Dual-Regime Reaction Kinetics of the Autocatalytic Hydrolyses of Aqueous Alkyl Lactates

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Abstract: Kinetic description of the hydrolysis of alkyl lactates has been limited to acid-catalyzed conditions despite the spontaneous hydrolysis of methyl lactate and ethyl lactate in aqueous solution. As the reaction progresses, generated lactic acid further catalyzes ester hydrolysis, while the rate of the reverse esterification reaction also increases with the accumulation of acid product. The reaction sequence of lactate hydrolysis is described in three kinetic stages: initiation/neutral hydrolysis, autocatalytic hydrolysis, and equilibrium. The evolution of lactate hydrolysis was measured for varying temperatures (1.5 °C to 40 °C) and initial concentrations of methyl or ethyl lactate (1 to 40 mol%) to quantify the kinetic transitions between reaction stages. Lower temperatures resulted in a distinct induction period where negligible hydrolysis was observed. The effect of initial concentration on the length of the induction period was non-monotonic and was divided into dilute (below about 6 mol% lactate) and concentrated (above about 6 mol%) regimes. Solutions of either lower or higher lactate concentration corresponded to longer induction periods and slower reactions. A dual kinetic regime best describes the observed hydrolysis behavior. For hydrolysis of alkyl lactates below 10 mol%, a rate law derived from the conventional ester hydrolysis mechanism effectively modeled behavior, while at higher lactate concentrations, an additional water molecule must be included in the rate-determining step to appropriately capture the hydrolysis behavior.

Introduction. The 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 chemicals 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 ingredients in pharmaceuticals and personal care products.[14–16]

Alkyl lactates are commonly 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 also 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, respectively)[21,22] relative to lactic acid (b.p. of 260 °C) enables easier separation of the lactic component from the water-rich fermentation broth and reduces the loss of lactic acid due to polymerization or coking that would occur if distillation were used for primary separation.[23–25]

While esterification occurs in the absence of added catalyst due to the autocatalytic effect of lactic acid, acid catalysts promote significant increases in the rate of alkyl lactate production.[26–30] [31,32] This reaction has been characterized to identify new and improved acid catalysts for production of many alkyl lactates, both as target products and for use in the purification of lactic acid described above.

The reverse reaction, ester hydrolysis, has also been studied for methyl lactate, ethyl lactate, and butyl lactate due to the importance of the regeneration of lactic acid following the reactive distillation process. Ester hydrolysis studies are often carried out in the presence of an acid catalyst but like the esterification reaction, ester hydrolysis can also be an autocatalytic system where the accumulating the organic acid product can act to further accelerate the reaction.[33–40]

For our experimental evaluation of the catalytic dehydration of alkyl lactates,[41,42] aqueous 6.9 mol% (30 wt%) solutions of methyl lactate were observed to slowly accumulate significant amounts of alcohol and lactic acid when stored at room temperature. Similar reaction behavior was observed with 6.2 mol% (30 wt%) solutions of ethyl lactate. No acid catalyst was intentionally present in these solutions, nor was lactic acid observed by gas chromatography in the freshly prepared samples (*i.e.*, from the start of sample storage). Spontaneous autocatalytic decomposition of esters via hydrolysis is problematic for chemical storage and transportation, which requires long-term stability to ensure consistent compound quality.

The initial stage of the ester hydrolysis should be described as uncatalyzed hydrolysis, where lactic acid is formed in the absence of an added acid catalyst. The uncatalyzed lactate hydrolysis kinetic stage is minimally described in the literature and is important to understand for the handling and use of lactate materials, particularly for the relatively low temperatures relevant to potential storage conditions (1.5 °C to 40 °C) for aqueous lactate solutions. To kinetically characterize this stage of the reaction, we conducted experiments to quantify the impact of water and lactate concentrations and temperature on the hydrolysis of methyl lactate and ethyl lactate over several weeks to months of reaction time.

Experimental Methods. *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 in water. All chemicals were used as received.

Experimental Procedure. For each initial set of experiments, four samples of 20 mL solutions of 15%, 30%, 45%, 60%, and 80% by weight of alkyl lactate in HPLC-grade water were prepared in borosilicate scintillation vials (Table 1). One vial for each concentration was placed in a chemical refrigerator with a measured temperature of 1.5 °C. The second vial was placed in a chilled water bath maintained at a temperature of 15 °C. A third vial for each concentration was kept on the laboratory benchtop where the ambient temperature was periodically measured to be between 20 °C and 22 °C. The final vial was placed in a drying oven with a set point of 40 °C. As the study progressed, we began to analyze additional samples containing each lactate at 5 and 10 weight percent.

At pre-determined sampling times, ~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 (GC) 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 maintained 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 observed detector analysis drift, the total carbon measured for any given sampling date was normalized to the total carbon measured on day zero.

Results & Discussion. Sample vials were prepared with varying compositions of methyl or ethyl lactate in water and stored in four different temperature conditions (1.5 °C, 15 °C, 22 °C, and 40 °C) allowing them to react to equilibrium, which was defined experimentally as no more than 1% deviation between three consecutive sampling dates, the first of which was then defined to be the time required to reach equilibrium. Each vial contained varying initial concentrations of methyl lactate or ethyl lactate. Samples were collected over time from each vial, and the overall reaction rate was determined by chemical analysis of the measured products. Within experimental error, no difference in equilibrium concentration was observed between samples of the same starting material and concentration for the samples held at 15 ºC, 22 ºC and 40 °C (**Figure 1**). 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 1.5 °C, equilibrium in any sample was only reached after 280-300 days, and data from this temperature was excluded from the quantitative analyses in the remainder of this work. Thus, no temperature dependence on equilibrium concentration was observed across the range of temperatures between 15 ºC and 40 ºC for either ethyl lactate or methyl lactate. This is consistent with prior literature and has been attributed to the small enthalpy of reaction (< 10 kJ/mol).[43,44]

Consumption of methyl lactate over time is shown in **Figure 2**. Methyl lactate samples ranging from 5% to 80% lactate by weight were stored for ~150 days at 40 °C. At this temperature, the hydrolysis reaction fully equilibrated within 20 days, with measurable production of lactic acid (and concomitant conversion of methyl lactate) in the 15%, 30%, and 45% samples within one day; all samples exhibited some measurable hydrolysis within one week. At 22 °C, hydrolysis occurred more slowly and with a more noticeable initiation dependence on initial lactate concentration. Samples at 45% and lower lactate had begun reacting within one week, but the 80 wt% sample exhibited no quantifiable production of lactic acid until day 21. Samples kept at 15 °C followed a similar trend as those at 22 °C, but with a longer induction period and time to reach equilibrium.

