The Rate of Ring Opening of γ- and δ-Lactones Derived from Meadowfoam Fatty Acids

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ABSTRACT: δ-Lactones derived from meadowfoam (*Limnanthes*) fatty acids were reacted with amine and alcohol nucleophiles in a second-order reaction to provide the acyclic 5-hydroxy eicosanoic acid esters and amides. The rate of reaction for the ring opening of δ-lactones was compared to the rate of ring opening of γ-lactones and the rate of derivatization of meadowfoam fatty acids. δ-Lactones showed a much larger rate for the formation of derivatives than the corresponding γ-lactones or fatty acids. δ-Lactone had a rate constant >7700 times larger for the formation of butyl ester than meadowfoam fatty acids. The formation of amides from δ-lactones is even faster than the esterification reaction and requires no catalyst or solvent when conducted at the melting point of the lactone.
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KEY WORDS: δ-Eicosanolactone, γ-eicosanolactone, 5-hydroxy eicosanamide, 5-hydroxy eicosanoate, meadowfoam fatty acids, rate, ring opening.

Meadowfoam (*Limnanthes alba*), a winter annual crop grown in the Willamette valley of Oregon, contains long-chain fatty acids (1,2) with 5-eicosenoic acid (64%) as the major fatty acid. The other main components are 5,13-docosadienoic acid (19%), 5-docosenoic acid (3%), and 13-docosenoic acid (10%). Commercialization of meadowfoam oil has been a focus of our group for some time, and several chemical modifications to the oil have been made. These modifications provided novel materials, such as factice (3–5), amides (6), dimer acids (7), estolides (8,9), and lactones (10,11). The latter material, δ-lactone, is capable of undergoing a facile ring opening.

In an early study by Brown *et al.* (12), γ-butyrolactone and δ-valerolactone were examined for their rates of hydrolysis. δ-Valerolactone reacted 22 times faster than γ-butyrolactone in the presence of alkali, and 170 times faster in acidic solutions. In a more recent study, γ-butyrolactone underwent ring opening to amides (13) with primary and secondary amines at 100°C, with the reaction reaching completion in 5 h. γ-Caprolactone was also reacted in this study (13) but exhibited a slower rate of reaction, possibly owing to the incorporation of the small alkyl side-chain.

Fatty γ-lactones have been available since the late 1960s when Showell established a synthetic method for the formation of γ-stearolactone from oleic acid (14). Subsequently, the γ-stearolactone was converted to its ethanol and diethanol amides in good yield (15). However, extensive use of this material has not been realized, and a study on the rate of derivitization (ring opening) with nucleophiles has not been performed. Consequently, we felt that the fatty γ- and δ-lactones might serve as useful intermediates to form oxygenated fatty amides and fatty esters under mild reaction conditions. This report is a comparative study on the ring opening of meadowfoam γ- and δ-lactones and the derivatization of fatty acids with alcohols and amines.

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EXPERIMENTAL PROCEDURES

Materials. γ-Eicosanolactone was obtained as a mixture with γ-docosanolactone and γ-docosenolactone by the method of Showell *et al.* (14) from meadowfoam fatty acids. δ-Eicosanolactone was obtained as a mixture with δ-docosanolactone and δ-docosenolactone by the method of Isbell and Plattner (10) from meadowfoam fatty acids. Meadowfoam fatty acids were obtained by hydrolysis of meadowfoam oil, supplied by The Fanning Corp. (Chicago, IL) and the Oregon Meadowfoam Growers Association (Salem, OR). Butanol, acetone, and methanol were obtained from Fisher Scientific Co. (Fair Lawn, NJ). Monoethanolamine was purchased from Mallinckrodt Inc. (Paris, KY).

