Monitoring Carbonyl−Amine Reaction and Enolization of 1-Hydroxy-2-propanone (Acetol) by FTIR Spectroscopy

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Infrared absorption bands characteristic of the *aldehydo, keto,* and enediol forms of 1-hydroxy-2-propanone (acetol) were identified and used to study the effect of solvent on the absorption frequencies and the effect of temperature and acid/base catalysis on the enolization reactions. The data indicated that, in addition to water, acids and bases can catalyze the enolization of 1-hydroxy-2-propanone and that the temperature inversely effects the rate of enolization under basic conditions. However, under acidic conditions, increasing the temperature favors the enolization process. In addition, the reaction of 1-hydroxy-2-propanone with a primary and a secondary amine was also monitored by Fourier transform infrared spectroscopy. The data indicated that at room temperature the rate of amine reaction was faster than the rate of its catalysis of enolization; however, below room temperature, the rate of base-catalyzed enolization became comparable with the rate of carbonyl−amine reaction forming both Heyns and Amadori adducts.

Keywords: *FTIR; α-hydroxycarbonyl moiety; enediol; enolization; 1-hydroxy-2-propanone (acetol); carbonyl−amine reactions; Heyns and Amadori product formation*

INTRODUCTION

Many chemical transformations of reducing sugars, such as cyclizations, enolizations, and isomerizations, are initiated by the presence of the α-hydroxycarbonyl moiety. The stabilization of the initial imine adduct formed during Maillard reaction, through rearrangement reactions (Amadori and Heyns), is also due to the presence of the α-hydroxyl groups (Yaylayan and Huyghues-Despointes, 1994). The physical and chemical properties of reducing sugars in solution depend on the relative concentrations of different forms originating from the α-hydroxycarbonyl moiety. Their biological properties can also have similar dependence. It appears that the enediol forms of certain sugar derivatives in biological systems are the active forms with which enzymes react. The conversion of cytotoxic methylglyoxal into lactate, for example, by the enzyme glyoxylase I (thioester hydrolase glyoxylase II, EC 3.1.2.6), involves an enediolate intermediate of the methylglyoxal derivative (Hamilton and Creighton, 1992). Rubisco (ribulose-1,5-bisphosphate carboxylase, EC 4.1.1.39) adds carbon dioxide to the 2,3-enediolate form of ribulose-1,5-bisphosphate (Lorimer et al., 1993). Enediol forms are known to play an important role in metal-catalyzed oxidative degradation of reducing sugars specially in biological systems (Thornalley et al., 1984). The complexity in the population of reducing sugars in solution makes their study a difficult task, especially in hexoses and pentoses, where the presence of more stable furanose and pyranose forms renders the α-hydroxycarbonyl moiety undetectable at room temperature due to their lower concentrations (<1%). Solvent interference, especially water, makes the detection of aldehydo forms even more difficult due to hydration. Fourier transform infrared spectroscopy (FTIR) has been used to study the effect of temperature (Yaylayan and Ismail, 1992) on acyclic forms of D-fructose, mutarotation of D-glucose and D-fructose (Back et al., 1984), and enolization and carbonyl group migration in selected sugars (Yaylayan and Ismail, 1995). Kobayashi et al. (1976) studied dimeric structures of D,L-glyceraldehyde and dihydroxyacetone by infrared and Raman spectroscopy. FTIR spectroscopy is ideally suited to study the different forms of α-hydroxycarbonyl moiety. Recently, the simplest α-hydroxyaldehyde (glycolaldehyde) was investigated by FTIR (Yaylayan et al., 1998). The data indicated that the glycolaldehyde cyclic dimer (2,5-dihydroxy-1,4-dioxane) undergoes a ring opening to form the acyclic dimer, which can recyclize into the 2-hydroxymethyl-4-hydroxy-1,3-dioxolane structure. The acyclic dimer can dissociate into monomeric glycoladehyde in equilibrium with the enediol form. In this paper, the enolization and its effect on the carbonyl−amine reactions of the simplest α-hydroxyketone (acetol) is investigated.

MATERIALS AND METHODS

All reagents and chemicals were purchased from Aldrich Chemical Co. (Milwaukee, WI) and used without further purification. All solvents used were of HPLC grade; D_2O was purchased from MSD Isotopes (Montreal, Quebec, Canada).

