts of sodium chloride. The course of racemization was monitored by the time decrease of the negative band in the c.d. spectra, observed at the maximal absorption namely $\lambda = 295$ nm for sodium hydroxide solutions and $\lambda = 293$ nm for using carbonate buffers.

The $\beta$-elimination reaction of 10mM 2,3-di-*O*-methyl-D-glyceraldehyde was conducted in aqueous, carbonate-free solutions of 0.01–0.50M sodium hydroxide at 25° and also in 0.05M sodium hydroxide over the temperature range 15–35 °. The course of $\beta$-elimination was monitored by polarographic curves of the 2-methoxypropenal formed in 0.1M acetate buffer of pH 4.62 at 20 °. Under the given concentration-conditions, the starting compound was not active, whereas the product was sufficiently stable and exhibited one well-defined polarographic wave. At preset time-intervals, 1-mL samples were withdrawn and acetate buffer (9 mL), thermostatted to 20°, was added to terminate the reaction. After purging with pure nitrogen to remove atmospheric oxygen, polarographic curves were recorded from 0.8 V versus a saturated calomel electrode. The $\beta$-elimination reaction of 0.2mM 2,3-di-*O*-methyl-D-glyceraldehyde was also performed in the aforementioned aqueous solutions of sodium hydroxide at 25 °, monitoring the u.v. spectrum of the 2-methoxypropenal formed at $\lambda_{max} = 248$ nm. The starting compound did not show u.v. absorption under the specified conditions. Polarographic curves and u.v. spectra showed the reaction product to be identical with that obtained from 2-methoxypropenal[7].

Deuteration studies on 10 and 100mM 2,3-di-*O*-methyl-D-glyceraldehyde (20 mL) were conducted in 10 and 50mM sodium deuteroxide in $D_2O$ at 25 °. The reaction

was terminated after 3 min by addition of a strong-acid cation-exchanger (Dowex 50-W) and the products, after successive extraction with ether, drying, and distillation, were analyzed by g.l.c.–m.s.

The basic activation-parameters of the reactions studied were determined from the variations with temperature of the rate constants for racemization and β-elimination of 2,3-di-*O*-methyl-D-glyceraldehyde. The energies of activation ($E_a$) were evaluated by least-squares analysis of plots of $\log k_x$ against $1/T$, and the activation enthalpies ($\Delta H^{\ddagger}$) by analysis of plots of $\log(k_x/T)$ against $1/T$. The free energy of activation ($\Delta G^{\ddagger}$) and activation entropy ($\Delta S^{\ddagger}$) values were calculated from the known relationships $\Delta G^{\ddagger} = -2.303RT\log(k_x hN/RT)$ and $\Delta S^{\ddagger} = (\Delta H^{\ddagger} - \Delta G^{\ddagger})/T$, where $k_x$ is either the catalytic rate-constant for racemization ($k_1^{OH^-}$) or the rate constant for β-elimination ($k_2$) of 2,3-di-*O*-methyl-D-glyceraldehyde at 25°.

## RESULTS

*Kinetics of racemization of 2,3-di-*O*-methyl-*D*-glyceraldehyde in aqueous solutions of sodium hydroxide and carbonate buffers.* — The racemization of 2,3-di-*O*-methyl-D-glyceraldehyde, under the aforementioned reaction-conditions, was first order with respect to the concentration of both substrate and base. Although comparable concentrations of both reactants were used, the experimental data obeyed pseudo-first-order kinetics with respect to the substrate, and the observed rate-constants were directly proportional to the concentration of hydroxide ions (Fig. 1). From the

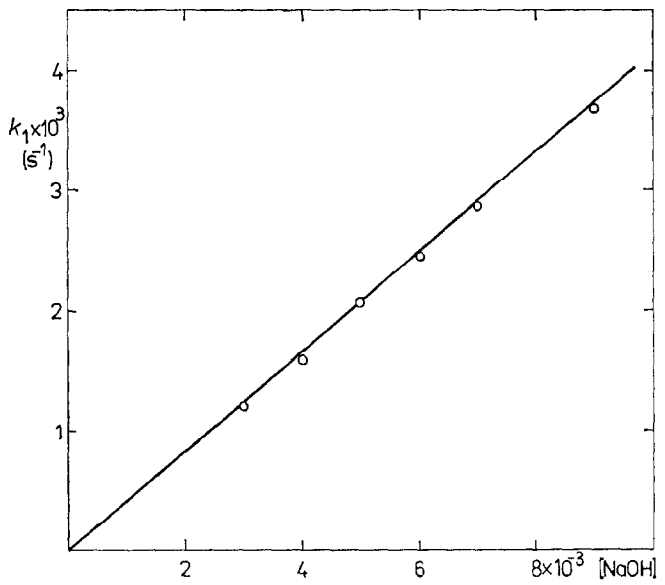



Fig. 1. Dependence of experimental rate-constants ($k_1$) for racemization of 10mM 2,3-di-*O*-methyl-D-glyceraldehyde on concentration of sodium hydroxide at 25°.

