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STUDY OF THE KINETICS AND MECHANISM OF THE ACID–BASE-CATALYZED ENOLIZATION OF HYDROXYACETALDEHYDE AND METHOXYACETALDEHYDE

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ABSTRACT

In acid and alkaline media, glycolaldehyde (hydroxyacetaldehyde) exists in equilibrium with its enediol form, which is quantitatively oxidized to glyoxal by an excess of Methylene Blue. In acid and alkaline media, the enol form of methoxyacetaldehyde is formed. In alkaline medium, this enol is stable; in acid, it undergoes hydrolysis to glycolaldehyde. The kinetics of enolization of glycolaldehyde and methoxyacetaldehyde were studied polarographically The mechanisms of enolization of glycolaldehyde and acid hydrolysis of methoxyacetaldehyde were established both from kinetic data and from deuterium-incorporation data. The proposed mechanisms were confirmed by quantum-mechanical calculation of the charge distribution in the two compounds studied and their reaction intermediates. The glyoxal obtained in the oxidation was isolated as quinoxaline and analyzed by mass spectrometry.

INTRODUCTION

It is now generally acknowledged that the acids or bases act on monosaccharides to produce their enodiol forms as primary, unstable intermediates that determine the course of all further acid–base-catalyzed changes. The formation of these enediols may be studied conveniently by using glycolaldehyde, as this compound, in contrast to all higher monosaccharides, does not undergo dehydration, and its aldol condensation can be prevented by suitable choice of reaction conditions. We have developed a method whereby the rate of formation of the glycolaldehyde enediol maybe monitored by oxidation with Methylene Blue to produce glyoxal, which technique broadens the choice of chemical and physico-chemical methods available for the study of keto–enol tautomerism[1].

The use of methylated derivatives of monosaccharides, in which the labile hydrogen atom is replaced by a methyl group, permits direct confirmation of the validity of some theories on the reactivity of simple sugars. The work of Lewis and coworkers[2–7] has made a great contribution to the clarification of these problems. They explained the marked stability of methylated saccharides in alkaline media by studying 2,3,4,6-tetra-*O*-methyl-D-glucose[2,3] and 2,3,4,6-tetra-*O*-methyl-D-mannose[4], for which they demonstrated only mutual epimerization by simple keto–enol tautomerism: there is no formation of the corresponding ketoses because of exclusion of the participation of selective addition and elimination of water in the Nef mechanism. Similar results were obtained with 2,3,4-tri-*O*-methylxylose[5] and 2,3,4-tri-*O*-methyl-L-arabinose[6], where the products obtained form 2-furaldehyde more rapidly in acid media than the initial methylated or unmethylated pentoses. The behavior of these permethylated aldohexoses and aldopentoses explains in greater detail the reaction of 3-*O*-methyl-D-glucose[7] and especially 2,3-di-*O*-methyl-D-glucose[8–11], from which methanol is split off in alkaline media in a β-elimination reaction with formation of the corresponding 2-methyl ether. It has been shown that direct action of mineral acids on permethylated pentoses[12] and hexoses[13] also produces 2-furaldehyde or 5-methoxymethyl-2-furaldehyde, respectively.

Fundamental, quantitative data were obtained in these studies on acid–base-catalyzed reactions. To broaden our knowledge and obtain necessary quantitative data on these reactions, the kinetics and mechanism of the acid–base-catalyzed transformations of the simplest models, namely, glycolaldehyde and its methyl ether, were studied.

EXPERIMENTAL

Instruments and apparatus. — Studies of the kinetics of the enolization of glycolaldehyde (**1**) and methoxyaldehyde dimethyl acetal (**2**) were conducted in aqueous hydrochloric acid and sodium hydroxide at defined temperatures, maintained with a precision of ±0.1°. The reaction was monitored polarographically (Type PO4g Polariter, Copenhagen). The products were analyzed by using a Jeol JMS-D 100 mass spectrometer. 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. — Glycolaldehyde (**1**, Fluka AG, Buchs SG), methoxyacetaldehyde dimethyl acetal (**2**, Aldrich Chemical Company, Inc.) and methoxyacetaldehyde **3**, obtained by hydrolysis of **2** (20mM in 40mM hydrochloric acid for 4 h at 50°) were used in the study. DCl (VEB Berlin Chemie) and D_2O (Koch–Light Laboratories, Ltd.) were also employed. All other chemicals used; Methylene Blue, hydrochloric acid, sodium hydroxide, calcium hydroxide, *o*-phenylenediamine, and sodium periodate, were of analytical purity.

Procedures. — The enolization of glycolaldehyde (**1**) was studied polarographically in a thermostatted polarographic vessel[14] at the required temperature, from the decrease in the height of the polarographic wave of Methylene Blue in acid and basic media. Before initiating the reaction, atmospheric oxygen was removed from the reaction vessel by purging with pure nitrogen. The polarographic waves were recorded by using a saturated mercury(I) sulfate electrode. The hydrolysis of 20mM **2** in aqueous hydrochloric acid was monitored by using the polarographic curves of the methoxyacetaldehyde (**3**) formed in a saturated solution of calcium hydroxide at 20°. At preset time-intervals, 0.5-mL samples were removed and 9.5 mL of saturated calcium hydroxide was added; after purging with pure nitrogen to remove atmospheric oxygen, the polarographic curve was recorded from −1.0 V.

The enolization and hydrolysis of methoxyacetaldehyde, with formation of glycolaldehyde, in aqueous solutions of hydrochloric acid was studied on the basis of the decrease in the height of the polarographic wave of methoxyacetaldehyde, after oxidation by sodium periodate of the glycolaldehyde formed. At preset time-intervals, 1-mL samples were taken from the 5mM initial solution of methoxyacetaldehyde or **2**, and 0.1M acetate buffer (pH 4.6, 8 mL, with a sodium hydroxide content such that the pH value of the buffer was maintained), was added with cooling. Sodium periodate (7.5mM, 1 mL) was added to this sample to oxidize the glycolaldehyde formed. After 15 min, the mixture was made alkaline by adding a small amount of solid calcium hydroxide, and the polarographic wave was recorded from —0.5 V at 20°. The polarographic curve consisted of a more-positive wave for the reduction of sodium iodate and a wave at more-negative potential corresponding to reduction of unreacted methoxyacetaldehyde, which was used for monitoring the kinetics.

Incorporation of deuterium into glycolaldehyde and methoxyacetaldehyde was controlled in the following manner.