FTIR Analysis. Infrared spectra were recorded on a Nicolet 8210 Fourier transform infrared spectrometer (Madison, WI) purged with dry air and equipped with a deuterated triglycine sulfate (DTGS) detector. The spectra were acquired on a CaF_2 IR cell with a 25-μm Teflon spacer at room temperature unless otherwise specified. A total of 128 scans at 4 cm^{-1} resolution were co-added. Processing of the FTIR data was performed using GRAMS/386 version 3.01. Second-order derivatization was performed using the Savitsky−Golay function (9 points) to enhance closely absorbing peaks.

Temperature Studies. Sample solutions were placed in a CaF_2 IR cell with a 25-μm Teflon spacer. The temperature of

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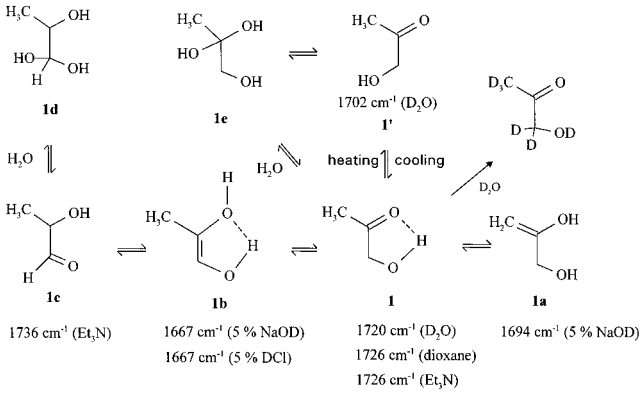
Scheme 1. Molecular Transformations of 1-Hydroxy-2-propanone (Acetol)



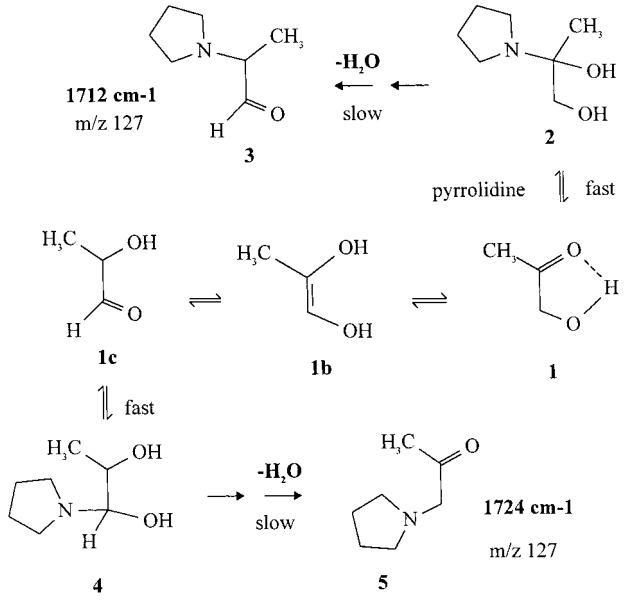
the sample was regulated by placing the IR cell in a temperature-controlled cell holder. Infrared spectra were recorded as described above. The initial temperature of the cell was raised by 5 °C/min, and every 10 min the temperature was kept constant for 2 min to record the spectra. A total of 128 scans at 4 cm^{-1} resolution were co-added.

GC/MS Analysis. A Hewlett-Packard GC/mass selective detector (5890 series II GC/5971B MSD, Palo Alto, CA) was used for the GC/MS analysis. The samples were introduced through the cool on-column injection port at constant pressure of 34 psi. The pressure was regulated by an electronic pressure controller (Hewlett-Packard, Palo Alto, CA). Capillary direct MS interface temperature was 180 °C; ion source temperature was 280 °C. The ionization voltage was 70 eV, and the electron multiplier was 2047 V. The mass range analyzed was 20−200 amu. The column used was Q-PLOT (30 m × 0.2 mm × 0.32 μm; Hewlett-Packard). The column initial temperature was set at −10 °C for 2 min and then increased to 50 °C at a heating rate of 30 °C/min; immediately the temperature was further increased to 250 °C at a rate of 8 °C/min and kept at 250 °C for 5 min.