At 1.5 °C, the relationship between initial lactate concentration and reaction initiation 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 showed no signs of hydrolysis until day 160. Samples from 15-60 wt% achieved equilibrium between days 300-340, while the 80 wt% sample is not near equilibrium as of day 380.

Conversion of ethyl lactate with time depicted in **Figure 3** showed similar reaction behaviors with that of methyl lactate. At 40 °C, all sample concentrations achieved equilibrium by 30 days, with the fastest sample (30 wt%) reaching equilibrium in fewer than 14 days. For samples stored at 22 °C, samples with ethyl lactate concentrations of 80 wt% or lower reacted to equilibrium within 100 days. The 80 wt% sample reached equilibrium at 220 days after sample preparation. At 15 °C, as was the case with methyl lactate, samples followed a similar trend as those at 22 °C, but with a longer induction period and time to reach equilibrium. For samples stored at 1.5 °C, no detectable change in ethyl lactate in water (80 wt%) was observed for the entire experiment (380 days), while lower ethyl lactate concentrations were observed to slowly react with only the 15-45 wt% samples reaching equilibrium by day 340. For all ethyl lactate samples, slower reactions were observed versus the methyl lactate sample of the same concentration.

As illustrated in **Figures 2** and **3**, the reactions proceeded to form alcohol and lactic acid with time, but the observed reaction kinetics were complex. All of the samples at 1.5 to 22 °C along with some of the high concentration ethyl lactate samples at 40 °C exhibited an initial period of ester stability with negligible change in lactate concentration within experimental error. The duration of this initial stable period, as well as the time required to react to equilibrium, varied with both temperature and lactate concentration in water; lower temperatures and higher lactate concentrations appeared to increase the period of initial stability and lengthen the time to reach equilibrium. However, the dependence of the initial stable period on concentration was not monotonic. In particular, the 30 wt% methyl lactate samples at 22 °C both (1) began reacting and (2) reached equilibrium earlier than both the 15% and 45% samples. To further investigate this phenomenon, four new vials were prepared for each alkyl lactate: concentrations of 5 and 10 wt%, each kept at 22 and 40 °C. These dilute samples reached equilibrium after the samples of 15 wt% (**Figure 4**).

Model Development. To fit the experimental data to a kinetic model for analysis, we began by deriving a mechanistic kinetic model. The proposed mechanism for acid-catalyzed lactate ester hydrolysis discussed in the literature is shown in Scheme 2. Hydrolysis is proposed to occur through a three-step process comprising: (1) protonation of the carbonyl oxygen, (2) attack of water onto the carbonyl carbon forming a tetrahedral intermediate which then collapses to yield alcohol and protonated lactic acid, followed by (3) deprotonation of the carbonyl oxygen. Typically, all protonation/deprotonation steps as well as the elimination of alcohol from the tetrahedral intermediate are thought to be rapid and therefore typically kinetically neglected. The reported rate-limiting step in all systems is the attack of water on the protonated ester to form the protonated acid (step 2), which is quickly deprotonated in step 3 by water present in solution (or the alcohol generated from the hydrolysis) to yield the uncharged acid.[36,45,46]

In our uncatalyzed reaction system, the hydronium ion present in the first step could conceivably come from two separate sources: (1) from lactic acid, or (2) from the autoionization of water. The autoionization pathway is often neglected in studies where an acid catalyst is added, as water is a much weaker acid (pKa=14.0 at 25 °C) than lactic acid (pKa= 3.86).[47] However, in cases of neutral hydrolysis as described in this work, the contribution of water autoionization which initiates the reaction cannot be neglected.

The concentration of hydronium ion present in solution is represented by equation 1 by assuming the acid catalysis of lactate hydrolysis occurs as a result of a solvated acidic proton.

$$[\mathrm{H_3O^+}] = \sqrt{\mathrm{K_w}}[\mathrm{H_2O}] + \sqrt{\mathrm{K_{a,Lactic}}[\mathrm{CH_3CH(OH)COOH}][\mathrm{H_2O}]} \qquad (1)$$

The simplest rate law predicted by the mechanistic argument of Scheme 2 incorporating forward and backward reactions leading to equilibrium then takes the general form shown in equation 2,

$$\frac{-\mathrm{d[ML]}}{\mathrm{dt}} = k_0\left(\frac{[\mathrm{H_3O^+}]}{[\mathrm{H_2O}]}\right)\left([\mathrm{ML}][\mathrm{H_2O}] - \frac{[\mathrm{MeOH}][\mathrm{LA}]}{\mathrm{K_{eq}}}\right) \qquad (2)$$

where ML is methyl lactate, MeOH is methanol, and LA is lactic acid. K_{eq} in equation 2 is the concentration-based equilibrium constant (equation 3).[37,40] A full derivation of equations 1 and 2 is available in the Supporting Information. For this and all rate laws discussed in this work, ethyl lactate (EL) and ethanol (EtOH) can be substituted into the equation without altering the form of the rate law. The kinetic rate constant k_0 represents the overall effect of the hydronium term, which can be further decomposed into rate constants k_n to model the hydronium concentration if not directly measured.