(*a*) Glycolaldehyde (10mM, 20 mL) was allowed to react in 4 5M DCl in D_2O for 3 h at 50°. After this time, Methylene Blue (64 mg, 10 mmol) was added, and the reaction was allowed to proceed for a further 3 h to oxidize the glycolaldehyde (through its enediol form) to glyoxal. After completion of the reaction, the sample was cooled, brought to pH 5–6 with solid potassium hydrogencarbonate, and an equivalent amount of *o*-phenylenediamine was added (2 mL of 0.1M solution). The quinoxaline formed was removed from the mixture by steam distillation and was then extracted into ether from the aqueous solution. The dried ether solution was evaporated and the quinoxaline obtained subjected to mass-spectrometric analysis.

(*b*) The procedure was the same as (*a*), except that Methylene Blue was added immediately at the beginning, and the reaction was allowed to proceed for only 3 h.

(*c*) The acetal **2** (20 mL of 10mM solution) was allowed to react with 20mM Methylene Blue in 4.5M DCl in D_2O 6 h at 50°. Further treatment was as under (*a*)

(*d*) Glycolaldehyde (20 mL, 10mM) was allowed to react with 10mM NaOD in D_2O for 30 min at 25°. After addition of 22 mg (10 mmol) of *o*-phenylenediamine and 64 mg (10 mmol) of Methylene Blue, the solution was allowed to react for an additional 30 min. The solution was brought to pH 5–6 with hydrochloric acid, and further treatment and analysis of the quinoxaline obtained was carried out as described under (*a*).

(*e*) Glycolaldehyde (20 mL, 10mM) was allowed to react with 20mM Methylene Blue in 10mM NaOD in D_2O in the presence of mM *o*-phenylenediamine for 30 min at 25°. The solution was made neutral with hydrochloric acid to pH 5–6, and further treatment and analysis of the quinoxaline obtained was performed as under (*a*).

Procedure for calculation of the conformation and electronic structure of glycolaldehyde, methoxyacetaldehyde, and their protonated and enol forms. — The conformational energies and electron distributions for the compounds studied were calculated by the semiempirical PCILO quantum-chemical method[15,16], which is based on the Rayleigh–Schrödinger energy expansion, where the individual terms of the perturbation expansion are expressed as interactions among the orthonormal sets of bonding orbitals. These bonding orbitals are composed of localized, bicentral, bielectronic wavefunctions, whose product yields the most suitable wavefunction for a molecule having the bonds specified. All integrals are calculated on the basis of the ZDO schemes[17]. The standard geometric parameters of Pople[17] were employed in the calculation:

r (C–C)	150.3 pm	(H–C–C)	108°
(C=O)	120.5	(O=C–C)	124
(C–O)	140.3	(C–O–C)	112
(O–H)	100.0	(O–O–C)	118
(C–H)	110.0	(C–O–H)	110
(C$\cdot^{+}\cdot$O)	130.0	(H–O$\cdot^{+}\cdot$–H)	120
(O$\cdot^{+}\cdot$H)	105.0		
(C=C)	134.0		
(C–C=)	136.0		

These parameters were kept constant throughout the calculation, and the most-stable conformation was found as the energy minimum in the dihedral angles characterizing rotation about the individual single bonds.

RESULTS

Enolization of glycolaldehyde in aqueous hydrochloric acid. — The method for measuring the rate of enolization of glycolaldehyde in aqueous hydrochloric acid is based on observations of the rapid oxidizability of the enediol of glycolaldehyde by Methylene Blue as found here and employed in the solution of a number of practical problems. As the two-electron oxidation of the enediol form of glycolaldehyde to glyoxal is accompanied by two-electron reduction of Methylene Blue to its leuco form, the concentration of unreacted glycolaldehyde may be determined directly from the decrease in the height of the polarographic wave of Methylene Blue. A practical example of the study of the enolization of glycolaldehyde by using Methylene Blue is given in Fig. 1. It was found that the enolization of glycolaldehyde in acid and alkaline media is first order with respect to glycolaldehyde and zero order with respect to Methylene Blue; that is, it is independent of the concentration of Methylene Blue, as also was found for halogenation of acetone[18]. It is obvious that both of these reactions are catalyzed by acids and by bases. It was found that the rate constants measured for the enolization in the range of 1–5mM glycolaldehyde studied with mM Methylene Blue; or mM glycolaldehyde with 1–3mM Methylene Blue in 4.5M hydrochloric acid at 50°, are comparable and independent of the concentration range chosen for the reactants used.

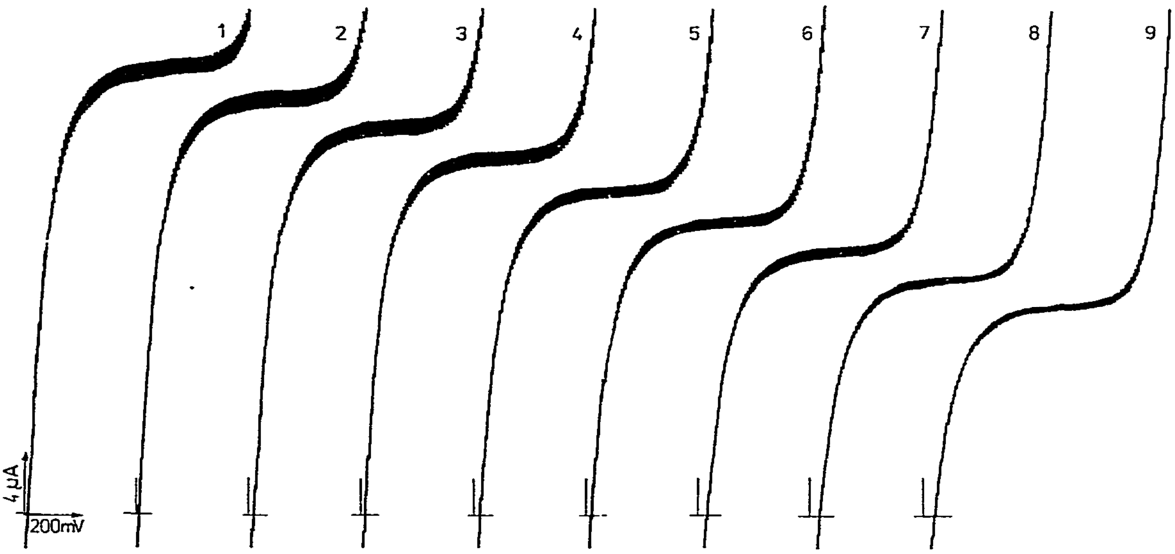


Fig. 1 Time dependence of the enolization of 5mM glycolaldehyde in 4.5M hydrochloric acid at 50° The rate of enolization was monitored on the polarographic wave for the reduction of 3mM Methylene Blue in dependence with time: 0 (1), 3 (2), 6 (3), 10 (4), 15 (5), 20 (6), 25 (7), 30 (8), and 35 (9) min.