RESULTS AND DISCUSSION

1-Hydroxy-2-propanone (**1** in Scheme 1), similar to other α-hydroxycarbonyl compounds, can undergo 1,2- and 2,3-enolizations to produce the enol **1a** and the enediol **1b**. The enediol **1b** can exist in equilibrium with 2-hydroxypropionaldehyde (**1c**) due to the reversal of the enediol−carbonyl equilibrium through both hydroxyl groups. However, unlike other short-chain α-hydroxycarbonyl compounds, 1-hydroxy-2-propanone is not known to exist in dimeric forms (Davis, 1973). Understanding the factors that influence this equilibrium can further our ability to rationalize the different products obtained during the interaction of 1-hydroxy-2-propanone with nucleophiles such as amines or amino acids. Identification of characteristic absorption frequencies of different forms of 1-hydroxy-2-propanone can aid in studying the effect of solvent, pH, and temperature on the extent of enolization. The absorption frequencies of the carbonyl and enediol moieties of hexoses and ketoses have been confirmed by studies with selected ^{13}C-substituted sugars (Yaylayan and Ismail, 1995). The presence of α-hydroxyl groups in reducing sugars was found to shift the stretching frequencies of sugar carbonyl bands to higher values relative to α-deoxy-derivatives. Using D-[2-^{13}C]ribose and D-[1-^{13}C]ribose, further evidence for the occurrence of enolization was provided by observing the migration of carbonyl group from C-1 to C-2 atom in D-ribose and subsequent formation of D-ribulose. These studies have indicated that the relative concentrations of the enediols

Scheme 2. Reaction of Pyrrolidine with 1-Hydroxy-2-propanone (Acetol) and Formation of Amadori (5) and Heyns Rearrangement (3) Products, in the Absence of a Solvent



are as important as *aldehydo* or *keto* forms of reducing sugars in aqueous solutions. In addition, knowledge of characteristic absorption frequencies can also allow monitoring of the carbonyl−amine interaction of 1-hydroxy-2-propanone. By observing changes in the intensities of the carbonyl bands of 1-hydroxy-2-propanone and the emergence of new bands, conclusions can be drawn regarding the formation of the so-called Heyns and Amadori rearrangement products (**3** and **5** in Scheme 2). 1-Hydroxy-2-propanone, similar to reducing sugars, can undergo Maillard reaction with amines to produce 2-aminopropionaldehyde (Heyns product) in addition to 3-amino-2-propanone (Amadori product).

Effect of Solvent on the Carbonyl Absorption Band of 1-Hydroxy-2-propanone. In general, ketones absorb at a lower frequency than aldehydes. However, the introduction of electron-withdrawing groups such as halogens or a hydroxyl group at the α-carbons is known to lead to a shift of the carbonyl stretching frequency to higher values, provided that the halogen can rotate to eclipse the carbonyl group. The magnitude of this shift depends on the torsional angle. The effect of the α-hydroxyl groups on the absorption frequency of sugar carbonyls was dependent on their ability to attain eclipsed conformation with respect to the carbonyl group. Sugars having more rotational freedom to attain an eclipse or near-eclipse conformation exhibited a higher shift. 1-Hydroxy-2-propanone in the gas phase has been reported to absorb at 1750 cm^{-1} (Coleman and Gordon, 1989); 10 cm^{-1} higher than acetone in the gas phase. Neat 1-hydroxy-2-propanone exhibits a strong carbonyl absorption band at 1726 cm^{-1} shifted by 9 cm^{-1} as compared to neat acetone that absorbs at 1717 cm^{-1} (see Table 1). In D_2O, this band was shifted to 1720 cm^{-1} due to solvent effect; however, the extent of this shift due to water indicates that 1-hydroxy-2-propanone is mainly intramolecularly hydrogen bonded (**1**), as has been confirmed by other investigators (Yasuda et al., 1995). On the other hand, the carbonyl band of acetone in D_2O is shifted to 1698 cm^{-1}, a 19 cm^{-1} shift as compared to only 6 cm^{-1} in the case of 1-hydroxy-2-propanone. In dioxane, the carbonyl group of 1-hydroxy-

Table 1. Carbonyl Absorption Frequencies of Relevant 2-Propanone (Acetone) Derivatives

acetone derivative[a]	carbonyl absorption frequency (cm^{-1})
acetone (g)	1740
acetone (D_2O)	1698
acetone (l)	1717
1-chloroacetone (g)	1743
1-chloroacetone (l)	1736
1,3-dichloroacetone (l)	1743
1,3-diaminoacetone (l)	1743
1-hydroxyacetone (D_2O)	1720
1-hydroxyacetone (g)	1750
1-hydroxyacetone (l)	1726

[a] g, gas phase; l, liquid.

