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Investigation of the mechanism of dissociation of glycolaldehyde dimer (2,5-dihydroxy-1,4-dioxane) by FTIR spectroscopy

Varoujan A. Yaylayan*, Susan Harty-Majors, Ashraf A. Ismail

McGill University, Department of Food Science and Agricultural Chemistry, 21,111 Lakeshore, Ste. Anne de Bellevue, Quebec, H9X 3V9, Canada

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Abstract

Glycolaldehyde represents the simplest α-hydroxycarbonyl moiety–a common structural feature of reducing sugars. It exists in solid state, only in crystalline dimeric form as 2,5-dihydroxy-1,4-dioxane. However, in solution phase or during heating, it dissociates into different dimeric and monomeric forms. FTIR spectroscopy was used to study the effect of temperature, pH and solvent on the dissociation and chemical transformations of glycolaldehyde. The infrared spectra were recorded in different solvents as a function of time and temperature (both during heating and cooling cycles) between 30 and 85 °C. During heating, glycolaldehyde cyclic dimer generated two bands in the carbonyl region, one at 1744 cm^{-1} and the other at 1728 cm^{-1}. These bands increased during the heating cycle and decreased during the cooling cycle. The data indicated that the glycolaldehyde cyclic dimer (2,5-dihydroxy-1,4-dioxane) undergoes a ring opening to form the acyclic dimer (1728 cm^{-1}) that can recyclize into the 2-hydroxymethyl-4-hydroxy-1,3-dioxolane structure. The acyclic dimer can also dissociate into monomeric glycoladehyde (1744 cm^{-1}) in equilibrium with the enediol form (1703 cm^{-1}). There is evidence to indicate oxidation of glycolaldehyde into glycolic acid during heating, in either neutral or basic aqueous solutions.

Keywords: FTIR; Glycolaldehyde; Glyoxal; α-Hydroxycarbonyl moiety; Dissociation mechanism; Autoxidation

1. Introduction

The α-hydroxycarbonyl moiety (**1a** in Scheme 1) imparts to reducing sugars exceptional molecular flexibility, manifested in such processes as enolization (**1b** and **1c**), isomerization (**1d**) and dimerization (**1f–1h**). In addition, it enables these sugars to undergo Amadori rearrangement in the presence of amines, that eventually transforms aldehydo sugars into their α-amino keto derivatives (**1e**). The physical and chemical properties of reducing sugars in solution depend on the relative concentrations of different monomeric and dimeric forms originating from the α-hydroxy carbonyl-moiety. Their biological properties can also have similar dependence [1]. It appears that the enediol forms of certain sugar derivatives in biological systems are the

* Corresponding author. Tel.: (514)-398-7918; fax: (514)-398-7977; e-mail: czd7@musica.mcgill.ca

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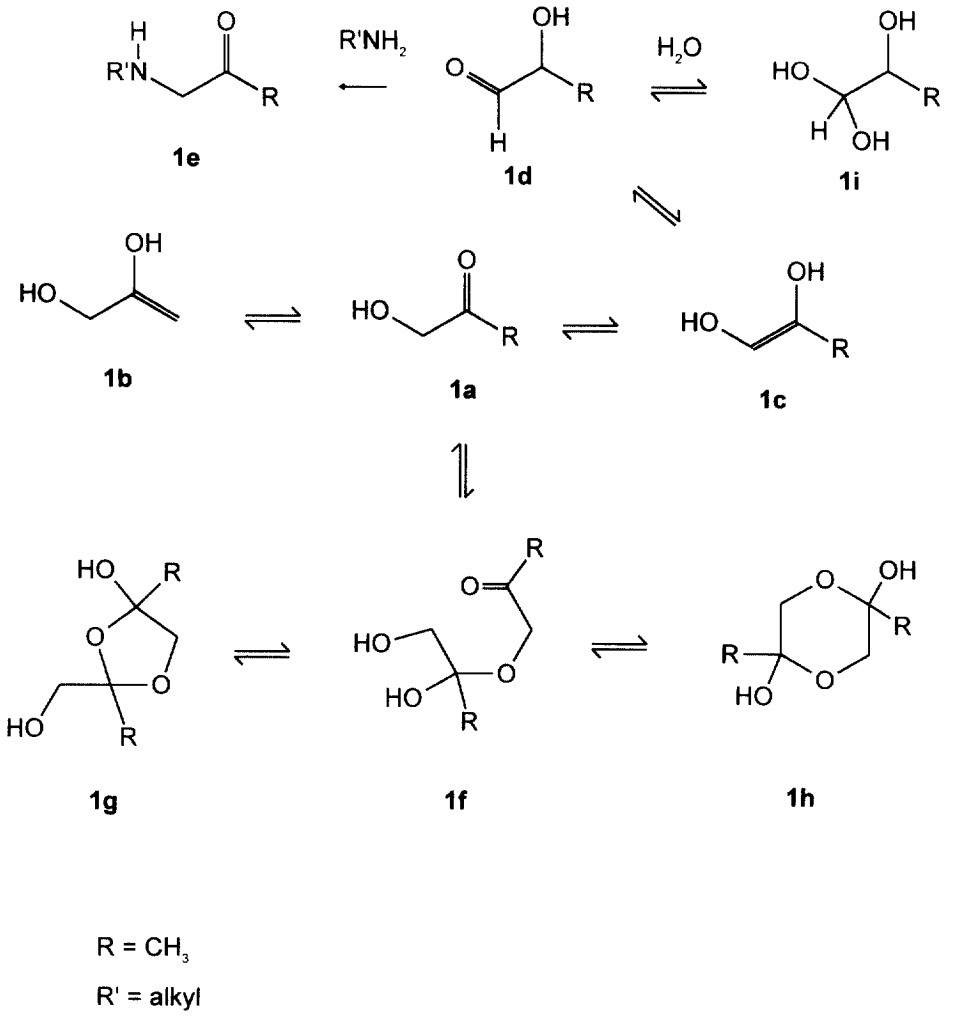


