Formation of 4-Alkoxy-γ-valerolactones from Levulinic Acid and Alcohols during Storage at Room Temperature

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Levulinic acid (LA) is a flavor ingredient used for many products. During the storage of LA in alcohols at room temperature, chemical changes were observed. Specifically, two groups of compounds were formed, esters of LA and 4-alkoxy-γ-valerolactones. All of these compounds were identified by spectral data and synthesis. Mechanistically, it is proposed that the alcohol reacts reversibly either with the keto group of LA to form 4-alkoxy-γ-valerolactone via a hemiketal intermediate or with the acid group of LA to form the ester. All of the data obtained from this study suggest that during the initial stages of storage the reactions are kinetically controlled to form the 4-alkoxy-γ-valerolactone more than the ester; however, as the reactions proceed toward equilibrium, they become thermodynamically controlled to form the ester more than the 4-alkoxy-γ-valerolactone.

Keywords: *Alkyl levulinates; benzyl levulinate; ethyl levulinate; 2-phenylethyl levulinate; cis-3-hexenyl levulinate; geranyl levulinate; 4-alkoxy-γ-valerolactone; 4-(phenylmethoxy)-γ-valerolactone; 4-ethoxy-γ-valerolactone; 4-(2-phenylethoxy)-γ-valerolactone; 4-(cis-3-hexenoxy)-γ-valerolactone; geranioxy-γ-valerolactone; levulinic acid*

INTRODUCTION

Levulinic acid (LA), a keto acid, is a flavor ingredient used for many products. Sometimes flavor formulations, which can be stored over long periods of time, contain LA in the presence of alcohols. To date the stability of LA in alcoholic solutions has not been the subject of previous study. The objectives of this study were to determine the stability of LA when stored in an alcoholic solution at room temperature, to estimate the profile of chemical changes that occurred, and to identify the compounds formed. Finally, potential mechanisms for the formation of these compounds will be proposed.

EXPERIMENTAL PROCEDURES

Alcohols Chosen. The following primary alcohols were chosen. 2-Phenylethyl alcohol, *cis*-3-hexenol, and geraniol were chosen because they are important flavor compounds, while benzyl alcohol and ethanol were chosen because of their widespread use as solvents. All chemicals were purchased from commercial suppliers and used as supplied.

Preparation of the Solutions and Storage Conditions. Each solution was prepared with 0.2 g of LA and 1.8 g of each of the above alcohols, and all the solutions were stored at room temperature.

Gas Chromatography/Mass Spectrometry (GC/MS) Analysis. Each solution was analyzed within 1–2 h of preparation and also at days 1 and 4 and weeks 3 and 7 by GC/MS on a DBWAX fused silica column (30 m × 0.32 mm, 0.25 mm film thickness, 50–190 °C at 6 °C/min) with a mass selective detector. Retention indices were calculated on the basis of the literature method (Majlat et al., 1974) on the same column.

Area Percent Quantitation. From GC/MS analysis, the peak areas of LA and the components formed during storage were integrated and reported as area percent.

Preparative GC. The peak of interest was collected from a preparative glass capillary column (Supelcowax 10; 30 m × 0.75 mm) with a thermal conductivity detector under the same chromatographic conditions.

Infrared (IR) Analysis. IR spectra of the GC-trapped material were obtained with a Mattson Polaris FT-IR microscope.

Nuclear Magnetic Resonance (NMR) Analysis. Proton NMR spectra were obtained from a Varian Unity 300 MHz spectrometer using $CDCl_3$ as solvent. All chemical shifts are reported in ppm downfield of internal TMS. Total spectral aquisition times were typically 8–9 h.

Synthesis of Esters of Levulinic Acid. A solution of levulinic acid (1 g), the alcohol (2 g), toluene (10 mL), and a trace amount of *p*-toluenesulfonic acid was refluxed until the product was formed. For the preparation of ethyl levulinate, no toluene was used. The reaction mixture obtained was then cooled to room temperature, and the toluene in the mixture was removed by the use of a rotary evaporator. The concentrated mixture was separated on a preparative GC column, and the ester of levulinic acid was isolated.