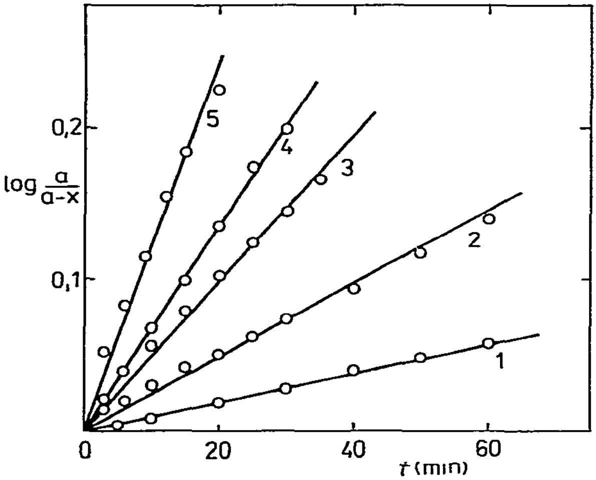


Fig. 2. The kinetic dependence of the enolization of 5mM glycolaldehyde studied in 2.5 (1), 3.5 (2), 4.5 (3), 5.5 (4), and 6.5M (5) hydrochloric acid at 50°.

The orientation experiments described for studying the rate of enolization of glycolaldehyde by using Methylene Blue, as catalyzed by aqueous solutions of hydrochloric acid, were used for selection of optimal reaction conditions. In most instances, 5mM glycolaldehyde and 3mM Methylene Blue were used in 2.5–6.5M hydrochloric acid at 50°.

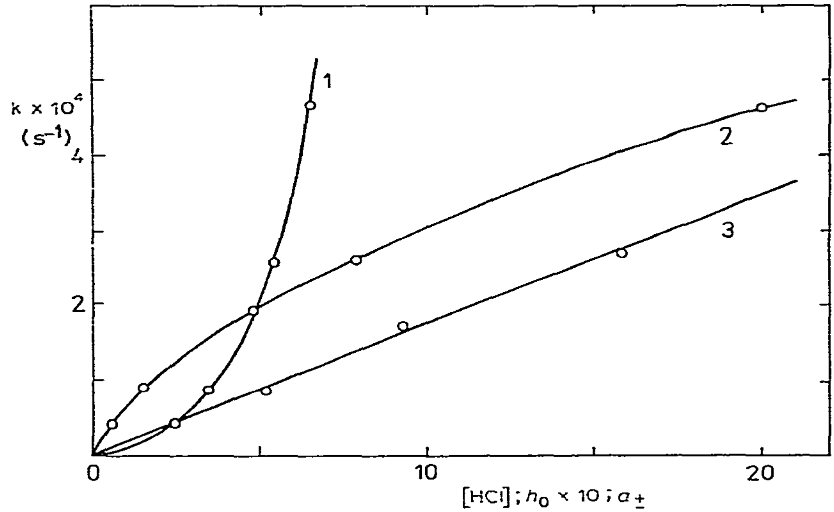


Fig. 3. Dependence of the rate constant for enolization of glycolaldehyde on the molar concentration of HCl (1), on the acidity function (h_0) (2), and the mean activity of hydrochloric acid ($a_\pm$) (3) at 50°.

The rate constants for enolization of glycolaldehyde for the selected concentrations of hydrochloric acid at 50° were determined from the dependences depicted in Fig. 2. As indicated in Fig. 3. the rate-constants measured increase more rapidly than the molar concentration of hydrochloric acid and, in contrast, when using the Hammett acidity function (h_0), more slowly than would correspond to linear dependences. These requirements are best met by the dependence of the rate constants on the mean activity of hydrochloric acid ($a_\pm$), as was also found for the dehydration of trioses[19]. The required values of the mean, molar-activity coefficients ($f_\pm$) for calculation of the mean activity of hydrochloric acid ($a_\pm = c.f_\pm$) at 50° were calculated from the known mean, molal activity-coefficients $(\gamma_\pm)$[20,21]. The values of the acidity function (h_0) were calculated[22] from H_0 at a temperature of 50°. A value of the catalytic constant for enolization of glycolaldehyde of $k_{a_\pm} = 1.60 \times 10^{-5}$L.mol^{-1}.s^{-1} was found from the dependences of the rate constants on the mean activity of hydrochloric acid at 50° (Fig. 3, No. 3).

Kinetic measurements on 5mM glycolaldehyde in 4.5M hydrochloric acid at a temperature of 30–60° was performed in order to determine the activation energy for enolization of glycolaldehyde. The activation energy was found graphically by using the Arrhenius equation: the calculation was performed with catalytic constants ($k_{a_\pm}$) obtained from the measured rate-constants (k) and the mean activity of hydrochloric acid ($a_\pm$) calculated for each temperature used[22]. An activation-energy value of $E_{a_\pm} = 112.2$ kJ.mol^{-1} was found from the measurements described and from calculations for the enolization of glycolaldehyde in an acid medium.

Enolization of glycolaldehyde in aqueous solutions of sodium hydroxide. — The reactivity of glycolaldehyde in alkaline solution was much higher than that in acid.

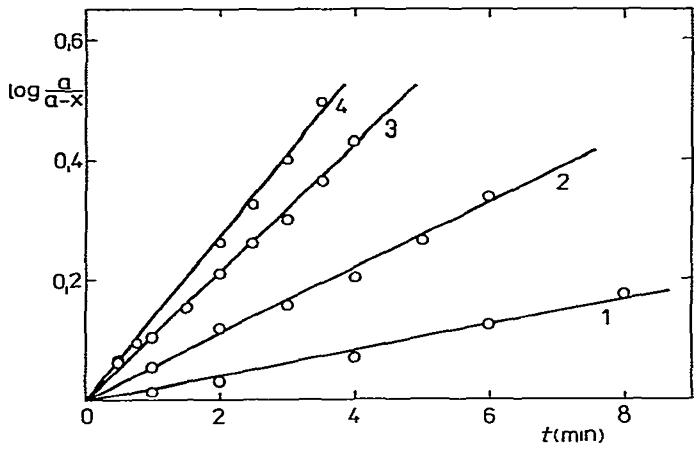


Fig. 4. The kinetic dependence of the enolization of mM glycolaldehyde in 1 × 10^{-2} (1), 2 × 10^{-2} (2), 4 × 10^{-2} (3) and 6 × 10^{-2}M sodium hydroxide (4) at 25°.