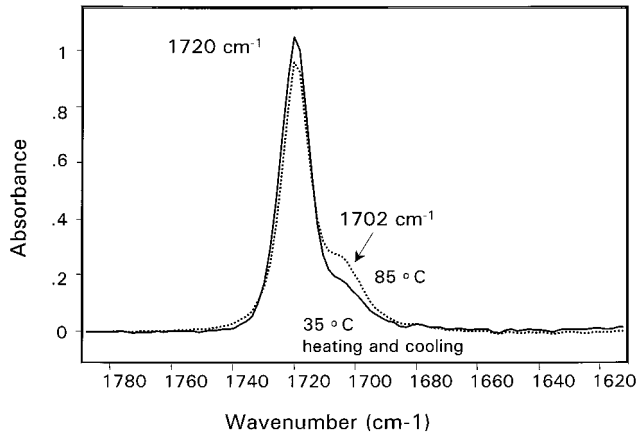


Figure 1. Effect of temperature on the intensity of carbonyl absorption bands (1680−1740 cm^{-1}) of 1-hydroxy-2-propanone (2% D_2O).

2-propanone absorbs at 1726 cm^{-1}. In 5% NaOD, due to the formation of a bulky sodium alkoxide at the α-carbon, prevented 1-hydroxy-2-propanone to attain eclipsed conformation, and consequently, the absorption frequency was lowered to 1712 cm^{-1}.

A solution of 1-hydroxy-2-propanone in D_2O, also exhibited a weak absorption band in the carbonyl region centered at 1702 cm^{-1} (see Figure 1) very close to the absorption frequency of acetone in D_2O (1698 cm^{-1}). Tentatively, this peak was assigned to the 1-hydroxy-2-propanone rotomer in which the hydroxyl group is near-staggered conformation (**1′**). By increasing the temperature of the 1-hydroxy-2-propanone solution, the intensity of non-H-bonded rotomer (**1′**) should increase on the expense of H-bonded rotomer (**1**). The initial temperature (30 °C) 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. During the heating cycle, the intensity of the band at 1702 cm^{-1} increased during the heating cycle and decreased during the cooling cycle, indicating reversibility of the process.

Effect of Acid/Base Catalysis and Temperature on the Enolization of 1-Hydroxy-2-propanone. Enolization of 1-hydroxy-2-propanone (**1**, acetol) can be initiated by both α-carbons to produce the enediol **1b** and the enol **1a**. This process can be catalyzed by acids and bases. Bases in general are more efficient catalysts than acids. Under basic conditions, enolization initiated from the more acidic α-hydrogens will predominate (Rappe and Sachs, 1967). In acidic and basic conditions, 1-hydroxy-2-propanone exhibited peaks in the alkene region; however, unlike reducing sugars (Yaylayan and Ismail, 1995), no evidence of enolization was observed

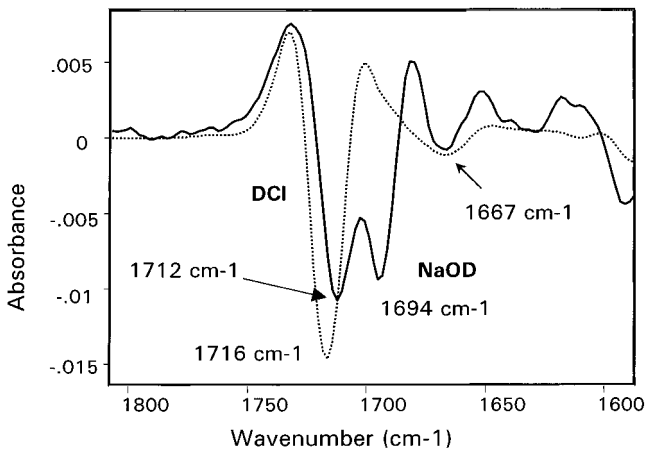


Figure 2. Second-derivative spectra (1600−1800 cm^{-1}) of a 2% solution of 1-hydroxy-2-propanone in 5% DCl in D_2O at 80 °C (dotted line) and in 5% NaOD in D_2O at 30 °C (solid line).