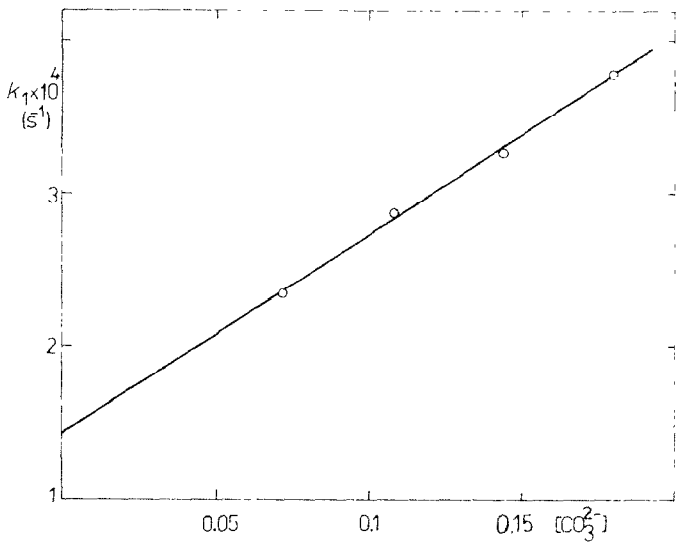



Fig. 2. Dependence of experimental rate-constants ($k_1$) for racemization of 10mM 2,3-di-*O*-methyl-D-glyceraldehyde on concentration of carbonate buffer at pH 10.52, ionic strength $I$ = 0.58 mol.dm$^{-3}$ at 25 °.

dependence of experimental rate-constants ($k_1$) on the concentration of sodium hydroxide, the catalytic rate-constant for racemization of 2,3-di-*O*-methyl-D-glyceraldehyde at 25 ° was found to be $k_1^{OH^-}$ = 0.42 dm$^3$.mol$^{-1}$.s$^{-1}$. The rate of racemization of 2,3-di-*O*-methyl-D-glyceraldehyde also increased linearly with increasing concentration of the carbonate buffer when the ratio of its components was kept constant, that is, at constant pH and constant ionic strength of the medium. The dependence of experimental rate-constants for racemization upon the concentration of sodium carbonate (Fig. 2) was used for determination of the appropriate catalytic rate-constant ($k_1^{CO_3^{2-}}$ = 0.0013 dm$^3$.mol$^{-1}$.s$^{-1}$). The intercept at zero concentration of carbonate ion represents the experimental rate-constant $k_1$ = 1.42 × 10$^{-4}$.s$^{-1}$ at the given activity of hydroxide ions in the carbonate buffer used (pH 10.52) and at the ionic strength $I$ = 0.58 mol.dm$^{-3}$ at 25 °. The calculated constant for catalysis of racemiza-

TABLE I

ACTIVATION PARAMETERS OF BASE-CATALYZED RACEMIZATION (A) AND $\beta$-ELIMINATION (B) OF 2,3-DI-*O*-METHYL-D-GLYCERALDEHYDE AT 25 °

| | $\Delta G^{\ddagger}$ (kJ mol$^{-1}$) | $\Delta H^{\ddagger}$ (kJ mol$^{-1}$) | $E_a$ (kJ mol$^{-1}$) | $\Delta S^{\ddagger}$ (J mol$^{-1}$.K$^{-1}$) |
|---|---|---|---|---|
| A | 75.2 | 70.5 | 72.8 | − 15.8 |
| B | 82.7 | 78.1 | 79.6 | − 15.4 |

tion by hydroxide ion ($k_1^{OH^-} = 0.43\ cm^3.mol^{-1}.s^{-1}$) agreed well with that obtained from the dependence shown in Fig. 1.

The basic activation-parameters of the reaction studied were determined from the dependence of the catalytic rate-constant on temperature (Table I).