Instrumentation. High-pressure liquid chromatography (HPLC) analyses were performed with a Spectra-Physics 8800 ternary pump (San Jose, CA) and a Spectra System AS3000 auto sampler/injector from Thermo Separation Products (Fremont, CA), coupled to an evaporative light scattering detector (ELSD III) from Varex (Burtonsville, MD). A Dynamax (250 mm × 4.6 mm, 60Å, 8 μm) C_{18} reverse-phase column, purchased from Rainin Instrument Co. (Woburn, MA), was used to separate the reaction mixtures. Components were eluted from the column with a 70:30 acetone/methanol mixture at a flow rate of 1 mL/min. The ELSD drift tube was set at 55°C, with the nebulizer set at 20 psi N_2, providing a flow rate of 2.0 standard liters per minute (SLPM). Retention times for eluted peaks were: *N*-(2-hydroxyethyl)-5-hydroxyeicosanamide, 3.7 min; *N*-(2-hydroxyethyl)-4-hydroxyeicosanamide, 4.0 min; δ-eicosanolactone, 5.2 min; γ-eicosanolactone, 5.6 min; butyl 5-hydroxyeicosanoate, 6.3 min; butyl oleate, 8.7 min.

Nuclear magnetic resonance (NMR). ^{1}H NMR and ^{13}C NMR were performed with a Bruker ARX 400 with a 5-mm dual proton/carbon probe (400 MHz ^{1}H/100.61 MHz ^{13}C), with $CDCl_3$ used as the solvent for the esters and CD_3OD for the amides. Distortionless enhanced polarization transfer (DEPT), correlation spectroscopy (COSY), and heteronuclear multiple quantum coherence (HHQC) experiments were used to make structural assignments. δ-Eicosanolactone and γ-eicosanolactone spectra were identical to those previously reported (10), and the amides are consistent with NMR data reported from the ring opening of γ-stearolactone (13,16).

^{1}H NMR of δ-eicosanolactone: δ 4.27–4.24 (*m*, 1H, -O-C*H*$CH_2CH_2CH_2$C=O), 2.59–2.53 (*m*, 1H, -O-CH$CH_2CH_2CH_2$C*H*$_2$C=O), 2.46–2.40 (*m*, 1H, -O-CH$CH_2CH_2CH_2$C*H*$_2$C=O), 1.92–1.81 (*m*, 3H, -O-C*H*$_2$C*H*$_2$$CH_2$C=O), 1.69–1.66 (*m*, 1H, -O-CHC*H*$_2$$CH_2CH_2$C=O), 1.58–1.47 (*m*, 4H, -CH_2C*H*$_2$C*H*$_2$-CHO), 1.30–1.15 (*m*, 27H, -CH_2C*H*$_2$C*H*$_2$-), and 0.86 ppm (*t*, *J* = 6.7 Hz, 3H, -CH_2C*H*$_3$). ^{13}C NMR: δ 172.0 (*s*, *C*=O), 80.6 (*d*, -O-*C*H-), 35.8 (*t*, *C*H_2CO), 31.9 (*t*, CH_2*C*H_2CH-O), 29.7 (*t*), 29.6 (*t*), 29.5 (*t*), 29.5 (*t*), 29.4 (*t*), 29.4 (*t*), 29.3 (*t*), 27.8 (*t*), 24.9 (*t*), 22.7 (*t*), 18.5 (*t*), and 14.1 ppm (*q*, *C*H_3).

^{1}H NMR of γ-eicosanolactone: δ 4.47 (*p, J* = 7.4 Hz, 1H, -O-C*H*CH_2CH_2CO-), 2.52 (*dd, J* = 9.4 Hz, 2.5 Hz, 2H, -O-CHCH_2C*H*$_2$CO), 2.29 (*h, J* = 6.5 Hz, 1H, -O-CHC*H*$_2$$CH_2$CO), 2.05–1.00 (*m*, 31H, -CH_2CH_2-CH_2-), and 0.87 ppm (*t*, *J* = 6.2 Hz, 3H). ^{13}C NMR: δ 174.0 (*s, C*=O), 81.0 (*d*, -O-*C*H-), 35.6 (*t*), 31.9 (*t*), 29.7 (*t*), 29.5 (*t*), 29.5 (*t*), 29.4 (*t*), 28.9 (*t*), 28.0 (*t*), 25.2 (*t*), 22.7 (*t*), and 14.1 ppm (*q*, *C*H_3).