in D_2O due to the presence of low concentrations of enolized species. Enolization in D_2O can be verified however by observing deuterium exchange at the α-hydrogens by GC/MS analysis. A solution of 1-hydroxy-2-propanone in D_2O was equilibrated overnight and analyzed by GC/MS. The data indicated the occurrence of deuterium exchange of all the six hydrogens of 1-hydroxy-2-propanone in the following percentages: M, 2%; M + 1, 10%; M + 2, 22%; M + 3, 28%; M + 4, 22%; M + 5, 12%; M + 6, 4%. When 1-hydroxy-2-propanone was equilibrated in 5% NaOD solution at 30 °C, the carbonyl peak was shifted to 1712 cm^{-1}, and two new bands appeared in the alkene region, a major band at 1694 cm^{-1} and a weaker band at 1667 cm^{-1} (Figure 2). Under basic conditions, the negatively charged alkoxide group should destabilize the developing partial negative charge on C-1 and make it less acidic relative to C-3. Accordingly, the stronger band at 1694 cm^{-1} was assigned to the enol **1a**, and the weaker band at 1667 $cm^{-1}$was assigned to the enediol **1b**. Under acidic conditions, the reverse trend should be observed where C-1 protons will be more acidic relative to C-3 protons due to the formation of alkyl oxonium ions. 1-Hydroxy-2-propanone was equilibrated in a 5% DCl solution at 30 °C, no absorption was observed in the alkene region, only the carbonyl band was observed at 1719 cm^{-1}. At temperatures higher than 65 °C, a new band appeared at 1667 cm^{-1} and increased with temperature with corresponding decrease in the intensity of carbonyl band. This observation is consistent with the assignment of the enol and enediol bands under basic conditions. The process was not reversible during cooling cycle due to the formation of stable intramolecular H-bonding in **1b**. To prevent hydration and consequently to observe the carbonyl band due to the formation of 2-hydroxypropionaldehyde (**1c**), 1-hydroxy-2-propanone was analyzed in 100% triethylamine solution. The appearance of two bands in the carbonyl region (see Figure 3) indicated the occurrence of enolization. The addition of a small amount of D_2O to this solution caused the *aldehydo* band (1735 cm^{-1}) to disappear and the keto (1726 cm^{-1}) band to shift to 1720 cm^{-1}. However, neither enol nor enediol bands were observed in the alkene region, indicating the presence of very low concentrations of enol or enediols forms in the equilibrium mixture under basic conditions. This might be due to the enhanced acidity (∼ 4−5 pK_a units) of enediol protons relative to α-hydrogens of their corresponding

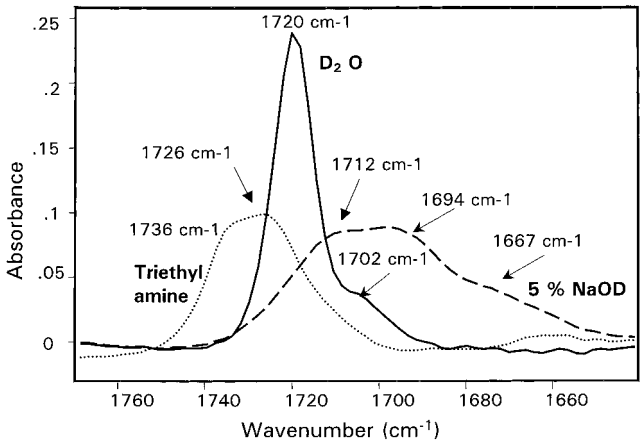


Figure 3. Absorption of the carbonyl and enediol region (1660−1760 cm^{-1}) of a 2% solution of 1-hydroxy-2-propanone in (a) D_2O (solid line), (b) triethylamine (dotted line), and (c) NaOD (dashed line).