For all rate laws presented here, differential rate expressions were integrated to calculate the predicted composition of reactants and products with time; integration was conducted numerically by a fifth-order implicit Runge-Kutta method of Radau IIA family, using the SciPy library in Python 3.11.[48] The calculated molar concentrations of alkyl lactate were then compared with the experimentally measured values. For an objective function, we utilized the sum of the squared differences in the fit to our experimental data normalized to the initial lactate concentration and divided the resulting sum by the number of iterations performed by the optimization algorithm. Objective function *F* as represented in equation 4 was minimized for each model by adjusting parameters k_n using the Simplex-Nelder-Mead method and the SciPy Python library. These minimizations were sensitive to the initial parameter values, possibly indicating a function with many local minima. To verify that the models were accessing global minima of the objective function, the Basin-hopping method of the SciPy library was also used for models where the qualitative fit was deemed appropriate.

$$\mathrm{K_{eq}} = \frac{[\mathrm{MeOH}][\mathrm{LA}]}{[\mathrm{ML}][\mathrm{H_2O}]} \qquad (3)$$

$$F = \frac{\left(\sum^{all\ samples}\frac{([\mathrm{Lactate}]_{\mathrm{calc}} - [\mathrm{Lactate}]_{\mathrm{experimental}})^2}{[\mathrm{Lactate}]_{\mathrm{experimental}}}\right)}{number\ of\ iterations} \qquad (4)$$

We initially modeled methyl lactate consumption using equation 5, hereafter referred to as the ‘mechanistic model.’ This equation assumes that the reaction is first order in water from the auto-ionization reaction pathway, and half order in water from the lactic acid pathway. The derivation is provided in the Supporting Information. As shown in **Figures 5** and **6**, this equation provides an adequate fit for methyl and ethyl lactate samples of 5-15 wt% of ester, which are common conditions for studies of neutral ester hydrolysis. Equation 5 holds all the way to 30 wt% lactate in the methyl system. For samples at 45 and 60 wt%, the mechanistic model underestimated the duration of the induction period and overestimated the rate of reaction overall **(Figures 7 and S1)**.

$$\frac{-d[\mathrm{ML}]}{dt} = \left(k_1 + k_2\sqrt{\frac{[\mathrm{LA}]}{[\mathrm{H_2O}]}}\right)\left([\mathrm{ML}][\mathrm{H_2O}] - \frac{[\mathrm{MeOH}][\mathrm{LA}]}{K_{eq}}\right) \tag{5}$$

The two mechanisms proposed in equation 5 account for lactic-acid catalyzed reactions (which should be faster with more lactate molecules present) and for catalysis from the autoionization of water (which should be faster with more water present). However, the per-molecule contribution of hydronium ion from lactic acid is 10 orders of magnitude higher than that of water, and thus the rate of the lactic acid contribution should be orders of magnitude greater than the rate caused by water dissociation, thereby predicting a monotonic increase in reaction rate with an increase in lactate concentration. The experimental data presented in this work do not behave this way: the hydrolysis reaction is slower at both highly dilute and highly concentrated conditions. This reaction behavior observed in our experiment has, to our knowledge, not been previously described in the literature.

We also evaluated the rate law shown in equation 6, which has been previously used in the literature to model the autocatalytic hydrolysis of formate and acetate esters.[37,40,49] These prior works found optimal fits to experimental data when the contribution of the acid was in the form of undissociated molecular acid, resulting in the difference in the lactic acid term of the hydronium expression. The prefactor here shows a first order dependence on lactic acid, whereas the mechanistic model of equation 5 predicts a ½ order dependence. In equation 6, the water dissociation constant has presumably been incorporated into k_1.

$$\frac{-d[\mathrm{ML}]}{dt} = (k_1 + k_2[\mathrm{LA}])\left([\mathrm{ML}][\mathrm{H_2O}] - \frac{[\mathrm{MeOH}][\mathrm{LA}]}{K_{eq}}\right) \tag{6}$$

This model, hereafter referred to as the 'literature model,' was also found to effectively fit the experimental data for ethyl lactate samples at or below 15 wt%, or below 30 wt% for methyl lactate (**Figure S2**). These samples are sufficiently dilute that the water concentration was relatively constant over the course of the experiment, decreasing by no more than 5%. In equation 6, water is approximated as constant and incorporated into the rate constants k_1 and k_2. Jogunola and coworkers applied equation 6 to analyze methyl and ethyl formate systems containing a molar ratio of water to ester of 1.8, although the hydrolysis experiments described in those works were conducted with methyl or ethyl formate at much higher temperatures (~60-110 °C) than used here.[37]

Samples at 45 wt% (12 mol%) lactate and above showed a marked decrease in water content over the course of reaction over 70 days **(Figure S3)**. The deviations from this model become increasingly apparent at these higher lactate concentrations. Equations 5 and 6 (the mechanistic and literature models, respectively) still exhibited the qualitative sigmoidal shape of the lactate decay for these more concentrated lactate samples but do not accurately capture the variation in the duration of the initially flat induction period as a function of initial solution composition (**Figures 7 and S1)**

The above models in equations 5 and 6 fail to represent our experimental data when the initial ratio of water to methyl lactate molecules decreased below 15:1 or in the case of ethyl lactate, below 35:1. This suggests (1) that the reaction can become water-limited at lower water to lactate ratios and (2) that the sterics of the ester alkyl group may be a factor in determining where this transition between regimes occurs (**Figure S4**). This may be due to water's role as a proton shuttle required for the assumed-fast protonation and deprotonation steps of scheme 2, or the need for clusters of water to favorably solvate a proton.

One potential explanation for the apparent suppressive effect of higher lactate concentrations on the hydrolysis rate is that the lactic acid product may be prone to dimerizing in a water-scarce regime, either in the linear form or as the cyclic lactide. While small amounts of lactide were indeed present in some samples kept at lower temperatures, gas chromatography analysis indicated that the molar ratio of lactic acid to cyclic or linear lactic acid oligomers was always at least 250:1 (**Figure S5)**. Gas chromatography analysis further confirmed that the cyclic dimer, lactide, did not spontaneously hydrolyze upon injection, supporting an assumption that the lactide measured in the experimental chromatograms is an accurate representation of any lactide present in the experimental reaction solution. Based on this, we do not believe oligomerization plays a significant role in controlling the reaction rate, and thus it is not represented in the proposed rate laws.