Synthesis of 4-Alkoxy-γ-valerolactones. The synthesis procedure used was a modification of the procedure of Langlois and Wolff (1948). A solution of α-angelica lactone (0.1 g), the alcohol (0.15 g), and HCl (37%, 1–2 mL) was heated at 55 °C in a water bath for 4 h and then cooled to room temperature. The solution obtained was immediately separated by preparative GC, and the 4-alkoxy-γ-valerolactone was isolated.

RESULTS AND DISCUSSION

It was generally observed that the GC profiles obtained from all the samples changed, and two additional peaks from each sample were formed as LA decreased during storage. Observations implied that LA was unstable in these alcohols and chemical changes took place.

Taking the solution of LA and benzyl alcohol as an example, the GC profile changes during storage at room temperature over 7 weeks showed that the peak at the retention time of 40.5 min (peak a) was formed first and increased to a maximum in 3 weeks, after which time it began to decrease. Meanwhile, the peak at the retention time of 35 min (peak b) was formed and continued to increase through 7 weeks. A similar trend

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Table 1. Mass Spectral Data and Retention Indices Obtained from this Study

component identified	mass spectral data, m/z (%)
benzyl levulinate	206 (M^+,2), 120 (13), 108 (25), 107 (64), 99 (60), 91 (100), 90 (11), 72 (11), 65 (19), 43 (73), 39 (11). $I_k = 2526$.
ethyl levulinate	144 (M^+,3), 129 (17), 102 (13), 101 (16), 99 (50), 74 (17), 73 (13), 71 (12), 55 (11), 43 (100), 29 (24), 27 (20). $I_k = 1610$.
2-phenylethyl levulinate	220 (M^+, 0), 105 (25), 104 (100), 99 (16), 91 (9), 78 (5), 77 (7), 65 (6), 43 (35). $I_k = 2617$.
cis-3-hexenyl levulinate	198 (M^+, 0), 99 (64), 82 (73), 71 (17), 67 (100), 55 (27), 43 (81), 41 (29), 39 (15), 27 (16). $I_k = 2064$.
geranyl levulinate	252 (M^+, 0), 136 (14), 121 (17), 99 (57), 93 (30), 80 (15), 69 (100), 68 (53), 67 (18), 43 (47), 41 (63). $I_k = 2504$.
4-(phenylmethoxy)-γ-valerolactone	206 (M^+, 7), 107 (11), 104 (18), 99 (83), 91 (100), 71 (11), 65 (16), 43 (44), 39 (9). $I_k = 2616$.
4-ethoxy-γ-valerolactone	144 (M^+, 0), 100 (14), 99 (68), 89 (10), 72 (20), 71 (14), 61 (13), 57 (19), 56 (12), 43 (100), 29 (19), 27 (19). $I_k = 1653$.
4-(2-phenylethoxy)-γ-valerolactone	220 (M^+, 0), 105 (54), 104 (27), 99 (100), 91 (10), 79 (8), 77 (12), 71 (11), 43 (37). $I_k = 2667$.
4-(*cis*-3-hexenoxy)-γ-valerolactone	198 (M^+, 0), 99 (100), 83 (13), 82 (22), 71 (10), 67 (13), 55 (27), 43 (41), 41 (17). $I_k = 2114$.
4-geranioxy-γ-valerolactone	252 (M^+, 0), 136 (12), 121 (14), 99 (96), 93 (42), 81 (36), 80 (17), 69 (95), 68 (100), 53 (24), 43 (71), 41 (78), 39 (18). $I_k = 2572$.