^{1}H NMR of butyl 5-hydroxyeicosanoate: δ 4.05 (*t, J* = 6.7 Hz, 2H, -O-C*H*$_2$$CH_2CH_2CH_3$), 3.57 (*m*, 1H, -$CH_2$C*H*OH$CH_2$), 2.31 (*t, J* = 7.4 Hz, 2H, C*H*$_2$C=O), 1.8–1.5 (*m*, 5H), 1.5–1.15 (*m*, 32H), 0.93 (*t, J* = 14.7 Hz, 3H, -O-$CH_2CH_2CH_2$C*H*$_3$), and 0.86 ppm (*t, J* = 7.0 Hz, 3H, CH_2C*H*$_3$). ^{13}C NMR: δ 173.9 (*s*, *C*=O), 71.4 (*d*, H*C*-OH), 64.2 (*t*, -O-*C*$H_2CH_2CH_2CH_3$), 37.5 (*t*), 36.7 (*t*), 34.1 (*t*), 31.9 (*t*), 30.6 (*t*), 29.7 (*t*), 29.6 (*t*), 29.3 (*t*), 26.6 (*t*), 22.7 (*t*), 21.0 (*t*), 19.1 (*t*), 14.1 (*q*), and 13.7 ppm (*q*).

^{1}H NMR of *N*-(2-hydroxyethyl)-5-hydroxyeicosanamide: δ 6.95 (*brs*, 1H, -N*H*), 3.56 (*t, J* = 5.0 Hz, 2H, -NHCH$_2$C*H*$_2$-OH), 3.47 (*m*, 1H, -C*H*-OH), 3.26 (*m*, 2H, -NHC*H*$_2$$CH_2$-OH), 2.16 (*m*, 2H, -C*H*$_2$C=O), 1.63 (*m*, 2H, -CH-OHCH$_2$C*H*$_2$$CH_2$C=O), 1.42–1.15 (*m*, 32H, -C*H*$_2$-), and 0.80 ppm (*t, J* = 6.7 Hz, 3H, -CH_3). ^{13}C NMR: δ 174.9 (*s*, *C*=O), 71.0 (*d*, -*C*H-OH), 61.2 (*t*, -NHCH$_2$*C*H_2-OH), 41.9 (*t*, -NH*C*H_2CH_2-OH), 37.3 (*t*, -*C*H_2CH-OHCH$_2$), 36.2 (*t*, -*C*H_2C=O), 36.0 (*t*), 31.8 (*t*), 29.6 (*t*), 29.6 (*t*), 29.6 (*t*), 29.3(*t*), 25.6 (*t*), 22.6 (*t*, -CH-OH*C*$H_2CH_2CH_2$-C=O), 21.7 (*t*, -CH-OHCH$_2$*C*H_2CH_2-C=O), and 14.0 ppm (*q*, -*C*H_3).

^{1}H NMR of *N*-(2-hydroxyethyl)-4-hydroxyeicosanamide: δ 6.85 (*brs*, 1H, -N*H*), 3.61 (*t, J* = 5.1 Hz, 2H, -NHCH$_2$C*H*$_2$-OH), 3.52 (*m*, 1H, -C*H*-OH), 3.31 (*m*, 2H, -NHC*H*$_2$$CH_2$-OH), 2.28 (*m*, 2H, -C*H*$_2$C=O), 1.80 (*m*, 1H), 1.60 (*m*, 2H), 1.47–1.17 (*m*, 34H), and 0.84 ppm (*t, J* = 6.7 Hz, 3H, C*H*$_3$). ^{13}C NMR: δ 175.1 (*s*, -*C*=O), 71.3 (*d*, -*C*H-OH), 61.3 (*t*, -NHCH$_2$*C*H_2-OH), 42.1 (*t*, -NH*C*H_2CH_2-OH), 37.5 (*t*, -*C*H_2CH-OHCH$_2$ CH_2C=O), 32.9 (*t*, -CH_2CH-OHCH$_2$*C*H_2C=O), 32.5 (*t*), 31.9 (*t*), 29.6 (*t*), 29.6 (*t*), 29.3 (*t*), 25.7 (*t*, -CH_2CH-OH*C*H$_2$ CH_2C=O), 22.6 (*t*), and 14.0 ppm (*q*, -*C*H_3).