Since oligomers do not appear to explain behavior of high lactate concentration solutions, we examined a kinetic reaction model where a second water molecule is required to facilitate the formation and/or collapse of the tetrahedral intermediate in the rate determining step, yielding the general form of equation 7, the derivation of which is provided in the Supporting Information. This addition is supported by various empirical and computational studies of other esters.[50–54]

$$\frac{-\mathrm{d[ML]}}{\mathrm{dt}} = k_0\left(\frac{[\mathrm{H_3O^+}]}{[\mathrm{H_2O}]}\right)\left([\mathrm{ML}][\mathrm{H_2O}]^2 - \frac{[\mathrm{MeOH}][\mathrm{LA}][\mathrm{H_2O}]}{\mathrm{K_{eq}}}\right) \tag{7}$$

This modification correctly modeled the behavior of samples at higher lactate concentrations (>45 wt%). Between 15 and 60 wt% methyl lactate, the best fit to the experimental data arises from the assumption, as in the literature model, that undissociated lactic acid acts as the acid catalyst, as well as assuming the autoionization of water requires three water molecules. Incorporating these assumptions yields the rate law shown in equation 8, hereafter referred to as the 'two-water molecular acid' model. This modification makes the model effective for the widest range of concentrations yet: 15-60 wt% for both alkyl lactates at 22 °C, with even 5 wt% samples passably fitting the model (**Figures 8 and S6**). However, this equation does not qualitatively predict the presence of induction periods at the low concentrations (<15 wt%).

$$\frac{-d[ML]}{dt} = (k_1[H_2O] + k_2[LA])\left([ML][H_2O]^2 - \frac{[MeOH][LA][H_2O]}{K_{eq}}\right) \tag{8}$$

At concentrations below 15 wt% alkyl lactate, the fit is further improved by assuming that lactic acid catalyzing the reaction does so primarily through the solvated acidic proton (**Figure 9)** This yields equation 9, analogous to equation 5, hereafter referred to as the 'two-water dissociated acid' model,

$$\frac{-d[ML]}{dt} = \left(k_1 + k_2\sqrt{\frac{[LA]}{[H_2O]}}\right)\left([ML][H_2O]^2 - \frac{[MeOH][LA][H_2O]}{K_{eq}}\right) \tag{9}$$

The lactate ester hydrolysis system at the conditions studied is sufficiently complicated that without independently monitoring hydronium concentration, it cannot be described with one model across all concentrations, as the relative importance of molecular and dissociated lactic acid species change with water concentration, lactate concentration, and time. With the current data set, it is challenging to distinguish the effect of high concentrations of lactate from the effect of low concentrations of water. Further experiments using a non-reactive diluent solvent would be necessary to decouple the observations we have made in this work. We also note the poor model fits to samples of 80 wt% lactate and hypothesize there may be a third kinetic regime requiring a third water molecule in the rate-determining step.

Temperature Dependence. The optimal k_1 and k_2 values for the models found to adequately represent the data for the appropriate regimes for each lactate were fit to the linearized Arrhenius equation (**Figures S7 and S8**) to obtain activation energies and pre-exponential factors for each reaction pathway. These results for methyl lactate are represented in Table 2, and those for ethyl lactate are shown in Table 3. Parameters were calculated from fitting the various models to the appropriate data as indicated in the table.

In the analysis of methyl lactate, all four considered models were in strong agreement regarding the activation barrier for the acid-catalyzed pathway (k_2), with three of the four models also yielding comparable values for the energy of activation of the neutral pathway (k_1). The literature model, equation 6, predicts an energy of activation approximately 20 kJ/mol lower than the other three models tested.

The models applied to the more dilute ethyl lactate samples (eqs. 5,6, and 9; <15 wt%) showed consistent activation barriers around 63 kJ/mol for the acid-catalyzed pathway. However, eq. 8, the two-water molecular acid model, as applied to 15-60 wt% samples, predicted an activation barrier for this same acid-catalyzed pathway approximately 20 kJ/mol higher. As with methyl lactate, the calculated energies of activation for the neutral pathway agreed across all models except the literature model (eq. 6). The activation energies for neutral hydrolysis are approximately 105±5 kJ/mol and 100±5 kJ/mol for methyl and ethyl lactate, respectively. The activation energies for the acid-catalyzed hydrolysis pathway are 71±2 kJ/mol and 62±3 kJ/mol for methyl and ethyl lactate, respectively (**Figure S9)**. Values for acid-catalyzed hydrolysis determined here are consistent with literature reports based on the study of the reverse esterification reaction.[31,44,55]

Conclusions. Methyl lactate and ethyl lactate undergo spontaneous hydrolysis in aqueous solution. The relative mole fractions of water and lactate determine the rate of hydrolysis, and we show here that the autocatalyzed hydrolysis reaction is slower at both highly dilute and highly concentrated conditions. Solutions at all concentrations studied here (5%-80 wt% lactate in water) exhibited an initial period of stability with negligible change in lactate concentration followed by an acid-catalyzed autocatalysis stage once lactic acid had been produced. Acid catalysis was the dominant reaction until equilibrium among lactate, water, alcohol, and lactic acid was reached.

As the hydrolysis reaction progressed, the production of lactic acid acted to accelerate the reaction as an autocatalytic system that continued until the system reached equilibrium with the reverse esterification reaction. The rate of hydrolysis was dependent on the relative concentration of water and lactate initially present in the system. At lower lactate concentrations, we showed that a kinetic model (the one- or two-water dissociated acid model) where the reaction was catalyzed by a solvated proton from dissociated lactic acid fits the data best. At higher lactate concentrations, the best fitting kinetic model (the two-water molecular acid model) was where an additional water molecule participates in the rate-determining step by facilitating the formation and/or collapse of the tetrahedral intermediate. Two possibilities whereby a 2nd water molecule participates in the reaction mechanism are shown in **Figure S10**.

In investigating temperatures from 15ºC to 40ºC, we were able calculate Arrhenius parameters for the water hydrolysis and lactic acid catalyzed pathways. The neutral hydrolysis pathway for each lactate had an activation barrier approximately 40 kJ/mol higher than that of the corresponding acid-catalyzed pathway. Quantitative analysis and modeling were not performed for samples kept at 1.5 ºC, as equilibrium in some samples has not been reached after a full year after preparation.