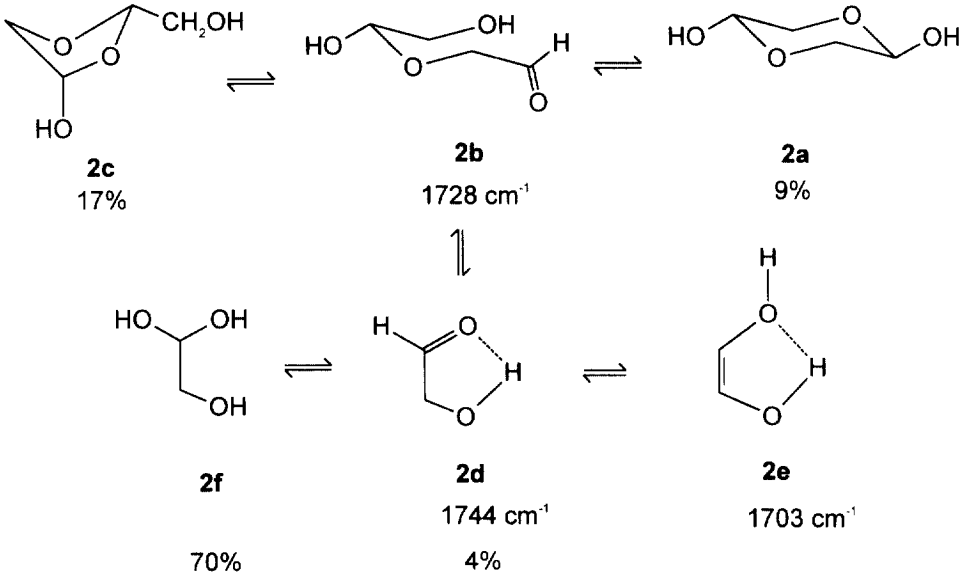
Scheme 1. Chemical transformations of the α-hydroxycarbonyl moiety of reducing sugars.

active forms with which enzymes react [2,3]. Enediol or enol forms are also known to play an important role in metal-catalyzed oxidative degradation of reducing sugars [4]. Such complexity in the population of reducing sugars in solution, makes their study a difficult proposition, especially for hexoses and pentoses, where the presence of more stable furanose and pyranose forms renders the α-hydroxycarbonyl moiety difficult to detect at room temperature due to their low concentrations (< 1%). Solvent interference, especially from water, makes the detection of aldehydo forms even more difficult due to hydration (**1i**). FTIR spectroscopy has been used to study the effect of temperature [5] on acyclic forms of D-fructose, mutarotation of D-glucose and D-fructose [6], and enolization and carbonyl group migration in selected reducing sugars [7]. Simple α-hydroxyl carbonyl compounds such as glycolaldehyde (**1a**, R = H), glyceraldehyde (**1d**, R = CH_2OH), and dihydroxyacetone (**1a**, R = CH_2OH) have the tendency to from stable cyclic (**1g** and **1h**) and acyclic (**1f**) dimers that dissociate into monomeric forms on standing in dilute aqueous solutions [8,9] or by increasing the temperature. Such dimer to monomer conversions can be followed by observing an increase in the intensity of the carbonyl band using FTIR spectroscopy. FTIR spectroscopy is ideally suited to study the different monomeric and dimeric forms of compounds possessing the α-hydroxycarbonyl moiety **1a**. The forms derived from **1a** absorb at different frequencies such as carbonyls, between 1700 and 1750 cm^{-1}, enediols between 1630 and 1700 cm^{-1} and C–O–C between 950 and 1300 cm^{-1}. Simple α-hydroxycarbonyl compounds such as glycoladehyde (**1a**, R = H), 1-hydroxyacetone (**1a**, R = CH_3), 1-hydroxy-2-butanone (**1a**, R = CH_2CH_3) and glyceraldehyde (**1d**, R = CH_2OH), could be used to investigate the ability of FTIR spectroscopy to monitor the

