

Reaction Kinetics of the Autocatalytic Hydrolyses of Alkyl Lactates

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ABSTRACT: Kinetic description of the hydrolysis reaction of alkyl lactates has been limited to acid-catalyzed conditions even though the reverse reaction, esterification of lactic acid with alcohols, has been well studied in the presence and absence of added acidic catalysts. Methyl lactate and ethyl lactate, like most esters, undergo spontaneous hydrolysis in aqueous solution. As the reaction progresses, the generated lactic acid serves to catalyze ester hydrolysis, while the rate of the reverse reaction to form esters increases with the accumulation of acid product. The reaction sequence of lactate hydrolysis can be described in three regimes: initiation/neutral hydrolysis, autocatalytic hydrolysis, and equilibrium. In these experiments, the evolution of lactate hydrolysis was measured for varying temperatures (6 °C to 40 °C) and initial methyl or ethyl lactate concentrations (3 to 40 mol%) to quantify the kinetics transition in reaction regimes with time.

INTRODUCTION. The growing importance of green chemistry and sustainable engineering principles combined with the goal of reduced reliance on fossil fuels has driven a need for renewably sourced and environmentally benign chemicals.¹⁻⁴ As renewable feedstocks are developed via novel synthetic routes, new challenges emerge with respect to chemical stability, performance, and purity.⁵⁻⁷ Lactic acid has drawn widespread attention for its use in the preparation of compostable polylactic acid plastics, its use as a food and pharmaceutical additive, and as an attractive platform chemical for the synthesis of high-value chemicals such as acrylic acid, acetaldehyde, and propylene oxide.⁸⁻¹¹ Because of difficulties in lactic acid vaporization due to self-polymerization even at room temperature, alkyl lactates such as methyl or ethyl lactate have often served as reactant surrogates to prevent oligomerization while preserving major reaction pathways.^{12,13} In addition to being a promising starting material for a variety of sustainable chemical syntheses, alkyl lactates (in particular, ethyl lactate) have already found widespread use as non-toxic green solvents, as well as in pharmaceuticals and personal care products.¹⁴⁻¹⁶

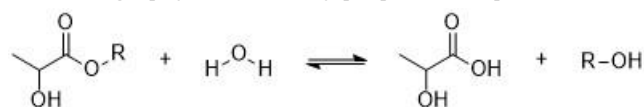
Traditionally, alkyl lactates are produced by esterification of lactic acid with alcohols of varying carbon chain length (reverse reaction, Scheme 1). Commercially practiced purification schemes for lactic acid fermentation often utilize reactive esterification-distillation as an initial step to concentrate the lactic acid from the fermentation broth.¹⁷⁻²⁰ The higher volatility of methyl and ethyl lactate (b.p. of 144 and 152 °C)^{21,22} relative to lactic acid (b.p. of 260 °C) enable easier separation of the lactic component from the water-rich fermentation broth and reduce the loss of lactic acid due to polymerization/coking that would occur if distillation were used in primary separation.²³⁻²⁵

While esterification occurs in the absence of added catalyst due to the autocatalytic effect of lactic acid, acid catalysts such as sulfuric acid promote significant increases in the rate of alkyl lactate production.²⁶⁻³⁰ Typically a fixed, heterogeneous acid catalyst such as an Amberlyst is used to catalyze the esterification reaction.^{31,32} This reaction has been

characterized to identify new and improved acid catalysts for production of many alkyl lactates, both as target products themselves or for use in the purification of lactic acid described above.

Much like the esterification of lactic acid, the reverse reaction, acid hydrolysis of methyl lactate, ethyl lactate, and butyl lactate has been studied considerably due to the importance of the regeneration of lactic acid following the reactive distillation process, but always in the presence of an acid catalyst such as Amberlyst or other cation-exchange resins.³³⁻³⁵ However, ester hydrolysis can be an autocatalytic system, as the lactic acid product can act to further accelerate the reaction.³⁶⁻⁴²

While continuing our studies of the catalytic dehydration of alkyl lactates,^{43,44} we observed that aqueous 6.9 mol% (30 wt%) solutions of methyl lactate slowly accumulated significant amounts of alcohol and lactic acid when kept at room temperature. The same was true with 6.2 mol% (30 wt%) solutions of ethyl lactate. No acid catalyst is intentionally present in these solutions, nor is lactic acid observed by gas chromatography in the freshly prepared samples.