Table 2. Percentage Data of Esters, Lactones, and LA during Storage

		day		week	
	fresh	1	4	3	7
	From LA/Benzyl Alcohol				
benzyl levulinate	0	0	2.24	5.91	18.64
4-(phenylmethoxy)-γ-valerolactone	3.07	9.73	16.68	16.91	13.47
LA	96.93	90.27	81.08	77.18	67.79
	From LA/Ethanol				
ethyl levulinate	0	0.98	2.17	5.99	15.42
4-ethoxy-γ-valerolactone	3.57	9.44	8.92	8.65	6.20
LA	96.43	89.58	88.91	85.36	78.38
	From LA/2-Phenylethanol				
2-phenylethyl levulinate	0	0	2.29	5.89	19.70
4-(2-phenylethoxy)-γ-valerolactone	0	4.98	10.31	13.24	11.98
LA	100	95.02	87.40	80.87	68.32
	From LA/*cis*-3-Hexenol				
cis-3-hexenyl levulinate	0	1.26	3.32	8.68	25.12
4-(*cis*-3-hexenoxy)-γ-valerolactone	1.37	7.20	16.58	21.00	16.40
LA	98.63	91.54	80.10	70.32	58.48
	From LA/Geraniol				
geranyl levulinate	0	0	4.70	11.51	32.02
4-geranioxy-γ-valerolactone	0	0.50	2.55	3.93	4.61
LA	100	95.50	92.75	84.56	63.37

was also observed for each of the other four samples. Categorically, the peak formed first from each sample possesses a longer retention time than the peak formed later. Over the storage period, the peak formed first continued to increase until the other peak was formed, after which the first peak decreased as the other peak increased.

As the mass spectra of the peaks from the solution of LA and benzyl alcohol were considered, both of the spectra revealed a molecular ion at m/z 206, indicating that one of the two compounds could be benzyl levulinate. When the two IR spectra for the above-mentioned peaks collected from the preparative GC column were compared, it was found that the two strong bands at 1720 and 1736 cm^{-1} (peak b) implied carbonyl absorptions of an aliphatic ketone and an aliphatic ester, respectively; however, the strong band at 1775 cm^{-1} (peak a) implied a γ-lactone, most likely a γ-valerolactone. This comparison strongly suggested that the compound (peak b) could be benzyl levulinate, the other compound (peak a) a γ-valerolactone bearing a side chain.

The proton NMR spectrum obtained from the GC trap corresponding to peak b revealed that the singlet at 5.10 ppm (2H) is consistent with the existence of a methylene group between the oxygen of an ester and a benzene ring, another singlet at 1.9 ppm (3H) is consistent with a methyl group adjacent to a carbonyl, a triplet at 2.61 ppm (2H, J = 6.4 Hz) is consistent with a methylene group adjacent to a carbonyl (ketone), another triplet at 2.73 ppm (2H, J = 6.4 Hz) is consistent with another methylene group adjacent to a carbonyl (ester), and the multiplet at 7.32 ppm (5H) is consistent with phenyl protons. Taking together these data confirms the identity of this compound as benzyl levulinate.

The proton NMR spectrum corresponding to GC peak a revealed that phenyl protons were shown at 7.30 ppm (5H, m) and a methyl group was at 1.70 ppm (3H, s). It is interesting to note that the chemical shift range between 2 and 3 ppm shows four clusters and each cluster is composed of eight peaks (some peaks are overlapping). Apparently, these are two pairs of methylene protons at the γ-lactone ring in an AA'XX' pattern. The pair of methylene protons adjacent to the carbonyl is shown at 2.53 ppm (1H, as H_a) and 2.795 ppm (1H, as H_b), and the other pair of methylene protons is at 2.152 ppm (1H, as H_c) and 2.372 ppm (1H, as H_d). The coupling constants derived from these four protons were found to be $J_{a\text{-}b}$ = 17.8 Hz, $J_{a\text{-}c}$ = 9.5 Hz, $J_{a\text{-}d}$ = 2.8 Hz, $J_{b\text{-}c}$ = 9.9 Hz, $J_{b\text{-}d}$ = 9.4 Hz, and $J_{c\text{-}d}$ = 13.2 Hz. The four peaks appearing between 4.56 and 4.70 ppm (2H) suggested that the methylene protons are located between benzene and an oxygen. It is also interesting to note that these four peaks are not quartets; instead, they are two distorted doublets due to the fact that the two diastereotopic protons are induced by the chiral center at C-4 of the lactone ring. These two methylene protons are shown at 4.60 ppm

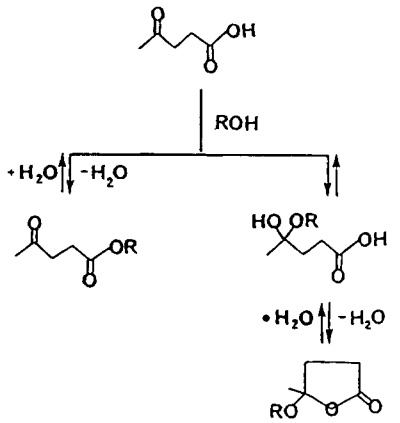

Figure 1. Formation mechanism proposed.