molecular transformations in these compounds under different environmental conditions. In this study, the effect of solvent, pH, and temperature on the dissociation of dimeric glycolaldehyde (**1h**, R = H) was investigated using FTIR spectroscopy.

2. Results and discussion

General observations.—In the solid state, glycolaldehyde is known [8] to exist in dimeric form as 2,5-dihydroxy-1,4-dioxane (**2a**) as shown in Scheme 2. In the molten state, it exists as a mixture of different monomeric and dimeric forms [10]. In the vapor phase, only the monomers exist in cis orientation exhibiting a single carbonyl absorption band at 1753 cm^{-1} [11]. In the solution phase, the dimer undergoes dissociation into monomeric forms; however, the dissociation rate and the relative concentration of different species depend on the temperature and the type of solvent [11,12]. Studies performed by NMR spectroscopy [13] at room temperature in D_2O indicated the presence of at least four molecular species (see Scheme 2): 2,5-dihydroxy-1,4-dioxane (**2a**, 9%), 2-hydroxymethyl-4-hydroxy-1,3-dioxolane (**2c**, 17%), monomeric glycolaldehyde (**2d**, 4%), and hydrated monomer (**2f**, 70%). In Me_2SO, the equilibrium concentration of **2d** remained the same, and the concentrations of **2a** and **2c** increased to 36 and 60%, respectively. However, the transformation of dioxane **2a** to dioxolane **2c** requires the intermediacy of the acyclic dimer **2b** that has been proposed [14] to form, but has not been detected by NMR studies. To investigate the ability of FTIR to detect the different monomeric and dimeric forms, glycolaldehyde was analyzed in different solvents and at different pH and temperatures. The data obtained from these studies revealed the following observations: (a) when glycolaldehyde dimer (**2a**) was studied at room temperature, either in solution phase (in D_2O or dioxane) or as a melt (Fig. 1), two carbonyl absorption bands, one at 1744 cm^{-1} and the other at 1732 cm^{-1} (shifted to 1728 cm^{-1} in D_2O and 1736 cm^{-1} in dioxane), were detected, along with a weaker band at 1703 cm^{-1}. These bands increased during the heating cycle and decreased during the cooling cycle, indicating their reversibility (Fig. 2). The intensity of the 1744 cm^{-1} band was higher than that of the 1728 cm^{-1} band. (b) In D_2O, two additional bands emerged at 1673 and 1593 cm^{-1} (Fig. 3). These new bands increased irreversibly with temperature. (c) In slightly basic D_2O (0.1% NaOD), the band at 1673 cm^{-1} disappeared (Fig. 3), and the band at 1593 cm^{-1} increased irreversibly with temperature. In addition, the intensities of the bands at 1744 and 1703 cm^{-1} decreased continuously, both during the heating and cooling cycles, whereas the intensity of 1728 cm^{-1} band increased during the heating cycle and decreased during the cooling cycle (Fig. 4). (d) Under strongly basic conditions (20% NaOD or 100% triethylamine), all the bands mentioned above disappeared except the band at 1593 cm^{-1}, which became the predominant band. (e) Under acidic conditions (1% DCl) and in the melt, the



Scheme 2. Mechanism of dissociation of glycoladehyde dimer. Percent composition in D_2O at room temperature [13].