To limit the undesirable aldolization reaction of glycolaldehyde to a negligible value, its initial concentration was decreased to 1mM. Similarly, Methylene Blue displayed a certain concentration-decrease in alkaline media; however, over the period used for kinetic measurement of the enolization of glycolaldehyde, the decrease was small. Although glycolaldehyde as well as Methylene Blue is polarographically active in alkaline media, the enolization was studied on the basis of the time-decrease in the limiting current of Methylene Blue.

The rate constants for enolization of glycolaldehyde at various concentrations of sodium hydroxide at 25° were found from the dependences depicted in Fig. 4. The rate constants observed were directly proportional to the corresponding concentrations of sodium hydroxide, from which the constant $k_{OH^-} = 8.9 \times 10^{-2}$ L.mol^{-1}s^{-1} at 25° was found for catalysis of the enolization of glycolaldehyde by hydroxide ion.

The kinetic measurements were conducted over the temperature range 20–40° to find the activation energy for the enolization of glycolaldehyde as catalyzed by hydroxide ion. An activation energy $E_{OH^-} = 82.9$ kJ.mol^{-1} was obtained from the given dependences.

Hydrolysis of methoxyacetaldehyde dimethyl acetal (**2**) *in aqueous hydrochloric acid.* — Although the hydrolysis of **2** with formation of methoxyacetaldehyde (**3**) is not really a part of the problem studied, it was conducted in order to determine whether the rate of this hydrolysis is sufficiently large not to affect the rate of the enolization of methoxyacetaldehyde. The practical importance of this study lies in determination of whether **2** may be employed directly in study of the kinetics of the enolization of methoxyacetaldehyde. The kinetics of the hydrolysis of 10mM **2** was studied polarographically in 8–80mM HCl at 50°, as described in the procedure. The dependence of hydrolysis of **2** to methoxyacetaldehyde on the concentration of hydrochloric acid at 50° is depicted in Fig. 5. The corresponding catalytic-constant

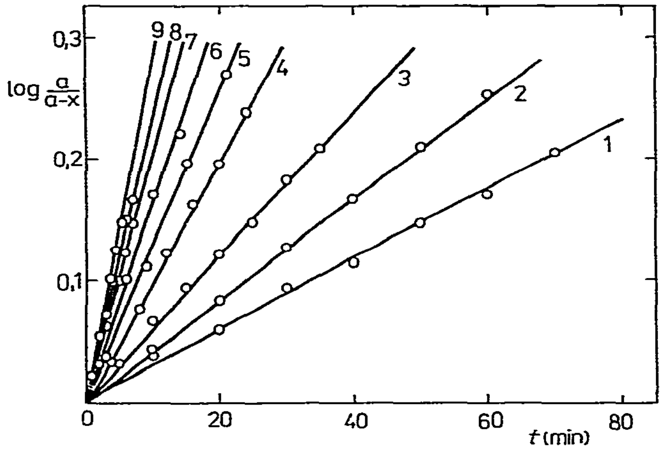


Fig. 5. The kinetic dependence of the hydrolysis of 10mM methoxyacetaldehyde dimethyl acetal in 0 008 (1), 0 01 (2), 0.02 (3), 0.04 (5), 0 05 (6), 0 06 (7), 0 07 (8), and 0.08M hydrochloric acid (9) at 50°.

for a temperature of 50°, ($k_{H_3O^+}$ = 1.5 × 10^{-2} L.mol^{-1}s^{-1}) was found from the dependence of the rate constants obtained for hydrolysis of **2** on the concentration of hydrochloric acid. A value of $E_{H_3O^+}$ = 112.2 kJmol^{-1} was obtained for the activation energy of the hydrolysis of **2** to methoxyacetaldehyde over the temperature range 30–70°.

Enolization of methoxyacetaldehyde and its hydrolysis to glycolaldehyde in aqueous hydrochloric acid. — It has already been found, from comparison of the catalytic constants for enolization of glycolaldehyde and hydrolysis of **2** to methoxyacetaldehyde in hydrochloric acid at 50°, that the rate of the latter reaction is 10^3 times greater, so that the enolization of methoxyacetaldehyde can be studied not only by using this compound but also with **2** itself. The kinetics for the enolization of methoxyacetaldehyde and the simultaneous elimination of methanol producing glycolaldehyde was studied by the methods already described.

In the enolization and elimination of methanol from methoxyacetaldehyde to produce glycolaldehyde, the rate constants were measured over the range 3.5–6.6M HCl at 50°. The linear dependence of the rate constants, similar to that found for glycolaldehyde (Fig. 3), corresponds best to the mean activity of hydrochloric acid. A value of $k_{a_\pm}$ = 0.22 × 10^{-5}L.mol^{-1}.s^{-1} was found for the catalytic constant for the enolization of methoxyaldehyde. It follows from comparison of this constant with the corresponding catalytic constant for glycolaldehyde alone ($k_{a_\pm}$ = 1.60 × 10^{-5}L.mol^{-1}s^{-1}) that the rate of formation of the enol form of methoxyacetaldehyde is 7.3 times smaller than for glycolaldehyde. The time-course of the concentrations of all three compounds may be found from the rate constants for the enolization of 5mM methoxyacetaldehyde and 5mM glycolaldehyde in 4 5M hydrochloric acid at 50°, by using known kinetic relationships for a system of two successive and irreversible, first-order reactions.