Scheme 1: Lactate hydrolysis yields lactic acid and alcohol.

The early stages of the ester hydrolysis should be described as uncatalyzed hydrolysis. Kinetic data is lacking in the literature regarding the lactate hydrolysis reaction in the absence of catalyst and at the relatively low temperatures relevant to potential storage conditions (6 °C to 40 °C) for aqueous lactate solutions. To better understand this kinetic reaction regime, we conducted experiments to characterize the impact of water and lactate concentrations and temperature on the hydrolysis of methyl lactate and ethyl lactate.

EXPERIMENTAL SECTION

Chemicals. Methyl lactate (98%) and ethyl lactate (98%) were purchased from Sigma-Aldrich. HPLC-grade water was purchased from Fisher Chemical. 200 proof ethanol was purchased from Decon Laboratories. Methanol (99.8%) was purchased from VWR international. Lactic acid was purchased from Asta-Tech as a 95% syrup. All chemicals were used as received.

Experimental Procedure. For each set of experiments, three samples of 20 mL solutions of 15%, 30%, 45%, 60%, and 80% by weight of alkyl lactate in HPLC-grade water were prepared in 20 mL borosilicate scintillation vials (Table 1). One vial for each concentration was placed in a chemical refrigerator with a set point of 6 °C. A second vial for each concentration was placed in a drying oven with a set point of 40 °C. The final vial was kept on the laboratory benchtop where the ambient temperature was periodically measured to be between 20 °C and 22 °C.

Table 1: Compositions by weight percent and mole percent of the prepared solutions.

Weight % lactate	Mole % methyl lactate	Mole % ethyl lactate
15%	3.0 %	2.6 %
30%	6.9 %	6.2%
45%	12.4 %	11.1%
60%	20.6 %	18.7%
80%	41.0%	37.9%

At pre-determined sampling dates, ~700 μL of solution was withdrawn by plastic pipette and transferred to a chromatography autosampler vial for analysis. Each sample was analyzed by gas chromatography in quadruplicate using an Agilent 7890B gas chromatograph fitted with an HP-FFAP column and a quantitative carbon detector in conjunction with a flame ionization detector. On the same day that samples were analyzed by gas chromatography, an injection of 200 proof ethanol was separately injected to identify changes in gas chromatograph analysis. All injections were of 0.5 μL of sample, with three 8 μL washes in HPLC-grade water. Injection port temperature was kept at 200 °C, with a 50:1 split ratio and a total flow of 163 mL/min of ultra-high purity nitrogen carrier gas (Airgas). For separation, a temperature ramp was used: 50 °C for 1 min, followed by 20 °C/min to 120 °C, then 40 °C/min to 240 °C, and held at 240 °C for the remainder of the run. All chromatographic peaks were integrated automatically in ChemStation, except for the lactic acid peaks which were manually integrated due to extreme tailing. Peak areas were converted to concentrations using a calibration curve of methanol and ethanol in HPLC-grade water. To account for any analysis drift observed, the total carbon measured for any given sampling date was normalized to the total carbon measured on day 0. We rely on an assumption that the carbon balance is closed.

RESULTS

Sample vials were prepared with varying compositions of methyl or ethyl lactate in water and stored in three different temperature conditions (6 °C, 20-22 °C, and 40 °C) allowing

them to react to equilibrium (**Figure 1**. Experimental equilibrium concentrations of methyl (\blacktriangle) and ethyl (\bullet) lactate samples in water.

For all samples, the reaction proceeded to form alcohol and lactic acid as expected, thereby decreasing the initial lactate concentration as shown in Figure 1. While the room temperature and 40 °C samples reacted quickly such that experimental equilibrium was reached within 150 days, the 6 °C samples are not yet at experimental equilibrium. Further testing is ongoing and these samples are not included in Figure 1.