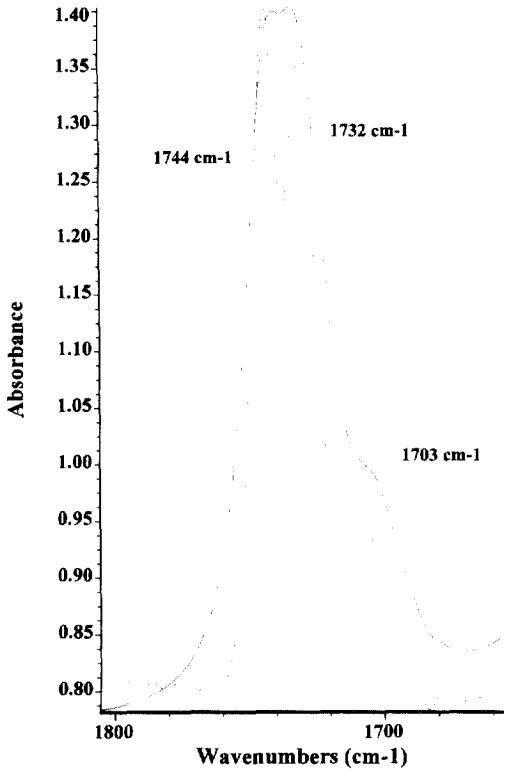


Fig. 1. Absorption of the carbonyl region (1700–1800 cm^{-1}) of glycolaldehyde (melt at 90 °C). Fourier self-deconvolution (·····) (Bandwidth 10.5, Enhancement factor 1.6).

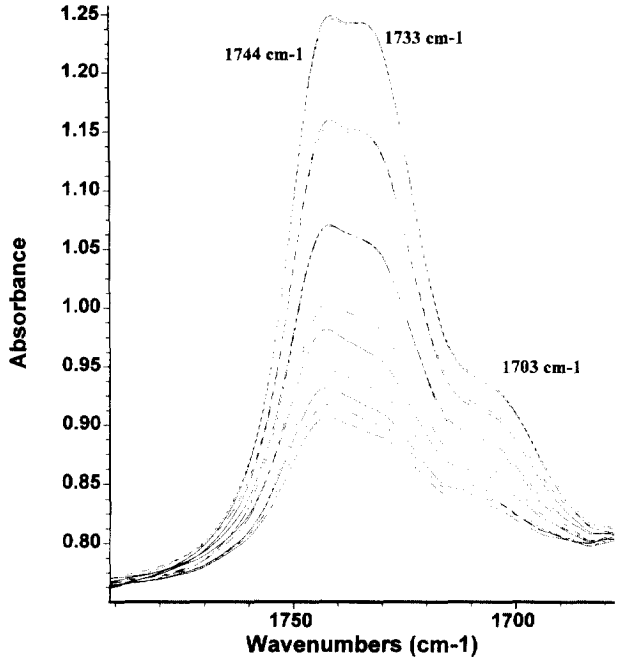


Fig. 2. Effect of heating (solid lines, 35–85 °C at 10 °C increments) and cooling (dotted lines, 85–35 °C at 10 °C increments) on the intensity of the carbonyl absorption bands (1700–1800 cm^{-1}) of glycolaldehyde melt.

bands at 1673 and 1593 cm^{-1} were not detected. However, the bands at 1744, 1728, and 1703 cm^{-1} increased during the heating cycle and decreased during the cooling cycle.

Two important conclusions can be drawn from these observations: one regarding the mechanism

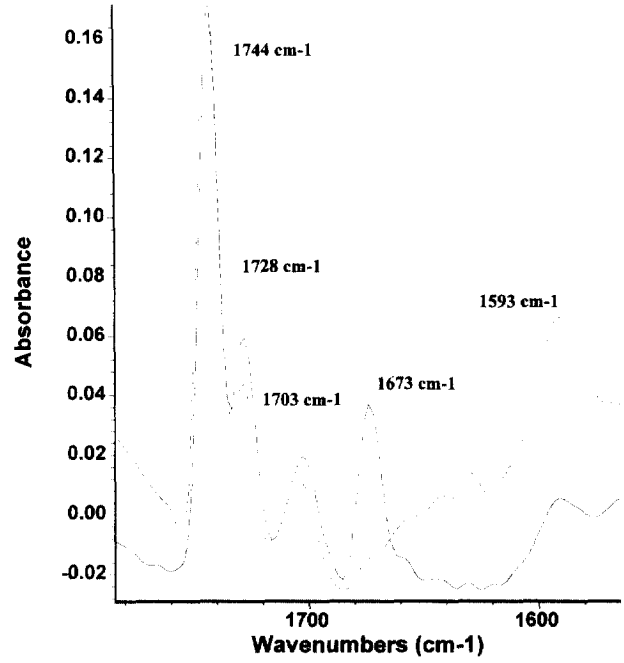


Fig. 3. Comparison of the absorption region between 1700 and 1600 cm^{-1} of 20% glycolaldehyde in D_2O (———) and in 0.1% NaOD (···).