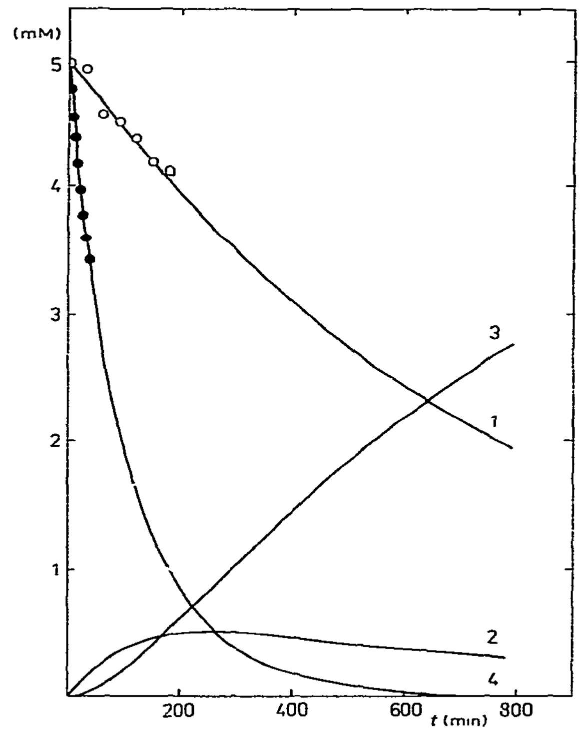
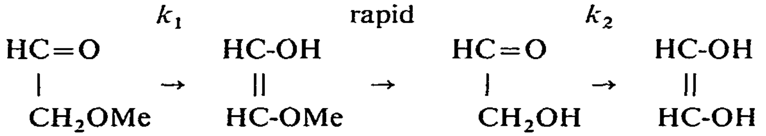


Fig. 6 The calculated course of the enolization of 5mM methoxyacetaldehyde (1), temporary formation of glycolaldehyde (2), and its enolization (3) in 4 5M hydrochloric acid at 50°. The experimentally determined values of the catalytic constant for enolization of methoxyacetaldehyde (1)(o) and enolization of glycolaldehyde (4)(•) were used in the calculation.



$$\begin{array}{c} HC{=}O \\ | \\ CH_2OMe \end{array} \xrightarrow{k_1} \begin{array}{c} HC\text{-}OH \\ \| \\ HC\text{-}OMe \end{array} \xrightarrow{\text{rapid}} \begin{array}{c} HC{=}O \\ | \\ CH_2OH \end{array} \xrightarrow{k_2} \begin{array}{c} HC\text{-}OH \\ \| \\ HC\text{-}OH \end{array} \qquad (1)$$

The calculated time-courses of the concentrations of all three compounds are depicted in Fig. 6. The points on the curves correspond to the experimental data.

The reaction of 5mM **2** in 4.5M hydrochloric acid over the temperature range 50–70° was studied in order to determine the activation energy for the enolization of methoxyacetaldehyde; this was found to be $E_{a\pm} = 134.6$ kJ.mol^{-1}.

Incorporation of deuterium into glycolaldehyde in solutions of DCl and NaOD in D_2O. — The incorporation of deuterium into glycolaldehyde was demonstrated in the reaction of 10mM glycolaldehyde in 4.5M DCl in D_2O at 50° over a period of 3 h under conditions listed under (*a*) in the procedure (without Methylene Blue). In the isolated quinoxaline, mass spectrometry demonstrated the presence of 40, 51, and 9% of quinoxaline having molecular weights of 130, 131, and 132, respectively. Under the experimental conditions described under (*b*) (in the presence of Methylene Blue), the presence of 95 and 5% quinoxaline having molecular weights of 130 and

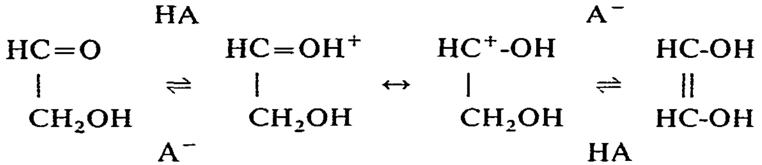
131, respectively, was demonstrated. Thus, in the former case, undisturbed incorporation of deuterium into the glycolaldehyde molecule occurred in the reversible reaction of glycolaldehyde and its enediol. In the latter instance, the enediol of glycolaldehyde is rapidly oxidized by Methylene Blue to glyoxal, and thus incorporation of deuterium into the glycolaldehyde molecule is small (~5%). Similarly, in alkaline medium under the conditions given under (*d*) (without Methylene Blue), incorporation into glycolaldehyde was demonstrated, and the quinoxaline obtained from this reaction contained 64.3, 28.3, and 7.4% of quinoxaline having molecular weights of 130, 131, and 132, respectively. In contrast, under the experimental conditions given under (*e*) (in the presence of Methylene Blue), only quinoxaline having a molecular weight of 130 was obtained. Consequently, no incorporation of deuterium into glycolaldehyde occurred, because its enediol form is rapidly oxidized to glyoxal by the Methylene Blue present; this compound condenses with *o*-phenylenediamine to yield the stable quinoxaline. It should be noted that, in previous work, we demonstrated that deuterium is not incorporated into quinoxaline itself either in acid or in alkaline media[23]. These experiments were performed to confirm the existence of a mobile equilibrium between glycolaldehyde and its enediol in both acid and alkaline media, accompanied by the incorporation of deuterium into the glycolaldehyde molecule, and also to demonstrate that, under the given experimental conditions, the consumption of Methylene Blue provides a quantitative measure of the rate of enolization of glycolaldehyde.

When using **2** (and, consequently methoxyacetaldehyde), under the experimental conditions listed under (*c*) (in the presence of Methylene Blue), a considerable proportion of deuterium was incorporated into the glycolaldehyde formed (79.1, 17.7, and 3.2% of quinoxaline having molecular weights of 130, 131, and 132, respectively). The formation of quinoxaline of mol. wt. 132 in this experiment and also quinoxaline having molecular weight 131 (5%) when using glycolaldehyde alone under experimental conditions (*b*), may be considered as a consequence of the inability of Methylene Blue at the concentration used to oxidize completely the glycolaldehyde enediol formed, so that the given amounts were converted back into glycolaldehyde during deuteration. Ignoring these inaccuracies, it was found that, under the given conditions, the enediol form of glycolaldehyde is oxidized by Methylene Blue to glyoxal without incorporation of deuterium, in contrast to methoxyacetaldehyde, from which 20.9% of monodeuterated quinoxaline is obtained under similar conditions. Whereas quinoxaline contains only two (66.6%) of the original three hydrogen atoms of glycolaldehyde (100%), calculations indicated that the deuterium content in the original glycolaldehyde was 31.3%, which is close to the theoretical value (33.3%) for incorporation of one deuterium into glycolaldehyde. The calculations were based on the simplifying assumption that elimination of an H^+ or D^+ ion from glycolaldehyde is equally probable during enolization.

DISCUSSION

Under the given reaction-conditions, glycolaldehyde, in contrast to higher monosaccharides[24], undergoes only enolization, the reversibility of which was demonstrated by incorporation of deuterium into glycoaldehyde in both acid and alkaline media. It is evident that the degree of incorporation is dependent in the reaction conditions and, with a sufficiently long reaction-time, all three hydrogen atoms bound to both carbon atoms in the glycoaldehyde molecule would be exchanged for deuterium.