Within experimental error, no difference in equilibrium concentration was observed between samples of the same starting material and concentration for the samples held at 22°C and 40 °C. Thus, no temperature dependence on equilibrium concentration was observed between these two temperatures for either ethyl lactate or methyl lactate.

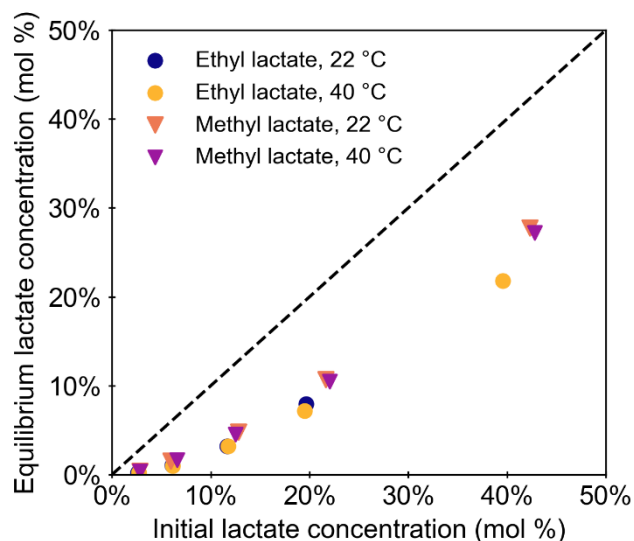


Figure 1. Experimental equilibrium concentrations of methyl (\blacktriangle) and ethyl (\bullet) lactate samples in water. The parity line is shown to illustrate that the equilibrium concentration of lactate is lower than the initial concentration for each sample. For a given starting composition, the equilibrium concentration appears to be temperature independent within this range.

Each vial contained varying initial concentrations of methyl lactate (**Figure 2**) or ethyl lactate (Error! Reference source not found.). As samples were collected over time, the overall reaction rate could be generally determined by chemical analysis of the products. All concentrations of either alkyl lactate stored at 40 °C reacted to equilibrium within 30 days. For alkyl lactates stored at room temperature, all but the most concentrated achieved equilibrium prior to ~150 days. For alkyl lactates stored at 6 °C, none achieved equilibrium after 150 days.

The consumption of methyl lactate over time is shown in Figure 2. Methyl lactate samples ranging from 15% to 80% lactate by weight were stored for ~150 days at 40 °C (**Figure 2A**). At this temperature, the hydrolysis reaction fully equilibrated within 20 days, with measurable production of lactic acid (and concomitant consumption of methyl lactate) in the 15%, 30%, and 45% samples within one day, and all