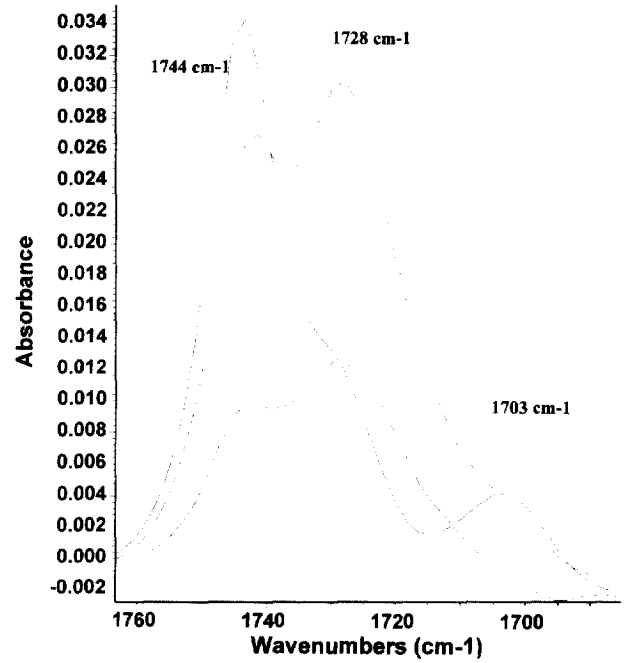


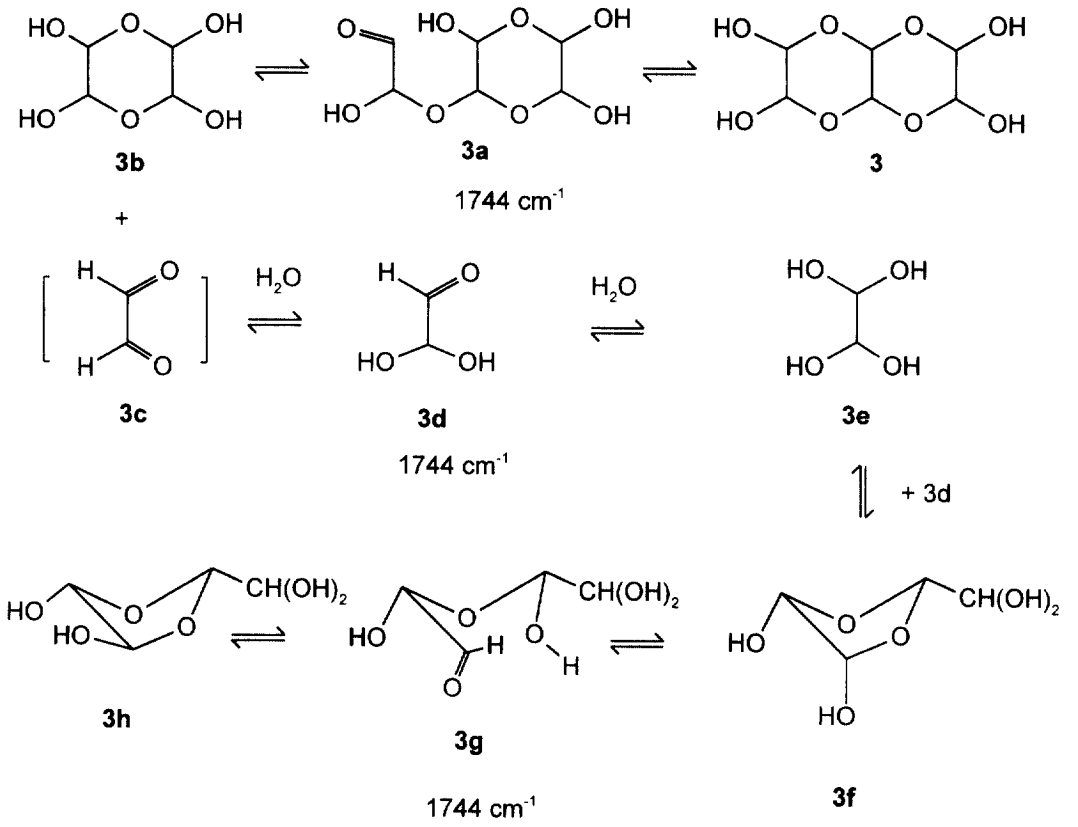
Fig. 4. Absorption of the carbonyl region (1700–1760 cm^{-1}) of a 20% glycolaldehyde solution (0.1% NaOD in D_2O) at 30 °C (———), 80 °C (-----) and at 30 °C cooling (·····).

of dissociation of the glycoladehyde dimer, and the second regarding its chemical stability in basic or neutral aqueous solutions. The detection of two carbonyl bands indicates the presence of another carbonyl species in addition to the glycolaldehyde monomer, and the detection of the band at 1593 cm^{-1} indicates oxidation of glycoladehyde into a carboxylate moiety such as glycolic acid or glyoxylic acid.