*Kinetics of β-elimination of 2,3-di-*O*-methyl-*D*-glyceraldehyde in aqueous solutions of sodium hydroxide.* — The experimental data show that β-elimination of methanol from 2,3-di-*O*-methyl-D-glyceraldehyde in aqueous solutions of sodium hydroxide, leading to 2-methoxypropenal, obeys first-order kinetics. However, the observed rate-constants ($k_{obs}$) for β-elimination increase more slowly than does the concentration of the catalyst, and reach a limit at a certain concentration of sodium hydroxide (Fig. 3). This means that β-elimination in 2,3-di-*O*-methyl-D-glyceraldehyde in alkali media is first order with respect to substrate, but the first-order dependence with respect to base declines towards zero with increasing concentration of base. The dependence of the rate of β-elimination (Fig. 3) and the kinetic data for racemization of 2,3-di-*O*-methyl-D-glyceraldehyde clearly indicate a two-step reaction following the ElcB mechanism[2,8]. This mechanism differs in principle from the common $E_1$ and $E_2$ mechanisms for β-elimination reactions[2]. This base-catalyzed β-elimination reactions may be expressed as follows:

$$HPX + A^- \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} PX^- + HA \qquad (1),$$

and

$$PX^- \xrightarrow{k_2} P + X^- \qquad (2),$$

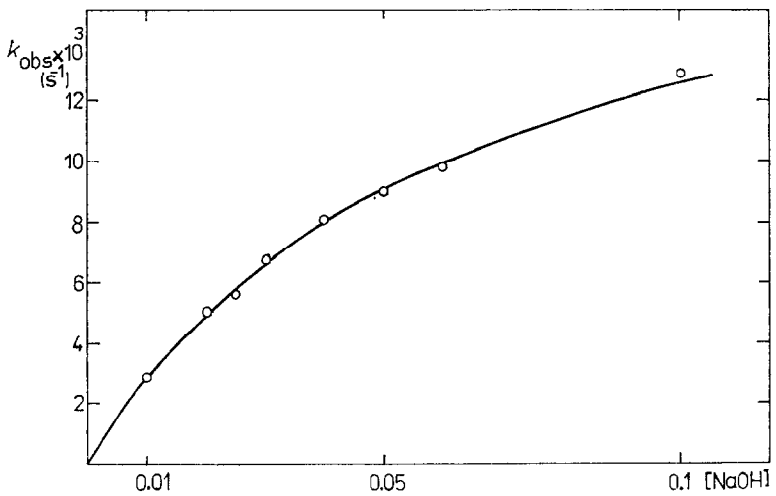



Fig. 3. Dependence of the observed rate-constants ($k_{obs}$) for β-elimination of 10mM 2,3-di-*O*-methyl-D-glyceraldehyde on concentration of sodium hydroxide at 25°.

where HPX is the substrate (2,3-di-*O*-methyl-D-glyceraldehyde), $PX^-$ the anionic intermediate, P the product of $\beta$-elimination (2-methoxypropenal), $X^-$ the ligand cleaved (methoxide ion), and $A^-$ a base ($OH^-$ or $CO_3^{2-}$) The general base ($A^-$) involved in Eq. *1* establishes that the reaction rates in both directions are general-base-catalyzed processes. After establishment of the equilibrium, subsequent cleavage of the intermediate ($PX^-$) formed constitutes a specific-base-catalyzed reaction (*2*) independent of the base used.

Our experimental data, mainly the finding of a nonlinear dependence of the rate constants on concentration of sodium hydroxide, represent important kinetic criteria for the mechanism of base-catalyzed reactions of 2,3-di-*O*-methyl-D-glyceraldehyde. The experimental data are best accommodated by the kinetic equation *3*, which permits determination of the equilibrium constant ($K = k_1/k_{-1}$) for reaction *1* and the rate constant ($k_2$) for reaction *2* from the observed pseudo-first-order constants ($k_{obs}$). This kinetic equation (*3*) was obtained by solution of a differential equation expressing the rate of formation of the end-product, namely 2-methoxypropenal, from the anionic intermediate, the concentration of which is expressed by the equilibrium equation (*1*) in a manner similar to that found for base-splitting of glycosides[9].