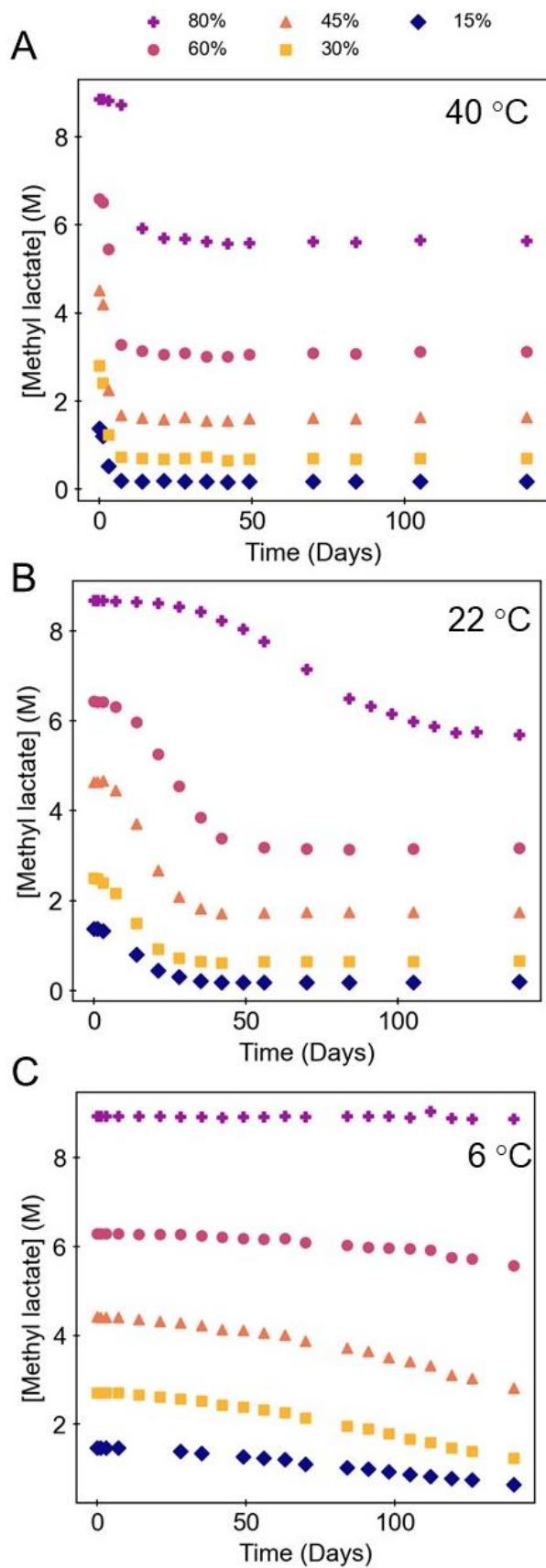


Figure 3. Hydrolysis of methyl lactate in water at 40 °C (A), 22 °C (B), and 6 °C (C) with varying initial concentrations of 80 wt% (+), 60 wt% (●), 45 wt% (▲), 30 wt% (■), and 15 wt% (◆).