Mechanism of the dissociation of glycolaldehyde dimer.—The presence of two reversible and temperature sensitive carbonyl bands, in the FTIR spectrum of glycolaldehyde dimer **2a**, provides the first evidence for the stepwise ring opening (see Scheme 2) of the dioxane structure **2a** to form the acyclic dimer **2b**, which dissociates into monomeric form **2d** or recyclizes into the dioxolane ring structure (**2e**). Apparently, this process is too fast for the time scale of NMR to be detected, while the time scale of FTIR allows the rapidly interconverting species to be detected. The process of interconversion of the four species (**2a–2d**) in solution is similar to the mutarotation of reducing sugars in which the acyclic form is in equilibrium with cyclic furanose and pyranose forms. Tentatively, the band at 1744 cm^{-1} was assigned to the monomer **2d**, the band at 1728 cm^{-1} to the acyclic dimer (**2b**), and the band at 1703 cm^{-1} to the enediol.

Confirmation of band assignments.—The initial assignments of the two carbonyl bands were based on the fact that in the presence of α-hydroxyl groups, the stretching frequencies of carbonyl bands are shifted to higher values relative to simple alkyl substituted carbonyl compounds, provided that the hydroxyl group can rotate to eclipse the carbonyl group. The magnitude of this shift depends on the torsional angle. This effect was demonstrated in monosaccharides [7] by observing a shift to a higher frequency in the carbonyl absorption bands of different sugars relative to their α-deoxy derivatives. Accordingly, the peak at 1744 cm^{-1} was assigned to the monomer that possesses a α-hydroxyl group. In gas phase, where only monomers exist, the single carbonyl band appeared at 1753 cm^{-1} [11]. To provide further evidence for this assignment, the reactivities of the two carbonyl bands were compared in the presence of glycine. The reaction of the monomer with glycine should produce a stable Amadori product similar to **1e** (R = H) with the appearance of a new carbonyl peak, whereas **2b** is unable to stabilize the initial imine adduct through similar rearrangement due to lack of an α-hydroxyl group and is thus not expected to generate a stable end product. A 20% solution of the dimer **2a** in D_2O was heated in a temperature-controlled cell in the absence and presence of glycine. The initial temperature (30 °C) of the cell was raised by 1 °C per min, and every 5 min the temperature was kept constant for 15 min to record the spectra. During the heating cycle, both carbonyl peaks increased in intensity in the absence of glycine. However, in the presence of glycine, the band at 1728 cm^{-1} increased with the temperature, unlike the band at 1744 cm^{-1} which decreased in intensity with the concomitant appearance and increase of a new band at 1765 cm^{-1}, consistent with the formation of an Amadori adduct. The sensitivities of the above-mentioned two bands to changes in pH were also studied. Both bands were stable under acidic pH as they increased during the heating cycle and decreased during the cooling cycle, similar to their behavior in neutral D_2O. However, at mildly basic pH, the band at 1744 cm^{-1} continuously decreased during both cycles, whereas the band at 1728 cm^{-1} increased during the heating cycle and decreased during cooling (Fig. 4). These observations are consistent with the band assignments. Furthermore, a 20% solution of trimeric glyoxal dihydrate (**3**, Scheme 3) in D_2O was also studied by FTIR and found to exhibit a very weak carbonyl absorption band at 1744 cm^{-1}. Investigation by NMR spectroscopy [15] of the principal species present in an aqueous solution of glyoxal has indicated the presence of hydrated monomer **3e**, dioxane dimer **3b** and two additional dimers whose structures contained a five-membered dioxolane rings (**3h** and **3f**) as shown in Scheme 3. However, no aldehydic protons were detected, although the formation and further transformation of **3f** into **3h** requires the presence of aldehydes **3d** and **3g**. All the carbonyl species (**3a**, **3d**, and **3g**) originating from glyoxal trimer in water, have an α-hydroxyl group and thus are expected to show similar absorption frequencies to that of monomeric glycoladehyde.

Additional supporting evidence for the band assignments was provided from the solvent effect. According to NMR studies [13], aprotic solvents can increase the relative concentrations of the dimeric versus monomeric forms, for example, in Me_2SO the percent composition of **2a** and **2c** increased to 36% (from 9%) and 60% (from 17%), respectively, relative to D_2O. In dioxane, the order



Scheme 3. Proposed mechanism of dissociation of glyoxal trimer.

of the intensity of the two carbonyl bands at 1728 and 1744 cm^{-1} was interchanged, where the band at 1728 cm^{-1} was more intense than the band at 1744 cm^{-1}, which is consistent with the NMR observations.