Both methyl lactate and ethyl lactate show the same kinetic behavior although slower reactions were observed for ethyl lactate samples versus the same concentration methyl lactate sample. This work kinetically characterizes the spontaneous autocatalytic decomposition of lactate esters via hydrolysis, describing two distinct regimes with different kinetic behavior. The results of this work offer solutions for chemical storage and transportation, showing that low storage temperature or low water concentration ensure long-term lactate ester stability.

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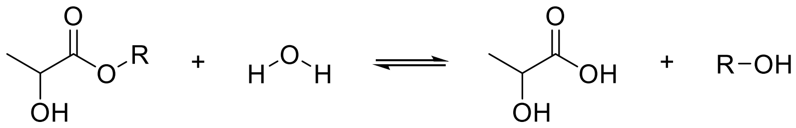
Author Contributions. The manuscript was written through contributions of all authors. / All authors have given approval to the final version of the manuscript. / SAB planned and executed experiments, analyzed and visualized the data, developed the kinetic models, and performed the optimization and fitting. / IAM executed experiments and visualized the data. / MAM executed 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.

Supporting Information: 10 additional figures, 2 additional schemes, and 16 equations (PDF)

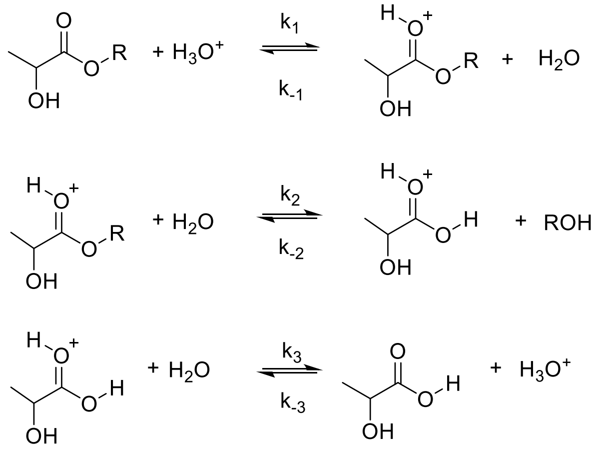
Acknowledgements. This material is based upon work that is supported by the National Institute of Food and Agriculture, U.S. Department of Agriculture Small Business Innovation Research (SBIR) Program, under award number 2022-33530-36988. This work was also supported in part by the farm families of Minnesota and their corn check-off investment (3098-23UT). CPN was supported in part by an appointment with the Chain Reaction Innovators Program sponsored by the U.S. Department of Energy (DOE), Office of Energy Efficiency and Renewable Energy (EERE), and Advanced Materials and Manufacturing Technologies Office (AMMTO). This program is administered by the Oak Ridge Institute for Science and Education (ORISE) for the DOE. ORISE is managed by ORAU under DOE contract number DE-SC0014664. SAB was supported in part by the University of Minnesota NSF Center for Sustainable Polymers under grant number CHE-1901635. The authors thank Jesse Canavan and Jnana Jagana for helping with the optimization; and Justin Hopkins, Tyler Weinstein, James McKone, and Will Collins for valuable discussions regarding possible mechanisms. The authors also thank the Minnesota Supercomputing Institute (MSI) at the University of Minnesota for providing resources for optimization.

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.

Keywords. methyl lactate, ethyl lactate, lactic acid, ester, hydrolysis, methanol, ethanol, autocatalysis



Scheme 1. Lactate hydrolysis yields lactic acid and alcohol.



Scheme 2. Proposed mechanism for acid-catalyzed lactate ester hydrolysis.

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

Weight % lactate	Mole % methyl lactate	Mole % ethyl lactate
5%	0.94%	0.80%
10%	2.0%	1.7%
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%

Table 2. Arrhenius values calculated from various models of methyl lactate hydrolysis.

Model Name	Eq.	Data Range	k_n at 22°C	E_a (kJ/mol)	Prefactor, A
Mechanistic model, k_1	5	5-30%	4.5 x 10^{-5} L mol^{-1} day^{-1}	108.5	8.3 x 10^{14} L mol^{-1} day^{-1}
Mechanistic model, k_2	5	5-30%	1.2 x 10^{-2} L mol^{-1} day^{-1}	70.9	4.0 x 10^{10} L mol^{-1} day^{-1}
Literature model, k_1	6	5-30%	4.2 x 10^{-4} L mol^{-1} day^{-1}	87.7	1.3 x 10^{12} L mol^{-1} day^{-1}
Literature model ,k_2	6	5-30%	1.3 x 10^{-3} L^2 mol^{-2} day^{-1}	72.2	8.9 x 10^{9} L^2 mol^{-2} day^{-1}
2-water dissociated acid model, k_1	9	5-30%	1.1 x 10^{-8} L^2 mol^{-2} day^{-1}	101.8	1.2 x 10^{10} L^2 mol^{-2} day^{-1}
2-water dissociated acid model, k_2	9	5-30%	2.6 x 10^{-4} L^2 mol^{-2} day^{-1}	71.9	1.5 x 10^{9} L^2 mol^{-2} day^{-1}
2-water molecular acid model, k_1	8	15-60%	1.6 x 10^{-7} L^3 mol^{-3} day^{-1}	105.7	8.5 x 10^{11} L^3 mol^{-3} day^{-1}
2-water molecular acid model, k_2	8	15-60%	4.2 x 10^{-2} L^3 mol^{-3} day^{-1}	70.7	1.4 x 10^{8} L^3 mol^{-3} day^{-1}

Table 3. Arrhenius values calculated from various models of ethyl lactate hydrolysis.