$$\frac{k_2K[OH^-]}{1 + K[OH^-]}\,t = \ln\frac{[HPX]_o}{[HPX]_o - [P]} \qquad (3),$$

where

$$\frac{k_2K[OH^-]}{1 + K[OH^-]} = k_{obs} \qquad (4),$$

Inversion of Eq. *4* gives:

$$1/k_{obs} = 1/k_2 + 1/k_2K.1/[OH^-] \qquad (5).$$

From the relationship *4* it may be seen that the rate-constants ($k_{obs}$) are determined by the expression in the denominator. For low concentrations of hydroxide ions, $K[OH^-] < 1$, and at high concentrations $K[OH^-] > 1$; this clearly determines the dependence of $k_{obs}$ on the concentration of hydroxide ions. The dependence of the observed rate-constant ($k_{obs}$) for $\beta$-elimination of 2,3-di-*O*-methyl-D-glyceraldehyde on the concentration of sodium hydroxide, illustrated in Fig. 3, is, according to Eq. *5*, a linear relationship (Fig. 4). The least-squares method was applied to establish the slope ($1/k_2K$) and the intercept ($1/k_2$) of this relationship (Fig. 4). The values obtained permitted calculation of the equilibrium constant ($K = k_1/k_{-1} = 16.4$) and the rate constant for $\beta$-elimination of methoxide ion from the anionic intermediate ($k_2 = 0.020\ s^{-1}$ at 25 ). The rate constants $k_{-1}$ ($k_{-1}^{OH^-}$) were calculated from the equilibrium constant (K) and the rate constants $k_1$ ($k_1^{OH^-}$). The catalytic rate-constant for the formation of racemic 2,3-di-*O*-methyl-DL-glyceraldehyde from its anionic intermediate was found to be $k_{-1}^{OH^-} = 0.025\ dm^3.mol^{-1}.s^{-1}$ at 25°.

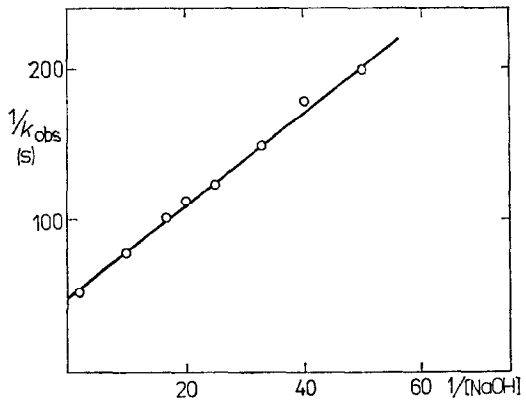



Fig. 4. Dependence of $1/k_{obs}$ on 1/NaOH for β-elimination of 10mM 2,3-di-*O*-methyl-D-glyceraldehyde in $H_2O$ at 25°.

Obviously, from the known equilibrium constant ($K$) and the ionic product of water ($K_W$), the ionization constant ($K_i$) for 2,3-di-*O*-methyl-D-glyceraldehyde in water may be calculated according to the relationship *6*:

$$K_i = K.K_W \qquad (6).$$

The value obtained for the ionization constant, $K_i = 1.64 \times 10^{-13}$, quantitates the acidity of H-2 in 2,3-di-*O*-methyl-D-glyceraldehyde in aqueous solution at 25°, and is comparable to or higher than the ionization constant found for monosaccharides[10,11], although the latter value is the acidity of the hydrogen atom of a hemiacetal hydroxyl group.

The foregoing kinetic parameters were determined for the same reaction performed in $D_2O$. The observed rate-constants for base-catalyzed reactions of 2,3-di-*O*-methyl-D-glyceraldehyde in both solvents and in NaOX are summarized in Table II. The average values observed for the solvent kinetic isotope-effect ($k^D_{obs}/k^H_{obs}$)

TABLE II

DEPENDENCE OF THE OBSERVED AND CALCULATED RATE-CONSTANTS FOR β-ELIMINATION OF 2,3-DI-*O*-METHYL-D-GLYCERALDEHYDE ON CONCENTRATION OF SODIUM HYDROXIDE AND DEUTEROXIDE, RESPECTIVELY, AT 25°