(1H, d, $J = 11.1$ Hz) and 4.67 ppm (1H, d, $J = 11.1$ Hz). Elucidation of this data and those from IR and MS concluded that this compound would be 4-(phenylmethoxy)-γ-valerolactone.

In order to confirm the spectrally elucidated structures of these two compounds, their synthesis was performed. A comparison of the spectral data and the retention times between the compounds synthesized and the ones isolated showed that they were identical. As a result, these two compounds have been positively identified as benzyl levulinate (peak b) and 4-(phenylmethoxy)-γ-valerolactone (peak a). Examination of the pattern of the chemical changes, the retention times, and the spectral data obtained from each sample studied has led us to propose that during storage 4-alkoxy-γ-valerolactone was formed first, while the ester of levulinate was formed later; as the former decreased, the latter increased.

The mass spectral data obtained from all of the samples studied are compiled in Table 1. One of the major fragments, m/z 99, can be thought of as being derived from the γ-valerolactone moiety as well as from the levulinate moiety. However, fragmentation leading to the m/z 99 is more favorable in the substituted γ-lactone because the bond associated with a ketal can be more readily broken than the bond associated with the ester.

The formation mechanism of these compounds has been proposed in Figure 1. It is believed that when the alcohol reacts with the keto group of LA, a hemiketal is formed, which is readily cyclized/dehydrated to form 4-alkoxy-γ-valerolactone. At the same time the alcohol reacts with the acid group of LA to form the ester.

Table 2 shows the percentage changes of the esters, lactones, and LA during storage. Figure 2 is the free-energy profile to illustrate the possible chemical changes that took place. The ester is thermodynamically more stable than the lactone due to the lower free energy (ΔG-ester), but the lactone is formed first due to the lower free energy of activation (ΔG_a-lactone). It is believed that, at an early stage during the storage, the total reaction was kinetically controlled to form more lactones than the esters. Because both reactions are reversible, at longer storage time the lactones are considered to be rearranged to LA more readily than the esters. As a result, we believe that the total reaction is themodynamically controlled to form more esters than lactones, and over time it proceeds before the reaction equilibrium is established.

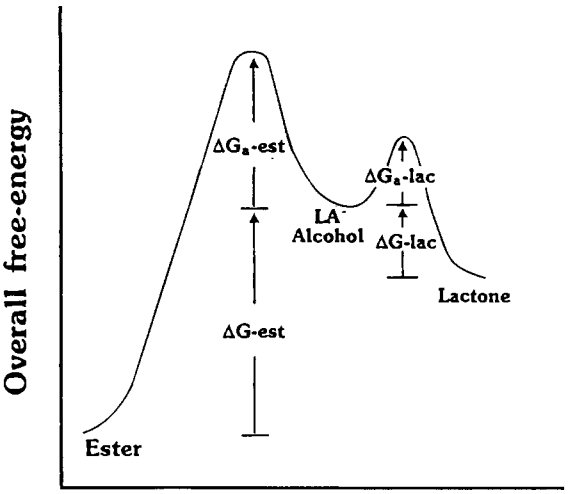

Figure 2. Free-energy profile.

CONCLUSION

During the storage of levulinic acid in alcohols at room temperature, chemical changes were observed. Specifically, two groups of compounds were formed, esters of levulinic acid and 4-alkoxy-γ-valerolactones. All of these compounds were identified by spectral data and synthesis. Mechanistically, it is proposed that the alcohol reversibly reacts either with the keto group of LA to form 4-alkoxy-γ-valerolactone via a hemiketal intermediate or with the acid group of LA to form the ester. All of the data obtained from this study suggest that during the initial stages of storage the reactions are kinetically controlled to form the 4-alkoxy-γ-valerolactone more than the ester; however, as the reactions proceeded toward equilibrium, they become thermodynamically controlled to form the ester more than the 4-alkoxy-γ-valerolactone. The mass spectra are reported herein for the first time in the literature.

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