Methods. Rate data were collected by performing the reaction in a constant-temperature reactor, connected to a constant-temperature bath maintained at 50 ± 0.1°C. Reactions were performed neat and mixed with a magnetic stir bar. Butyl oleate was mixed with the lactone prior to addition of the nucleophile, and served as an internal standard. Samples were drawn at 1-min intervals through 5 min, then every 5 min thereafter. Samples were diluted in acetone and injected onto the C_{18} column described above. Data were collected and integrated by a Hewlett-Packard 3365 chem station (Palo Alto, CA). All reactions were run in duplicate, and standard curves for each analyte were derived to correct for the nonlinear response of the ELSD.

Butyl ester rate reactions. Butyl ester rate reactions were performed by melting 2.00 g (6.45 mmoles) of δ-eicosanolactone, γ-eicosanolactone, or meadowfoam fatty acids in a 50°C constant-temperature reactor. Butyl oleate (0.90 g, internal standard) and butanol (0.87 mL, 9.5 mmoles) were added, and the magnetically stirred solution was allowed to equilibrate for 10 min. Concentrated H_2SO_4 (17 μL, 0.64 mmoles) was added, and samples were drawn as described above.

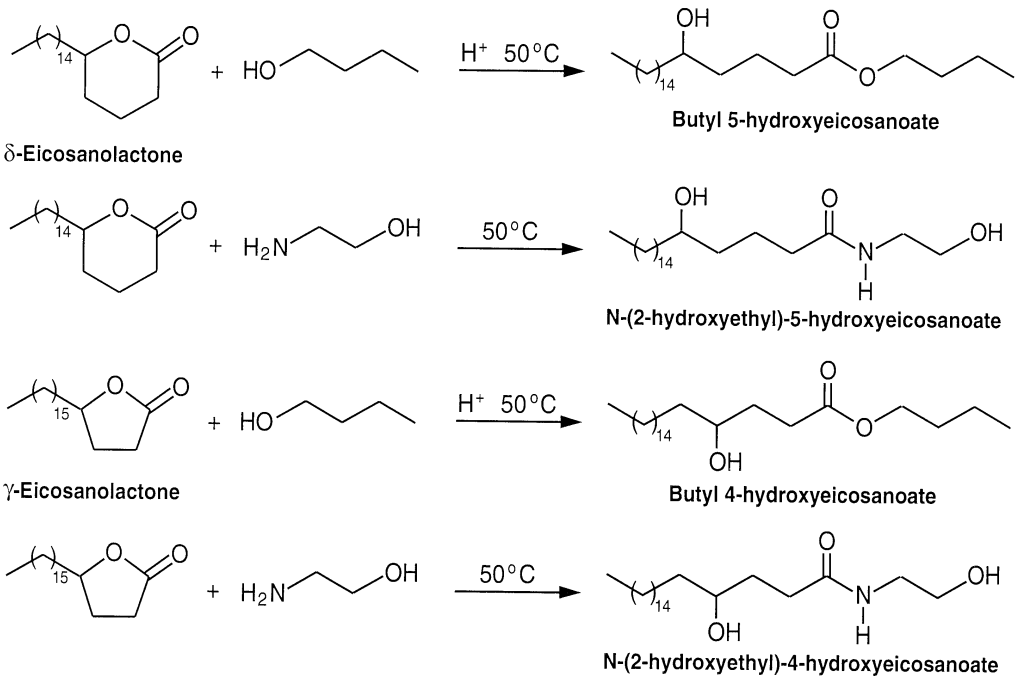
Amide rate reactions. Amide rate reactions were performed by melting 2.00 g (6.45 mmoles) of δ-eicosanolactone, γ-eicosanolactone, or meadowfoam fatty acids in a 50°C constant-temperature reactor. Butyl oleate (0.90 g, internal standard) was added, and the magnetically stirred solution was allowed to equilibrate for 10 min. Monoethanolamine (0.58 mL, 9.6 mmoles) was added, and samples were drawn as described above.