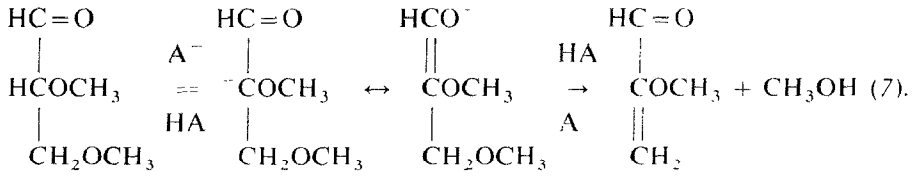
| $NaOX \times 10^3$ ($mol/dm^3$) | $k^H_{obs} \times 10^3$ ($s^{-1}$) | $k^D_{obs} \times 10^3$ ($s^{-1}$) | $k^D_{obs}/k^H_{obs}$ | $k^D_{calc}/k^H_{calc}$ |
|---|---|---|---|---|
| 3 | 0.95 | 1.23 | 1.30 | 1.33 |
| 4 | 1.20 | 1.59 | 1.32 | 1.33 |
| 5 | 1.40 | 1.92 | 1.37 | 1.34 |
| 6 | 1.71 | 2.30 | 1.35 | 1.34 |
| 8 | 2.24 | 2.99 | 1.33 | 1.33 |
| 10 | 2.73 | 3.68 | 1.35 | 1.33 |

and those calculated ($k^{D}_{calc}/k^{H}_{calc}$) according to Eq. *4* are practically identical (1.33), and fit into the range of deuterium effects reported for the ElcB mechanism[12,13].

The existence of the equilibrium of reaction *d* was confirmed by incorporation of deuterium from the medium onto C-2 of the starting 2,3-di-*O*-methyl-D-glyceraldehyde. It was found that the reaction of a 10mM solution of the substrate and 10mM NaOD in $D_2O$ at room temperature for 3 min resulted in only ~5% incorporation of deuterium, but increasing the concentration of the substrate to 100 and NaOD to 50mM under the same reaction conditions raised the incorporation of deuterium from the medium to as high as 22%.

## DISCUSSION

As mentioned in our preceding paper[5], 2,3-di-*O*-methyl-D-glyceraldehyde undergoes base-catalyzed β-elimination with formation of 2-methoxypropenal. This behavior differs in principle from that of the isomeric 1,3-dimethoxy-2-propanone. All experimental results indicate that the base-catalyzed β-elimination of methanol from 2,3-di-*O*-methyl-D-glyceraldehyde proceeds by the ElcB mechanism, namely, in two reaction steps through the corresponding anionic intermediate. As this compound is optically active, it was possible to study the kinetics of both steps separately and thus obtain sufficient experimental data to explain the mechanism of the reactions in detail. The mechanism established for racemization and β-elimination of methoxide ion from the anionic intermediate of 2,3-di-*O*-methyl-D-glyceraldehyde is shown in Eq. *7*:



In the first, reversible step removal of H-2 by base $A^-$ gives the resonance-stabilized, anionic intermediate. Reversibility of the process was confirmed by the observation of incorporation of deuterium from the medium and loss of optical activity of the starting compound. The fact that this reversible reaction is also catalyzed by carbonate ion proves that this step involves a general-base-catalysis. The subsequent β-elimination of methoxide from the anionic intermediate is a specific-base-catalyzed reaction[8,12]. In this step, the solvent might also be involved, but the nature of solvent (water) participation cannot be explained on the basis of simple kinetic measurements because water is present in large excess. The role of solvent in the cleavage of methoxide ion and its neutralization and regeneration of the hydroxide ion can affect, to a certain extent, the values of the activation parameters and rate constants. Therefore both reaction steps may constitute two successive, bimolecular reactions. The first step is a reaction of a strong base with the substrate as a weak acid, whereas in the second step the strongly basic anionic intermediate reacts with water as a weak acid.

To determine the character of participation of water in this process in detail, further investigation is necessary, for instance to observe the effect of other hydroxylic solvents of different polarities on the course of this type of reaction. The higher rates for the first step of the reaction correspond to lower activation enthalpies and energies in comparison with those for the second step (Table I). However, the differences in energies and rates of both steps are low in comparison with those found for analogous types of reactions with β-methoxyketones[12].

In contrast to the activation energies, the activation entropies for both steps of the reaction are practically the same. It is of interest that in our case, as in analogous reactions[9,12], the activation entropies are negative, suggesting that both reaction steps are bimolecular[14].

Evaluation of all rate and equilibrium constants for base-catalyzed reactions of 2,3-di-O-methyl-D-glyceraldehyde has permitted kinetic characterization of both reaction steps. The rate and equilibrium constants were determined without any approximations[12], and have made it possible to calculate the deuterium solvent kinetic-isotope effect and thus prove the validity of the ElcB mechanism.

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