carbonyl forms (Bender and Williams, 1966). Although enol and enediol forms were not detected, they can be trapped as stable trimethylsilyl enol ethers using trimethylchlorosilane (TMS), a reagent commonly used for this purpose under alkaline conditions. A solution of 1-hydroxy-2-propanone in excess trimethylchlorosilane dissolved in acetonitrile was monitored at 30 °C for 6 h, after addition of a catalytic amount of triethylamine to initiate enolization. As expected, no aldehydic peak was detected due to trapping by TMS of the enediol intermediate (**1b**) leading to it. By the time of the first scan, a new band had appeared at 1698 cm^{-1}, in addition to the *keto* band at 1724 cm^{-1}, indicating the formation of trimethylsilyl ether of **1b** instead of aldehyde **1c**. However, over time, the *keto* band at 1724 cm^{-1} decreased in intensity with an increase of both 1698 cm^{-1} and a new band at 1714 cm^{-1}. The latter was assigned to the trimethylsilyl ether of **1a**.

To study the effect of temperature on enolization, 1-hydroxy-2-propanone solutions in TEA were equilibrated separately for 20 min at 30 and 60 °C, and the relative percentages of *keto* and *aldehydo* forms were estimated based on the peak heights of the second-derivative spectra. At 30 °C, the 1-hydroxy-2-propanone solution exhibited ∼40% *keto* form and ∼60% *aldehydo* form. However, at 60 °C, the percent of *keto* form increased to ∼55%, indicating a slower rate of enolization at higher temperatures. At higher temperatures, the rate of enolization was also slowed in reducing sugars (Yaylayan and Ismail, 1995). It is interesting to note that under acid catalysis the rate of enolization increased with increasing temperature due to different mechanisms of catalysis (Lienhard and Wang, 1969).

Monitoring Carbonyl−Amine Reactions of 1-Hydroxy-2-propanone. To provide further evidence for the formation of 2-hydroxypropionaldehyde (**1c**) in the presence of basic amines, 1-hydroxy-2-propanone was reacted with amylamine (a reactive 1° amine) and pyrrolidine (a reactive 2° amine) in separate time-run experiments. These reactive amines, in addition to their ability to catalyze the enolization of 1-hydroxy-2-propanone (Bender and Williams, 1966), can also react with carbonyl compounds and form stable Amadori and Heyns rearrangement products (Scheme 2). Consequently, the carbonyl peaks due to **1** and **1c** should decrease over time with concomitant formation and an increase of new peaks in the carbonyl region during

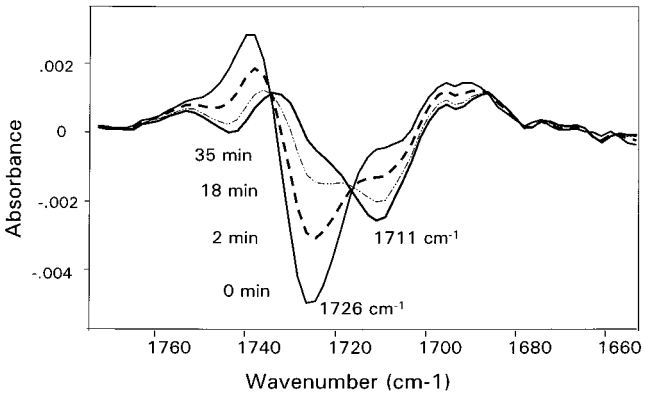


Figure 4. Time-dependent second-derivative spectra (1660−1760 cm^{-1}) of a equimolar mixture of amylamine and 1-hydroxy-2-propanone at room temperature.

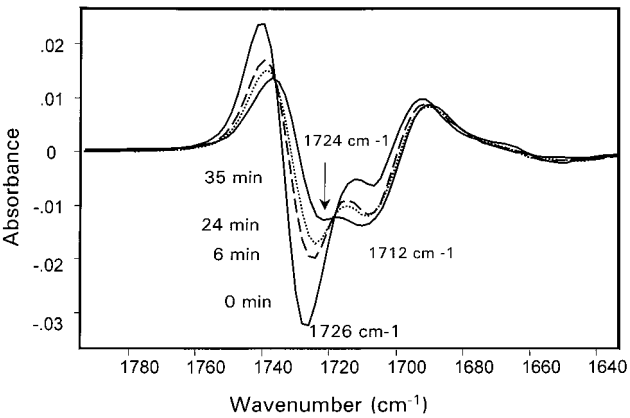


Figure 5. Time-dependent second-derivative spectra (1660−1760 cm^{-1}) of a equimolar mixture of pyrrolidine and 1-hydroxy-2-propanone at room temperature