Monitoring oxidation of glycoladehyde by FTIR spectroscopy.—Simple aldehydes are known to undergo autoxidation into their corresponding carboxylic acids in the presence of water [16]. The accepted mechanism involves the reaction of molecular oxygen with the enediol moiety of the aldehyde to form α-hydroperoxides [17] and subsequent loss of hydrogen peroxide [18]. A freshly prepared solution (20%) of the crystalline dimer **2a** in D_2O at 25 °C, showed only weak carbonyl absorption bands at 1744 and 1728 cm^{-1}. When the solution was monitored by FTIR over a 3 h period at 30 °C, a new band at 1593 cm^{-1} emerged and increased slowly over time. Similarly, a solution (20%) of the crystalline dimer **2a** in D_2O was monitored at 70 °C for 4 h by scanning the FTIR spectra every 15 min. During the 4 h of incubation, the intensities of the bands at 1744, 1728 and 1703 cm^{-1} decreased with the appearance and increase of a new band at 1593 cm^{-1} (see Fig. 5), indicating the conversion of glycoladehyde into a carboxylate moiety. To demonstrate the irreversibility of the new bands, a 20% solution of glycolaldehyde dimer in D_2O was also subjected to heating (30–80 °C) and subsequent cooling cycles (80–30 °C). The initial temperature (30 °C) of the cell was raised by 1 °C per min, and every 5 min the temperature was kept constant for 15 min to record the spectra. At 30 °C the dimer solution showed weak absorption bands at 1744 and 1728 cm^{-1}. During the heating cycle the existing bands and the new emerging bands at 1703, 1673 and 1593 cm^{-1} increased with increasing temperature. However, during cooling cycle the bands at 1744, 1728 and 1703 cm^{-1} decreased and the bands at 1673 and 1593 cm^{-1} continued to increase, demonstrating the irreversibility of the process giving rise to these bands. In addition, during cooling, the 1728 cm^{-1} band shifted slowly to 1725 cm^{-1} (see Fig. 6). Under acidic pH or in dioxane the bands at 1673 and 1593 cm^{-1} did not appear.

To confirm the identity of the new product formed, the FTIR spectra of the free and sodium salts of the two possible carboxylic acids, glyoxylic and glycolic acids, were acquired in D_2O. The glycolic acid absorbed at 1725 cm^{-1} and glycolate ion at 1593 cm^{-1}. One the other hand, the glyoxylic

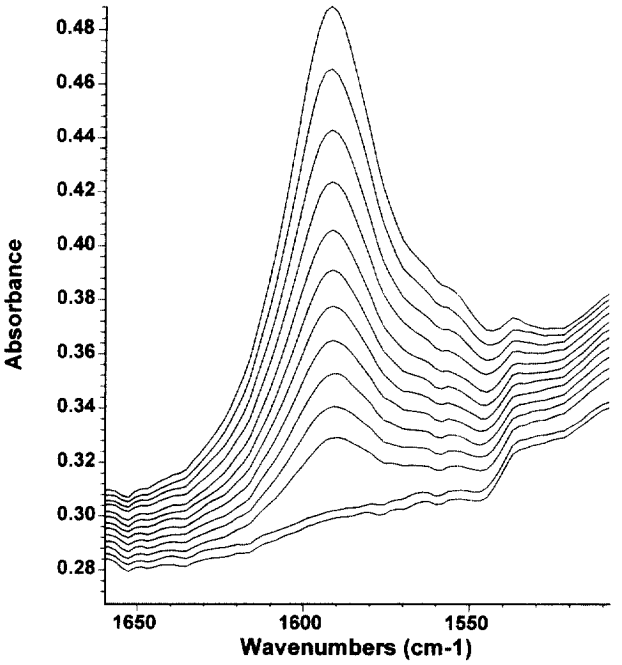


Fig. 5. Effect of time (0–4 h) on the intensity of the carboxylate band at 1593 cm^{-1} of a 20% solution of glycolaldehyde in D_2O monitored at 70 °C.