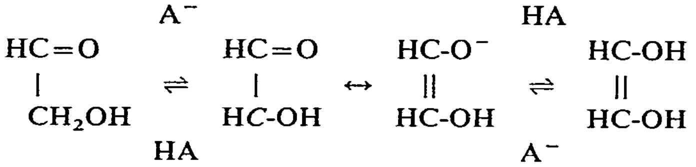
In agreement with conclusions for similar types of reaction[18,24,25], the experimental data obtained for the acid-catalyzed enolization of glycolaldehyde are described by the following reaction scheme (*2*).



$$\begin{array}{c}HC{=}O\\|\\CH_2OH\end{array} \underset{A^-}{\overset{HA}{\rightleftharpoons}} \begin{array}{c}HC{=}OH^+\\|\\CH_2OH\end{array} \leftrightarrow \begin{array}{c}HC^+\text{-}OH\\|\\CH_2OH\end{array} \underset{HA}{\overset{A^-}{\rightleftharpoons}} \begin{array}{c}HC\text{-}OH\\\|\\HC\text{-}OH\end{array} \qquad (2)$$

This reaction is subject to general acid catalysis, as confirmed in preliminary experiments by the finding that the rate constants for enolization of glycolaldehyde increase with the concentration of the chloroacetate buffer at a constant pH value of the medium, namely, at a constant ratio of the acid and its sodium salt. The given reaction is bimolecular (A-2 mechanism), in which the slow, rate-determining step involve abstraction of a proton by the general base (A^-), to produce the enediol. This reaction is preceded by rapidly equilibrating protonation of glycolaldehyde with formation of the given mesomeric forms. The protonation of glycolaldehyde affects its electronic and thus also its geometric structure. The positive charge is delocalized over the whole molecule, stabilizing the protonated form and leading to considerable charge-redistribution as compared with the unprotonated form. From the point of view of formation of the enol form, a large change in the strength of the C–H bond on the α-carbon atom is most important; that is, a considerable increase in the acidity of the hydrogen atoms of which dissociation of one leads to formation of the corresponding enediol (1,2-etenediol). The hydrogen charge-values (Q_H) clearly confirm this (Fig. 7, structures 1,1a). The re-formation of glycolaldehyde from 1,2-ethenediol occurs after protonation of any carbon atom forming the double bond, as the charge-density is the same on both carbon atoms of this symmetrical molecule (Fig. 7, structure 1b).

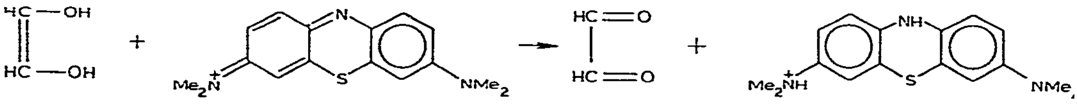
The enolization of glycolaldehyde is also a general-base-catalyzed reaction, as found for the mutual isomerization of trioses[19]. However, in the given instance, abstraction of a proton in the α-position with respect to the carbonyl in the glycolaldehyde molecule by the general base (A^-) is the rate-determining step (*3*).



$$\begin{array}{c}HC{=}O\\ |\\ CH_2OH\end{array} \underset{HA}{\overset{A^-}{\rightleftharpoons}} \begin{array}{c}HC{=}O\\ |\\ HC\text{-}OH\end{array} \leftrightarrow \begin{array}{c}HC\text{-}O^-\\ \|\\ HC\text{-}OH\end{array} \underset{A^-}{\overset{HA}{\rightleftharpoons}} \begin{array}{c}HC\text{-}OH\\ \|\\ HC\text{-}OH\end{array} \qquad (3)$$

It follows from the values obtained for the rate constants that the enolization of glycolaldehyde as catalyzed by acids is much slower as compared with catalysis by bases. This observation explains the proposed mechanism in which the rate-determining step is abstraction of a proton from the glycolaldehyde molecule (in acid medium from the protonated form, whose concentration is small as a result of the low basicity of the carbonyl oxygen atom of glycolaldehyde and also of the low concentration of the free unhydrated form) by the general base in either acid or alkaline medium. Clearly, the basicities of the bases used for base-catalyzed enolization of glycolaldehyde are incomparably greater than the basicity of the conjugated bases of the acids used, and of water. Consequently, it seems that the formation of enediol in acids is the slowest step, not only with glycolaldehyde, but also with higher monosaccharides. In contrast, the formation of their enol intermediates in alkaline media is rapid in comparison with the subsequent reactions[10].

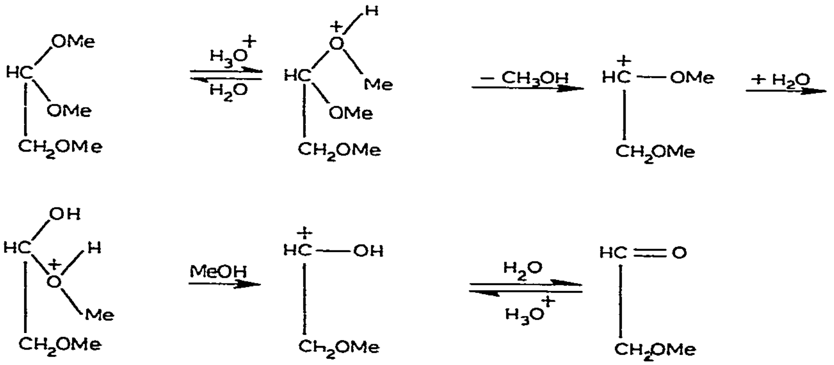
As already mentioned, the rapid oxidation of 1,2-ethenediol to glyoxal by Methylene Blue in acid and alkaline media prevents the reverse reaction and thus also incorporation (*4*) of deuterium into glycolaldehyde.



(*4*)

It should be noted that not only Methylene Blue, but also other inorganic or organic redox systems, could be useful for studying these types of reaction.