Model Name	**Eq.**	**Data Range**	**k_n at 22°C**	**E_a (kJ/mol)**	**Prefactor, A**
Mechanistic model., k_1	5	5-15%	1.0 x 10^{-5} L mol^{-1} day^{-1}	95.1	9.1x 10^{11} L mol^{-1} day^{-1}
Mechanistic model., k_2	5	5-15%	1.3 x 10^{-2} L mol^{-1} day^{-1}	63.3	2.1x 10^{9} L mol^{-1} day^{-1}
Literature model, k_1	6	5-15%	2.2 x 10^{-4} L mol^{-1} day^{-1}	69.0	3.8x 10^{8} L mol^{-1} day^{-1}
Literature model, k_2	6	5-15%	2.4 x 10^{-3} L^2 mol^{-2} day^{-1}	60.1	1.1x 10^{8} L^2 mol^{-2} day^{-1}
2-water dissociated acid model, k_1	9	5-15%	1.1 x 10^{-8} L^2 mol^{-2} day^{-1}	102.1	1.3 x 10^{10} L^2 mol^{-2} day^{-1}
2-water dissociated acid model., k_2	9	5-15%	2.6 x 10^{-4} x L^2 mol^{-2} day^{-1}	64.6	7.2 x 10^{7} L^2 mol^{-2} day^{-1}
2-water molecular acid model, k_1	8	15-60%	1.6 x 10^{-7} L^3 mol^{-3} day^{-1}	95.9	1.6x 10^{10} L^3 mol^{-3} day^{-1}
2-water molecular acid model, k_2	8	15-60%	2.6 x 10^{-2} L^3 mol^{-3} day^{-1}	81.8	9.7x 10^{9} L^3 mol^{-3} day^{-1}

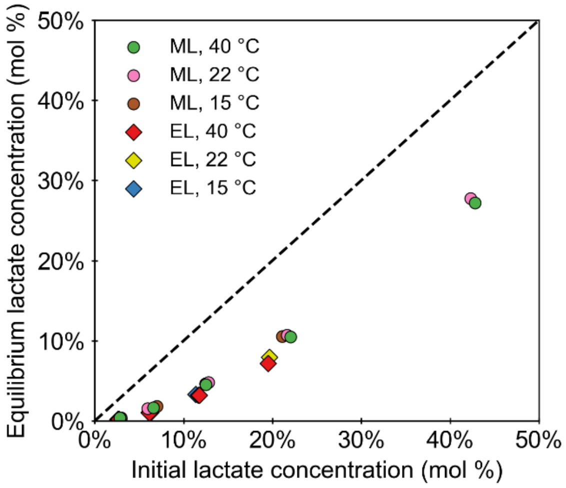


Figure 1. Experimental equilibrium concentrations of methyl (●) and ethyl (■) lactate samples in water. For a given starting composition, the equilibrium concentration appears to be temperature independent within this range.

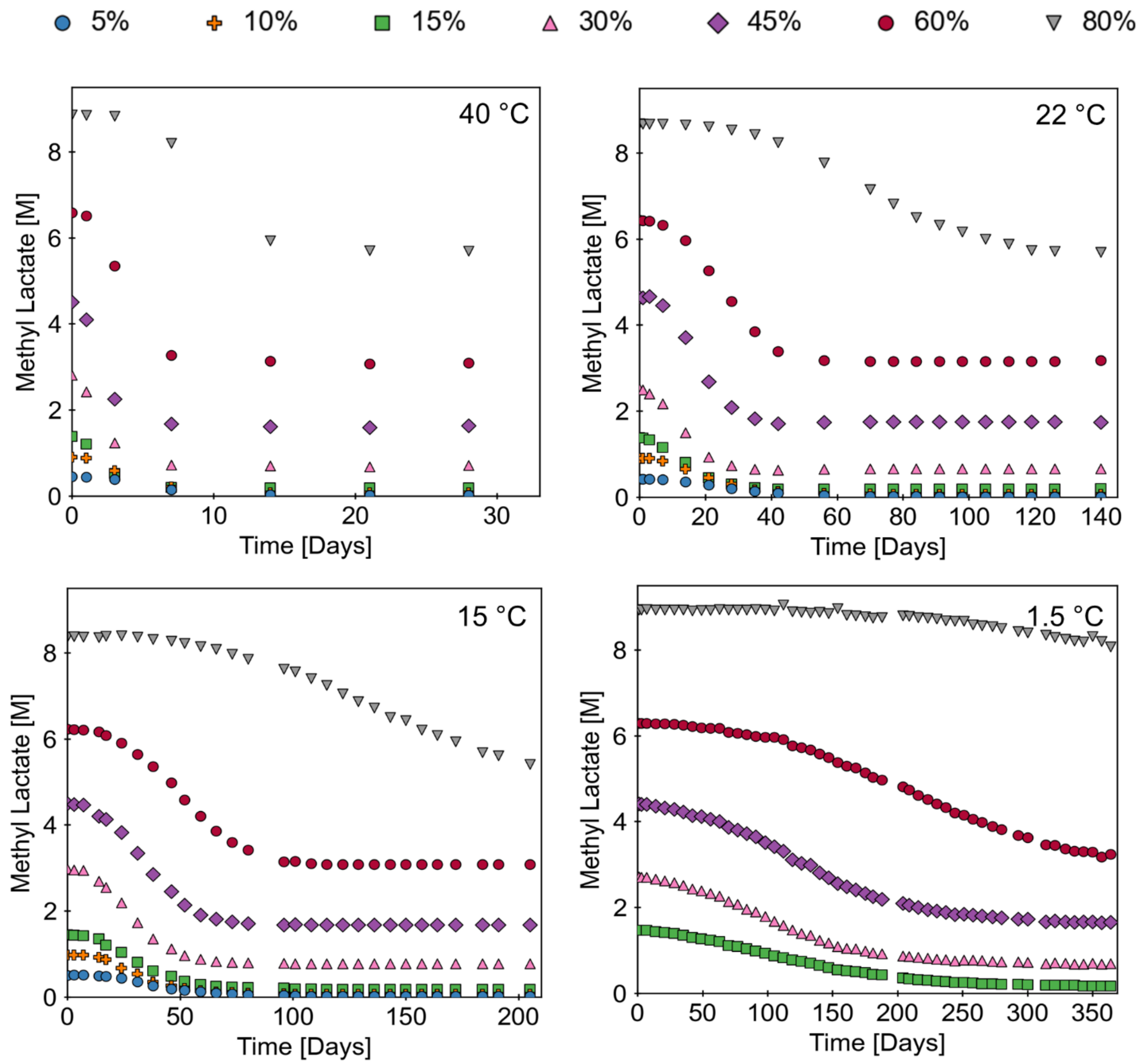


Figure 2. Hydrolysis of methyl lactate in water to form methanol and lactic acid at 40°C, 22°C, 15°C, and 1.5°C with initial concentrations of 5-80 weight percent lactate in water.