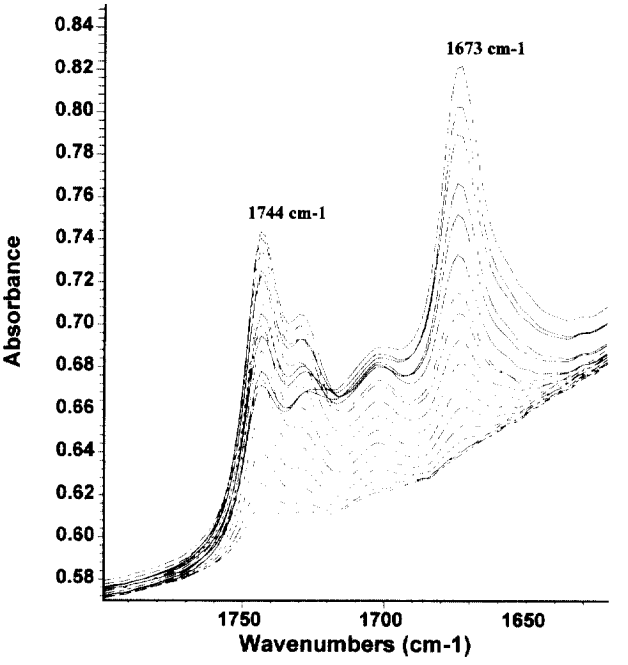
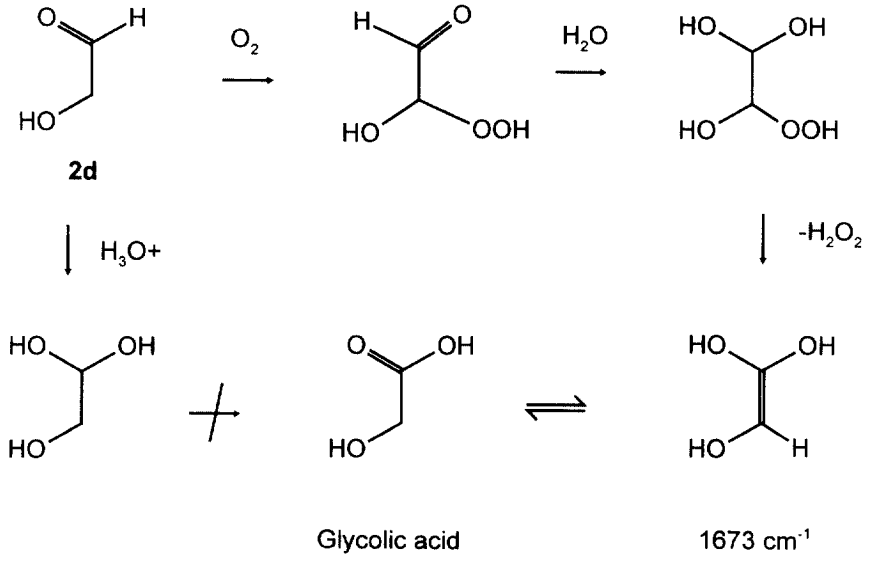


Fig. 6. Effect of heating (dotted lines, 30–80 °C) and cooling (solid lines, 80–30 °C) on the intensity of the absorption bands (1750–1650 cm^{-1} region) of a 20% solution of glycolaldehyde dimer in D_2O.

acid absorbed at 1735 cm^{-1} and glyoxylate ion at 1577 cm^{-1}, indicating autoxidation of glycoladehyde into glycolic acid in aqueous solution. When the pH of a freshly prepared solution of glycoladehyde dimer in distilled water was monitored at 45 °C, the pH quickly dropped to pH 4 in 2 min and continued to decrease to pH 3.6 during 1 h of monitoring. Scheme 4 shows a simplified proposal for the autoxidation mechanism consistent with the above observations.

3. Experimental

Glycoladehyde dimer and glyoxal trimeric dihydrate were obtained from Aldrich Chemical Co. Dioxane was purchased from Fisher Scientific. D_2O was obtained from MSD Isotopes (Montreal, Canada). Solutions (20%) of the samples were prepared in D_2O or dioxane. The spectra were acquired on an CaF_2 IR cell with a 25 μm Teflon



Scheme 4. Proposed mechanism of autoxidation of glycolaldehyde into glycolic acid.

spacer. Glycolaldehyde melt was obtained by microwave irradiation for 120 s in a domestic microwave oven (700 W). The spectra of the melt were acquired without spacer. Processing of the FTIR data was performed using GRAMS/386 version 3.01 (Galactic Industries Corporation, 1994).

Temperature studies.—Sample solutions in D_2O were placed in a CaF_2 IR cell with a 25 μm Teflon spacer. The temperature of the sample was regulated by placing the IR cell in a temperature-controlled cell holder. Infrared spectra were recorded on a Nicolet 8210 Fourier-transform spectrometer, purged with dry air, and equipped with a deuterated triglycine sulfate (DTGS) detector. The initial temperature of the cell was raised by 1 °C/min, and every 5 min the temperature was kept constant for 15 min to record the spectra. A total of 128 scans at 4 cm^{-1} resolution were co-added.

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