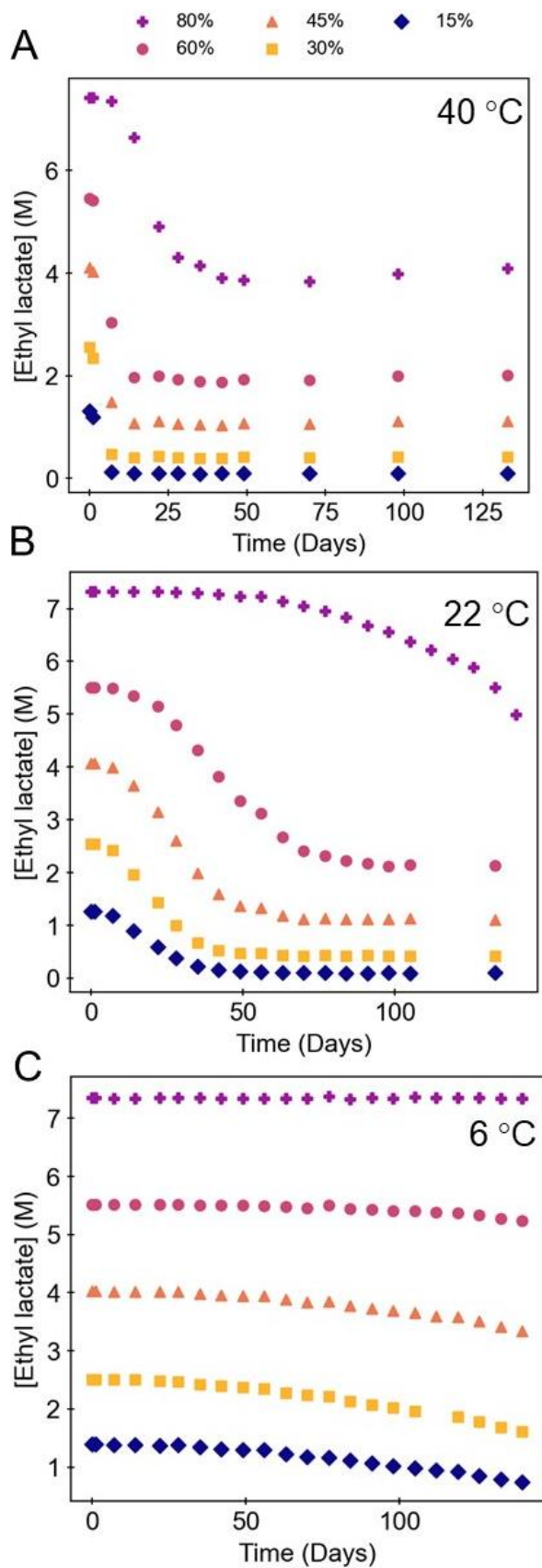


Figure 2. Hydrolysis of ethyl lactate in water at 40 °C (A), 22 °C (B), and 6 °C (C) with varying initial concentrations of 80 wt% (+), 60 wt% (●), 45 wt% (▲), 30 wt% (■), and 15 wt% (◆).

samples showing some hydrolysis within one week. Nearly all samples reached equilibrium compositions by day seven of the analysis, with the most concentrated sample reaching equilibrium at day 14. At 22 °C (**Figure 2B**), the hydrolysis occurred more slowly and with a more pronounced initiation dependence on initial lactate concentration. Most of the samples had begun reacting within one week, but the 80 wt% sample exhibited no quantifiable production of lactic acid until day 21. At 6 °C (**Figure 2C**), the relationship between initial lactate concentration and reaction rate was significant: while the more dilute (15%-45%) samples showed onset of hydrolysis within 14 days, the 60 wt% sample remained stable for 35 days. The 80 wt% sample has shown no signs of hydrolysis as of 140 days after preparation.

The conversion of ethyl lactate with time is depicted in **Error! Reference source not found.** At 40 °C (**Error! Reference source not found.A**), all sample concentrations achieved equilibrium by 30 days, with the lowest ethyl lactate concentration (15 wt%) reaching equilibrium in fewer than 10 days. For samples stored at 22 °C (**Error! Reference source not found.B**), samples with ethyl lactate concentrations of 80 wt% or lower reacted to equilibrium within 100 days, while the 80 wt% sample has not reached equilibrium within 150 days. As in the methyl lactate system, the equilibrium concentration of ethyl lactate is determined not by temperature in the 20-40°C range, but by starting ethyl lactate concentration. For samples stored at 6 °C (**Error! Reference source not found.C**), no detectable change in ethyl lactate in water (80 wt%) was observed for the entire experiment, while lower ethyl lactate concentrations were observed to slowly react with minimal conversion over the first 150 days of study.

As described, the reactions proceeded to form alcohol and lactic acid with time, but the observed reaction kinetics exhibited complex behavior. All of the reactions at 6 °C and room temperature along with some of the high concentration ethyl lactate samples at 40 °C exhibited an initial period of stability with negligible change in lactate concentration within experimental error.. The duration of this initial stable period varied with both temperature and lactate concentration in water; lower temperatures and higher lactate concentrations increased this period of initial stability.

It should be noted that while the experimental solutions were prepared with even increments of lactate by weight percent, the molar composition of these solutions varies less smoothly, which may account for the drastically different behaviors exhibited by the 60 wt% (~20 mol%) samples as compared to the 80 wt% samples (~40 mol%). We hope to fill gaps in this region at the higher concentrations.

We also note the difference in reactivity between the methyl and ethyl lactate samples at high concentrations, particularly at lower temperatures. Despite being at a lower lactate molar concentration, i.e. greater reactivity as shown by Figures 2 and 3, 80wt% ethyl lactate remains stable for two weeks longer than 80wt% methyl lactate at 22 °C (**Figure 4**). This effect also persists for other concentrations of ethyl lactate, though not in as pronounced a fashion, suggesting that size of alkyl chain may have an impact on rate of initiation/neutral hydrolysis.