RESULTS AND DISCUSSION

δ-Eicosanolactone and γ-eicosanolactone were ring-opened with butanol and monoethanolamine to form 5- and 4-hydroxy esters and amides, respectively, as outlined in Scheme 1. The reactions were run above the melting point of the lactones (50°C) with good mixing of the reactants. The reactions were performed neat to exclude any effects that solvent polarity might play on the rate of reaction. The reactions are overall second-order, and first-order with respect to lactone.

Table 1 summarizes the rate data for the conversion of the δ- and γ-lactones to esters and amides with respect to the rate of derivitization of the parent fatty acids. δ-Eicosanolactone has a high rate of reaction with both nucleophiles. The reaction of the δ-lactone with butanol reached equilibrium within 1 min, and 88% of the δ-lactone was converted to butyl 5-hydroxyeicosanoate. When this reaction was allowed to continue for 24 h, nearly all of the butyl ester was converted back to the δ-lactone. In contrast, the ring opening of the δ-lactone to form the 5-hydroxy amide was irreversible under the reaction conditions and showed a quantitative conversion to the amide within 3 min at 50°C.

δ-Eicosanolactone reacts >7700 times faster than fatty acids to make esters under these conditions. In contrast, γ-eicosanolactone failed to react even after 24 h. These results are similar to Brown's predictions (12) about the stability of



SCHEME 1

the 5-membered lactone with respect to the 6-membered lactone. However, these data suggest that the fatty lactones show a much larger difference in ring stability, and consequently a more pronounced difference in rates of ring opening. The relative rate of δ:γ-eicosanolactone ring opening with respect to δ:γ-butyrolactone is ~10 times larger.

As expected, the fatty acids failed to make amides under these mild conditions where δ-eicosanolactone reacted at a rate >9200 times faster than the esterification of meadowfoam fatty acids. The γ-eicosanolactone also proceeded at a good rate to the 4-hydroxy amide, but was considerably slower than the δ-lactone. Typical reaction conditions for the formation of amides generally require high temperatures and extended reaction times (6), and often provide incomplete conversions in conjunction with nitrile by-products. Some of these problems have been overcome by a recently developed method by Feairheller (16) in which amides are synthesized from triglycerides under low-temperature conditions (50–60°C) with the primary amine as the solvent and catalyst. Removal and recycling of the excess amine will be required on an industrial scale. In contrast, amides formed from the lactones can be obtained directly from the reactor as a white crystalline solid when a 1:1 mole ratio of δ-lactone and amine is used.

TABLE 1
Second-Order Rate Constants for Derivatization

Starting material[a]	Nucleophile	Rate constant ($mol^{-1}min^{-1}$)	Relative rate
δ-Eicosanolactone	Butanol	76.4	7780
γ-Eicosanolactone	Butanol	0.0	0
Meadowfoam FA	Butanol	9.8×10^{-3}	1
δ-Eicosanolactone	Monoethanolamine	91.1	9276
γ-Eicosanolactone	Monoethanolamine	0.4	40.7
Meadowfoam FA	Monoethanolamine	0.0	0

[a]FA, fatty acid.

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