For the foregoing reasons, a kinetic study was also made of the hydrolysis of methoxyacetaldehyde dimethyl acetal (2) with formation of methoxyacetaldehyde. It was found that this hydrolysis is catalyzed only by acids, and not by bases. The



(*5*)

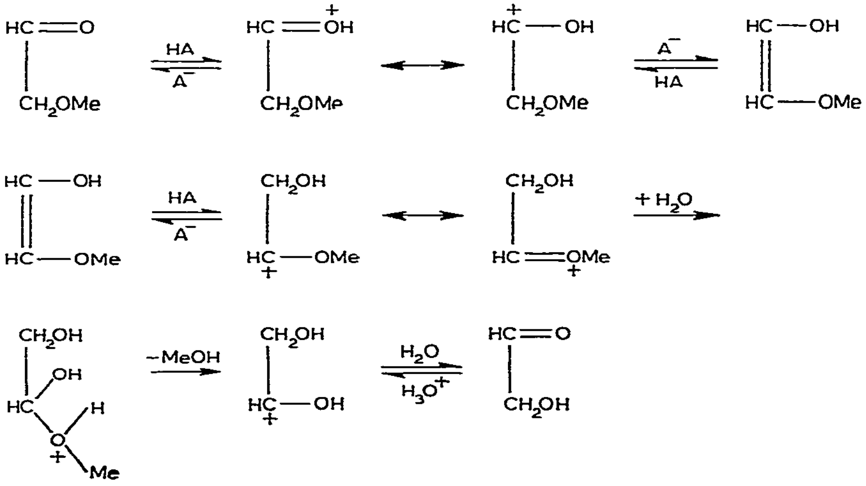
mechanism of this hydrolysis is in agreement with that proposed for similar types of reaction[25,26].

The rapidly established equilibrium of protonation of the acetal is followed by the rate-determining step of formation of the resonance-stabilized, alkoxy-carbonium ion. The reaction is specifically acid-catalyzed, that is, the breakage of the covalent bond of the protonated acetal, with formation of the carbonium ion and methanol, is unimolecular, and independent of any effect of the solvent as a nucleophilic agent (A-1 mechanism).

In study of the reaction of methoxyacetaldehyde or its dimethyl acetal in more-concentrated solutions of hydrochloric acid, it was found that glycolaldehyde is formed from both compounds. As the rate constants for hydrolysis of methoxyacetaldehyde (found from the decrease in its concentration or from the formation of glycolaldehyde) are found to be practically identical, it may be assumed that the enolization of methoxyacetaldehyde is the rate-determining step for the whole reaction.

It is known that the acid-catalyzed hydrolysis of common aliphatic ethers is 10^{13}-times slower than that of the corresponding vinyl ethers[27]. It follows unambiguously from detailed study of the kinetics and, primarily, the mechanism of the hydrolysis of aliphatic[28-33] and cyclic[34,35] vinyl ethers, that their hydrolysis is subject to general acid catalysis, where the rate-determining step is proton transfer from the catalyzing acid to the substrate (A-SE2 mechanism). It is assumed that the ready hydrolysis of vinyl ethers is a result of formation of the resonance-stabilized, oxonium–carbonium ion.

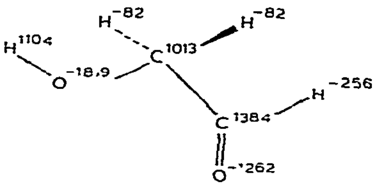
It is assumed that, in the reaction of methoxyacetaldehyde, elimination of methanol does not occur directly, but takes place from the enol formed as an intermediate, through the mechanism operative in hydrolysis of the foregoing vinyl ethers. The following mechanism is proposed for the overall course of the acid-catalyzed reactions of methoxyacetaldehyde.



(6)

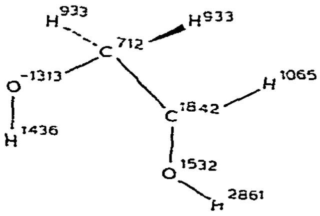
(1)

μ = 3 69 D



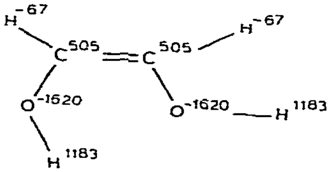
(1a)

μ = 4 75 D



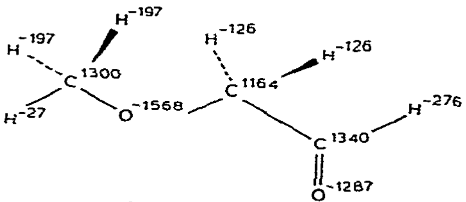
(1b)

μ = 3 08 D



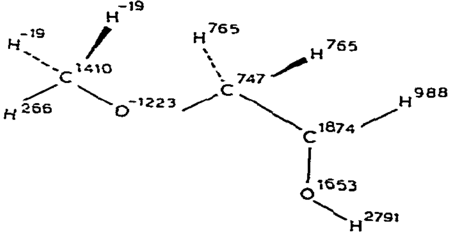
(2)

μ = 3 56 D



(2a)

μ = 5 94 D



(2b)

μ = 3 00 D

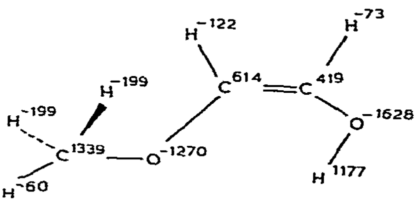


Fig 7. Charge distribution (in 10^4 e) in the most-stable conformation of glycolaldehyde and methoxyacetaldehyde in their protonated and enol forms.

The mechanism for acid-catalyzed enolization of methoxyacetaldehyde is the same as that (*2*) given for enolization of glycolaldehyde; however, the value of the catalytic constant is 7.3 times smaller and the value of the activation energy is, on the other hand, 22.4 kJmol^{-1} greater than for glycolaldehyde. The difference in the rate of enolization of methoxyacetaldehyde and glycolaldehyde is also a measure of the decreased acidity of the α-hydrogen atoms (in methoxyacetaldehyde) caused by the positive induction-effect of the methoxyl group (Fig. 7, structures 1,2). As, in the given instance, it is not possible to study individually the hydrolysis of the enol form of methoxyacetaldehyde produced, that is, of the corresponding vinyl ether, and it is possible only to employ knowledge obtained in study of similar vinyl ethers. Consequently, it is assumed that the hydrolysis of 2-methoxy-1-ethenol is a general acid-catalyzed reaction, where the slowest step is proton transfer from the general acid to the β-carbon atom of the given enol ether, with formation of the resonance-stabilized oxonium–carbonium cation[35]. This preferential protonation of the given carbon atom in the 2-methoxy-1-ethenol molecule is in agreement with the calculated distribution of electron charges on the carbon atoms of the multiple bond in the particular molecule (Fig. 7, structure 2b). At this stage, deuterium is incorporated into the molecule of glycolaldehyde formed. All of the subsequent reactions, namely, addition of water with formation of the corresponding hemiacetal and elimination of methanol with formation of glycolaldehyde, are rapid. Interestingly, disregarding the different mechanisms of hydrolysis of acetals (A-1) and vinyl ethers (A-SE2), their intermediates have the same structure and similar rates[28,29]. Application of these observations to the reactions studied here indicates that not only the hydrolysis of **2** to methoxyacetaldehyde, but also the hydrolysis of its enol ether to glycolaldehyde, is approximately 10^3 times greater than the enolization of methoxyacetaldehyde.