time-run experiments. When equimolar amount of amylamine was added to neat 1-hydroxy-2-propanone, directly on the IR cell, the keto band of 1-hydroxy-2-propanone centered at 1726 cm^{-1} decreased rapidly over time with the formation and increase of a new band at 1711 cm^{-1} as shown in Figure 4. The reaction was completed within 35 min. The same experiment was repeated with pyrrolidine. Again, the *keto* band of 1-hydroxy-2-propanone decreased with the formation of a new band at 1712 cm^{-1}. However, at the end of 35 min, a new band at 1724 cm^{-1} started to form as shown in Figure 5. In both systems, the *aldehydo* band expected at 1734 cm^{-1} was not detected. This could mean either enolization did not occur fast enough or the aldehyde formed reacted very fast. To study this interaction in more detail, the reaction of pyrrolidine with 1-hydroxy-2-propanone was further investigated at a lower initial temperature, and the reactants were mixed prior to FTIR analysis to avoid diffusion control of the reaction rates. Both reactants were cooled separately to −2 °C and vortexed outside of the IR cell for 20 s, and a sample was removed for time-run analysis. The first scan, obtained 5 min after mixing, indicated the formation of a new peak at 1712 cm^{-1} and the presence of an unreacted *keto* peak of the 1-hydroxy-2-propanone at 1726 cm^{-1} (see Figure 6). The second scan, obtained 10 min after mixing, indicated the complete disappearance of the *keto* peak and the formation of a new band centered at 1724 cm^{-1}. For the next 50 min both new peaks increased continuously as shown in Figure 6. Monitoring the reaction for another hour indicated that

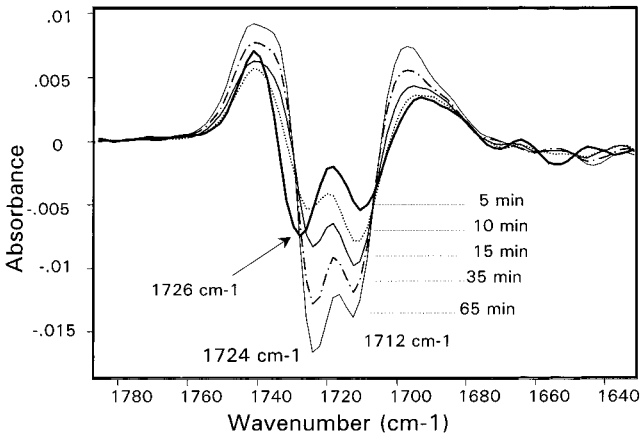


Figure 6. Time-dependent second-derivative spectra (1660−1760 cm^{-1}) of a equimolar mixture of pyrrolidine and 1-hydroxy-2-propanone mixed at −2 °C and vortexed before monitoring at room temperature.

the new peaks reached their optimum concentrations after around 80 min. A small amount of D_2O was added to the IR cell after the final spectrum had been collected to identify the presence of *aldehydo* bands. The band at 1712 cm^{-1} disappeared due to hydration, and the band at 1724 cm^{-1} was shifted to 1719 cm^{-1} due to hydrogen bonding with D_2O. A similar shift of the *keto* band and disappearance of the aldehyde peak was also observed when D_2O was added to a solution of 1-hydroxy-2-propanone in TEA. Consequently, the band centered at 1712 cm^{-1} was assigned to the Heyns product (**3**).