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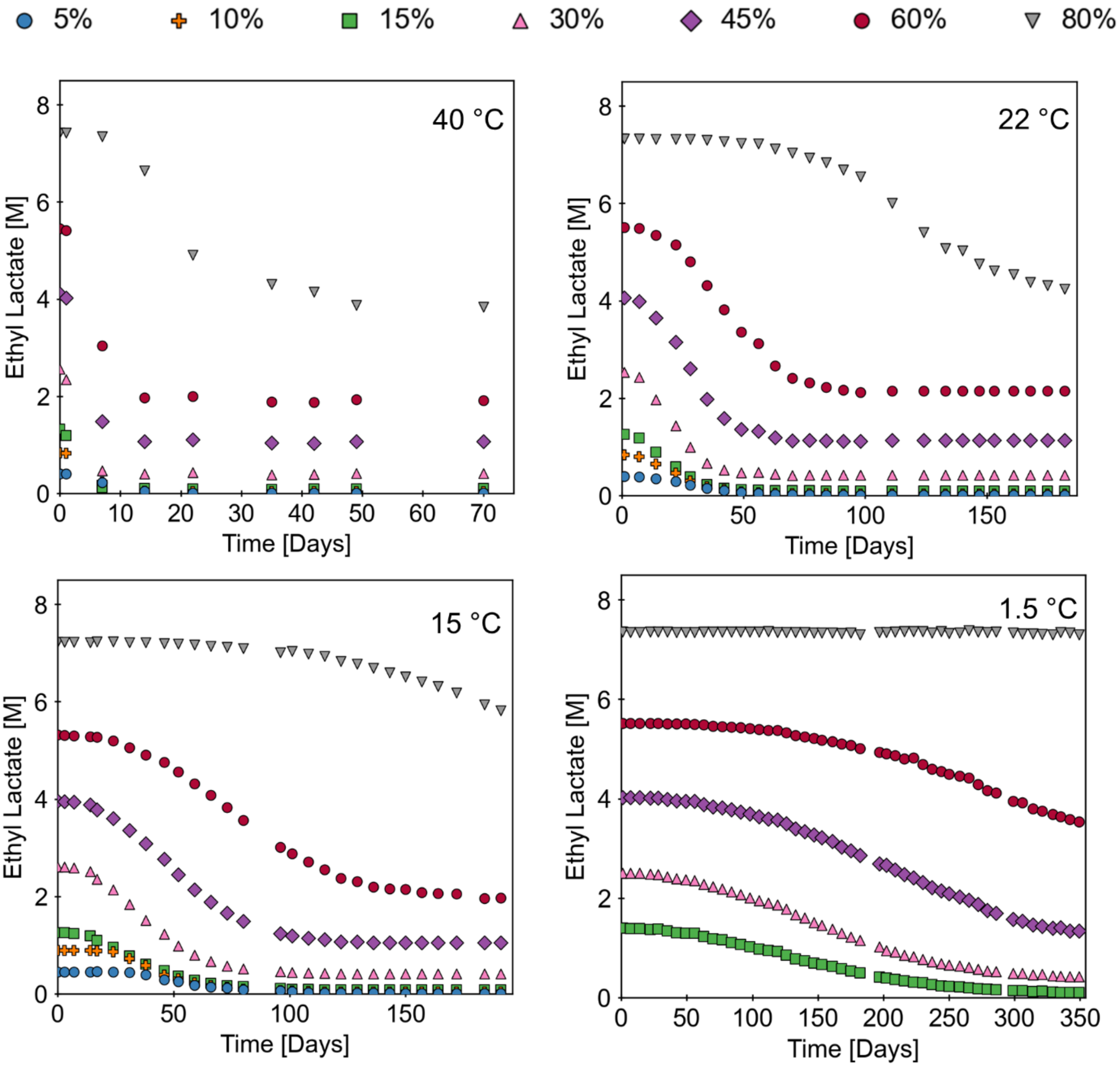

Figure 3. Hydrolysis of ethyl lactate in water to form ethanol and lactic acid at 40°C, 22°C, 15°C, and 1.5°C with initial concentrations of 5-80 weight percent lactate in water.

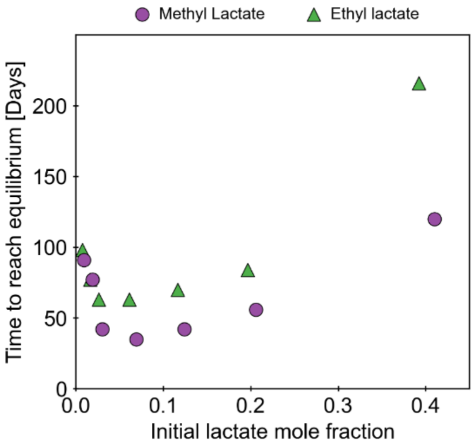

Figure 4. Time needed to react to equilibrium at 22 °C as a function of initial alkyl lactate mole fraction. There is a minimum (indicating a faster rate of reaction) at an initial mole fraction of 0.06 (30 wt%) for methyl lactate, while this minimum is at 0.026 (15 wt%) for ethyl lactate.