Methoxyacetaldehyde also undergoes enolization in alkaline media in a manner similar to that demonstrated for glycolaldehyde, higher monosaccharides, or their methylated derivatives. The finding that addition of water to 2-methoxy-1-ethenol, as demonstrated for vinyl ethers, is not direct but occurs on a protonated intermediate, also explains the corresponding stability of methylated sugars in alkaline media.

In connection with the kinetic studies described for the enolization of glycolaldehyde and its methyl ether, calculations by the PCILO method[15,16] also yielded the energy differences in the stability of the two forms of the compounds studied. The fact that the carbonyl forms of simple aldehydes and ketones are more stable than their corresponding enols is well known; however, the difference in stability of the two forms can be changed by simple substitution. The calculated energy-difference between glycolaldehyde and its enol form (Fig. 7, structures 1, 1b) is $\Delta E = E(\text{enol}) - E(\text{aldehyde}) = 52.1$ kJ.mol^{-1} and indicates a marked shift in the equilibrium towards the aldehyde form of glycolaldehyde. Replacement of the hydroxyl group in glycolaldehyde by a methoxyl group leads to a decrease in this difference to 34.1 kJ.mol^{-1} (Fig. 7, structures 2,2b), which is in agreement with the results of Hehre and Lathan[36], who found that increasing the π-electron donor character of the α-substituent decreases the energy difference between the aldehyde and enol forms of the acetaldehyde derivatives

REFERENCES

1 J. Zabicky, *The Chemistry of the Carbonyl Group*. Vol. II, Interscience Publishers, London, 1970, pp. 157–240.
2 E. L. Gustus and W. L Lewis, *J. Am. Chem. Soc*, 49 (1927) 1512–1521.
3 M L. Wolfrom and W L. Lewis, *J. Am. Chem. Soc.*, 50 (1928) 837–854
4 R D. Greene and W. L. Lewis, *J. Am. Chem Soc*, 50 (1928) 2813–2825.
5 C. E. Gross and W. L. Lewis. *J. Am. Chem. Soc*, 53 (1931) 2772–2784.
6 H. T. Neher and W. L. Lewis, *J. Am. Chem. Soc*, 53 (1931) 4411–4423.
7 D. J. Loder and W L. Lewis, *J. Am. Chem. Soc.*, 54 (1932) 1040–1054.
8 J. Kenner and G. N. Richards, *J. Chem. Soc.*, (1956) 2921–2925.
9 A. Klemer, H Lukowski, and F. Zerhusen, *Chem Ber.*, 96 (1963) 1515–1519.
10 E. F L. J. Anet, *Aust. J. Chem.*, 16 (1963) 270–277.
11 E. F L. J. Anet, *Adv. Carbohydr. Chem.*, 19 (1964) 181–218.
12 H. G. Bott and E. L. Hirst, *J. Chem. Soc.*, (1932) 2621–2624.
13 W. N. Haworth, E. L. Hirst, and V. S. Nicholson, *J. Chem. Soc.*, (1927) 1513–1526.
14 M. Fedoroňko and P. Zuman, *Collect. Czech. Chem. Commun.*, 29 (1964) 2115–2133.
15 S. Diner, J. P Malrieu, and P. Claverie, *Theor Chim Acta*, 13 (1969) 1–17.
16 S. Diner, J. P. Malrieu, F. Jordan, and M. Gilbert, *Theor. Chim. Acta*, 15 (1969) 100–110
17 J. A. Pople and D. L Beveridge, *Approximate Molecular Orbital Theory*, McGraw–Hill, New York, 1970.
18 L. P. Hammett, *Physical Organic Chemistry*, 1st edn, McGraw–Hill, New York and London, 1940, pp. 96–97, 104–107.
19 M. Fedoroňko and J Königstein, *Collect. Czech. Chem. Commun.*, 34 (1969) 3881–3894
20 H. S. Harned and B. B. Owen, *The Physical Chemistry of Electrolytic Solutions*, Reinhold Publishing Corp., New York, 1943, pp. 12, 547, 577.
21 C. Kortüm and J. O M Bokris, *Textbook of Electrochemistry*, Elsevier, New York, 1951, p. 79–80.
22 A. J. Gelbstein, G. G. Shcheglova, and M. J Temkin, *Dokl. Akad. Nauk SSSR*, 107 (1956) 108–111.
23 J. Konigstein and M. Fedoroňko, *Chem. Zvesti*, 33 (1979) 515–520
24 J. C. Speck, Jr., *Adv. Carbohydr. Chem*, 13 (1958) 63–103.
25 C H. Bamford and A. F. Tipper, *Proton Transfer*, Vol 8, Elsevier, 1977, pp. 1–89.
26 E. H. Cordes, *Progr. Phys. Org. Chem.*, 4 (1967) 1–44.
27 A. Zahorka and K. Weimann, *Monatsh. Chem*, 71 (1938) 229–240.
28 P. Salomaa, A. Kankaanperä, and M. Marttilajunen, *Acta Chem Scand.*, 20 (1966) 1790–1801.
29 P. Salomaa and A. Kankaanpera, *Acta Chem Scand*, 20 (1966) 1802–1810.
30 A. J Kresge and Y. Chiang, *J. Chem. Soc B*, (1967) 53–57.
31 A. J. Kresge, H L Chen, Y. Chiang, E. Murrill, and M. A. Payne, *J. Am. Chem. Soc*, 93 (1971) 413–423.
32 M. M. Kreevoy and R. Eliason, *J. Phys. Chem.*, 72 (1968) 1313–1316.
33 M. M. Kreevoy and J. M. Williams, Jr, *J. Am. Chem. Soc.*, 90 (1968) 6809–6813.
34 T. H. Fife, *J. Am. Chem. Soc.*, 87 (1965) 1084–1089.
35 G. E Lienhard and Tung-Chia Wang, *J. Am. Chem Soc.*, 91 (1969) 1146–1153.
36 W J. Hehre and W. A Lathan, *J. Chem. Soc. Chem Commun.*, (1972) 771–772.