When 1-hydroxy-2-propanone was equilibrated in TEA, a nonreactive tertiary amine, FTIR analysis indicated the presence of an aldehyde (**1c**) and a ketone (**1**) in the equilibrium mixture (Figure 3). Decreasing the temperature favored the enolization process and the formation of the aldehyde (**1c**). When a reactive primary amine (amylamine) was added to the neat 1-hydroxy-2-propanone, on the IR cell, and the reaction mixture was immediately scanned, only one carbonyl product was formed on the expense of 1-hydroxy-2-propanone (see Figure 4). Disappearance of this band after the addition of D_2O to the IR cell at the end of the last scan indicated the formation of an aldehyde (Heyns product **3**) rather than a ketone. Evidently, the rate of nucleophilic addition of the primary amine reaction with 1-hydroxy-2-propanone was much faster than the rate of its catalysis of enolization. As a result, only a Heyns product was formed. When the primary amine was replaced by a less nucleophilic but a more basic secondary amine (pyrrolidine), enolization was catalyzed to a small extent to generate toward the end of the reaction a new peak centered at 1724 cm^{-1} in addition to the major peak at 1712 cm^{-1}. The rate of formation of the new peak (1724 cm^{-1}) increased, as expected, by lowering the initial temperature of the reaction due to the decreased rate of the nucleophilic addition and the increased rate of enolization. Lowering the initial temperature allowed the enolization to proceed to a greater extent relative to the rate of nucleophilic addition and establish higher equilibrium concentrations of 2-hydroxypropionaldehyde (**1c**). This enabled the amine to react and produce the Amadori product **5**. The data indicated that within 5 min all the ketone **1** and the aldehyde **1c** have already been converted into their respective tetrahedral intermediates **2** and **4** and that the rate of conversion of tetrahedral intermediate into

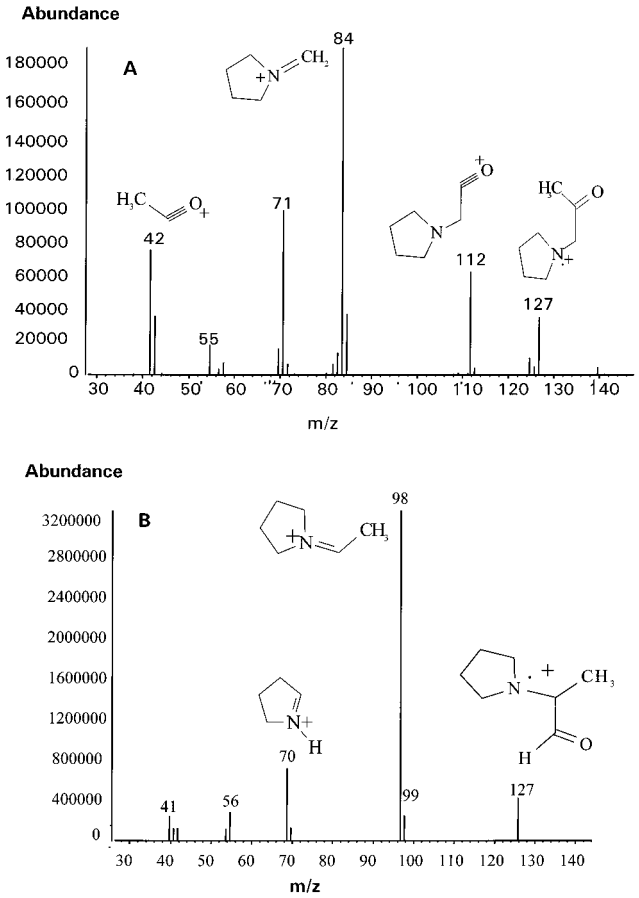


Figure 7. Mass spectra of two products extracted from the reaction mixture of pyrrolidine and 1-hydroxy-2-propanone. A, Amadori product (**5**); B, Heyns product (**3**).

iminium ion and subsequently into **3** and **5** is much slower. Consequently, the rate of increase of the bands centered at 1712 and 1724 cm^{-1} over time, shown in Figure 6, corresponds to the rate of conversion of the tetrahedral intermediates into their corresponding Heyns (**3**) and Amadori (**5**) products. This observation is consistent with the literature data (Williams and Bender, 1966), which indicate that the conversion of the tetrahedral intermediate into imine is the rate-limiting step during the reaction of acetone with reactive amines. To provide direct evidence for the formation of Heyns (**3**) and Amadori products (**5**), the reaction solution was extracted with chloroform and analyzed by GC/MS. The analysis indicted the presence of two products with molecular weights of 127 amu and with mass spectral fragmentation patterns consistent with the assigned structures (see Figure 7).

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