CONCLUSIONS Methyl lactate and ethyl lactate undergo spontaneous hydrolysis in aqueous solution which begins at

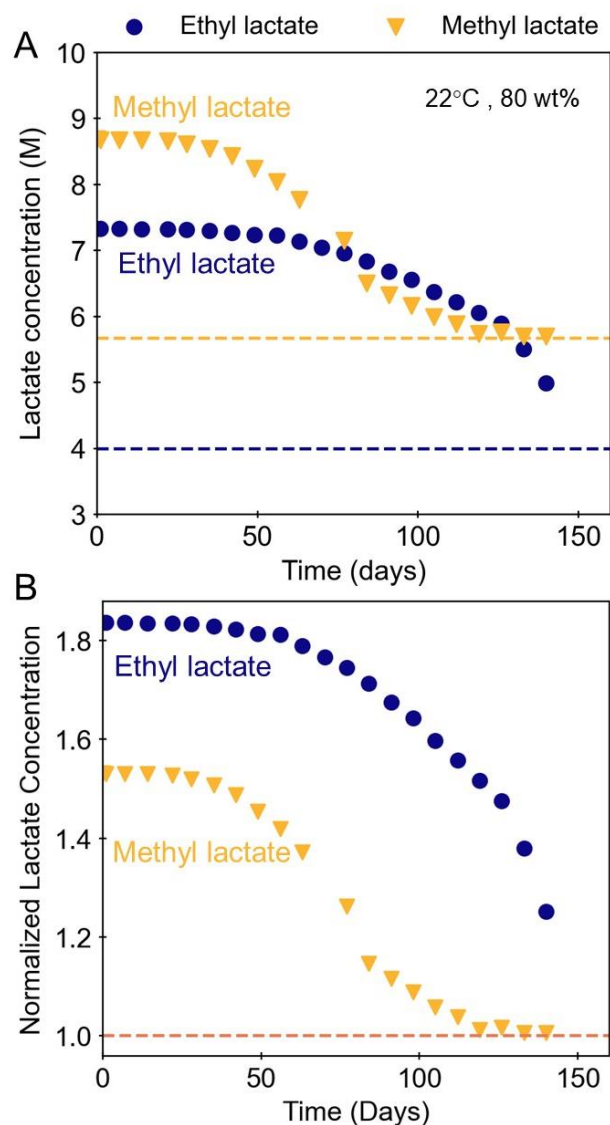


Figure 4. 80 wt% methyl (\blacktriangle) and ethyl (\bullet) lactate samples at 22 °C. (A) Molar concentration over time, where the dashed lines represent the equilibrium expected equilibrium concentration of the lactate as predicted by the relevant equilibrium concentration at 40 °C. (B) Molar concentration normalized to equilibrium compositions. The dashed line at 1.0 represents the expected equilibrium concentration of the lactate as predicted by the relevant equilibrium concentration at 40 °C.

neutral conditions. As the hydrolysis reaction progresses, the production of lactic acid acts to accelerate the reaction as an autocatalytic system that continues until the system reaches equilibrium with the reverse esterification reaction. The length of time within the neutral hydrolysis regime is dependent on both the temperature and composition of the solutions, with higher temperatures and lower lactate-to-water ratios promoting faster initiation. Lastly, we see an impact of the alkyl chain length on the initiation / neutral hydrolysis regime, with the longer ethyl chain showing a longer hydrolysis timeframe than the shorter methyl chain.

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Author Contributions

The manuscript was written through contributions of all authors. / All authors have given approval to the final version of the manuscript. / SB planned and executed the experiments, analyzed and visualized the data, developed the kinetic model, and performed the optimization and fitting. / IM executed the experiments and analyzed the data. / MM executed the experiments. / BRH and LEM conceptualized the study. PJD provided resources and supervision and analyzed data. CPN conceptualized the study, analyzed data, administered the project and acquired funding.

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Notes

The authors declare the following competing financial interest(s): Paul Dauenhauer and Christopher Nicholas co-founded and hold equity in Låkril Technologies. All opinions expressed in this paper are the authors' and do not necessarily reflect the policies and views of DOE, ORAU, or ORISE nor have findings and conclusions been disseminated by the U. S. Department of Agriculture and therefore should not be construed to represent any agency determination or policy.

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