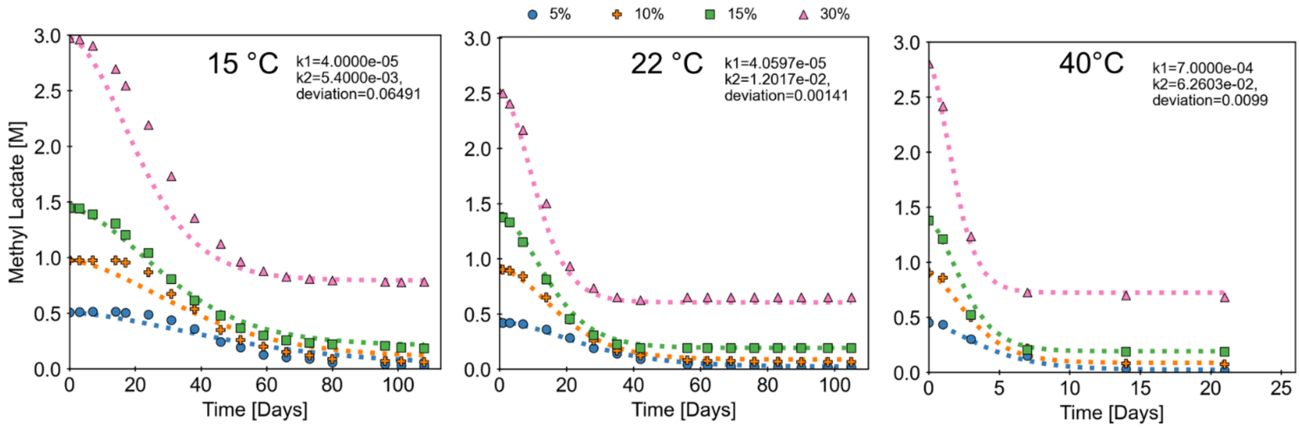

Figure 5. Mechanistic model fits of Equation 5 to low concentrations of methyl lactate at 15ºC, 22ºC, and 40°C. The markers represent experimental measurements and the dashed lines represent the proposed 'mechanistic' model.

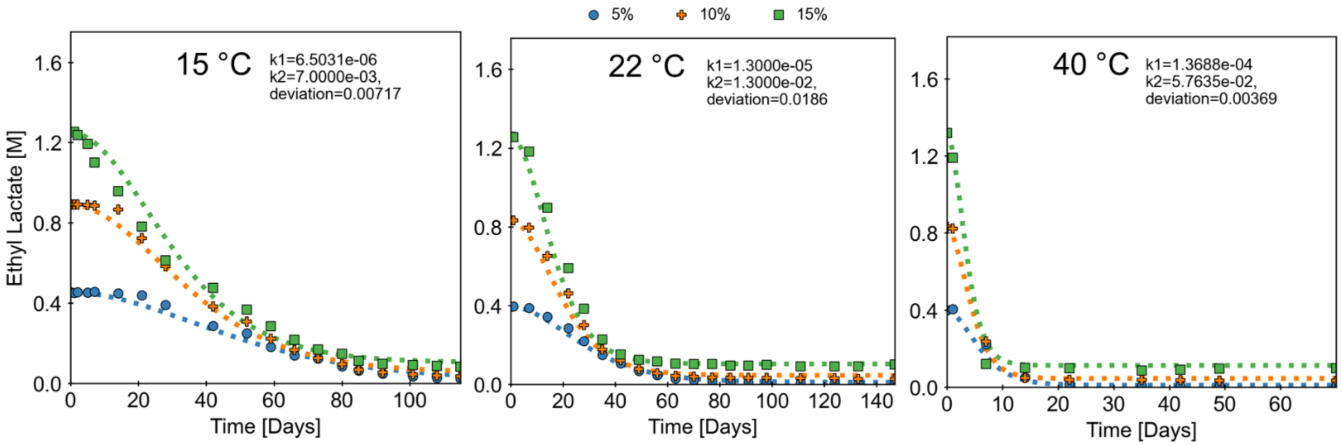

Figure 6. Mechanistic model fits of Equation 5 to low concentrations of ethyl lactate at 15ºC, 22ºC, and 40°C. The markers represent experimental measurements and the dashed lines represent the proposed 'mechanistic' model.

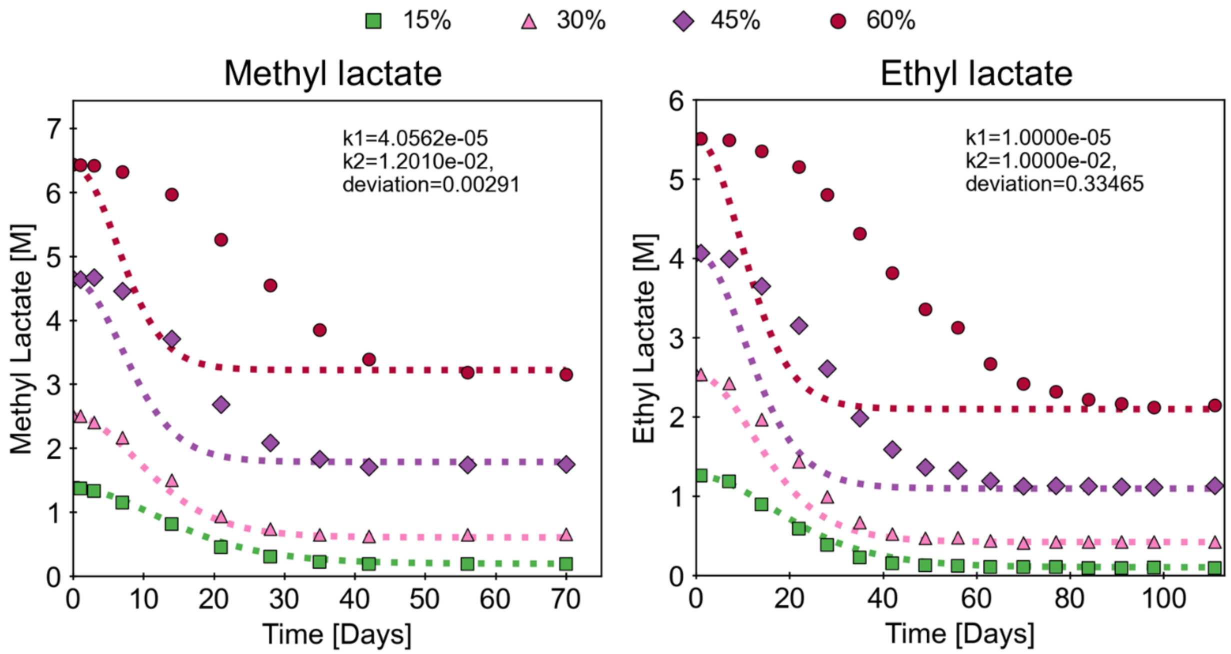

Figure 7. Mechanistic model fits of Equation 5 to mid-to-high concentrations of methyl and ethyl lactate at 22°C. The markers represent experimental measurements and the dashed lines represent the proposed 'mechanistic' model.

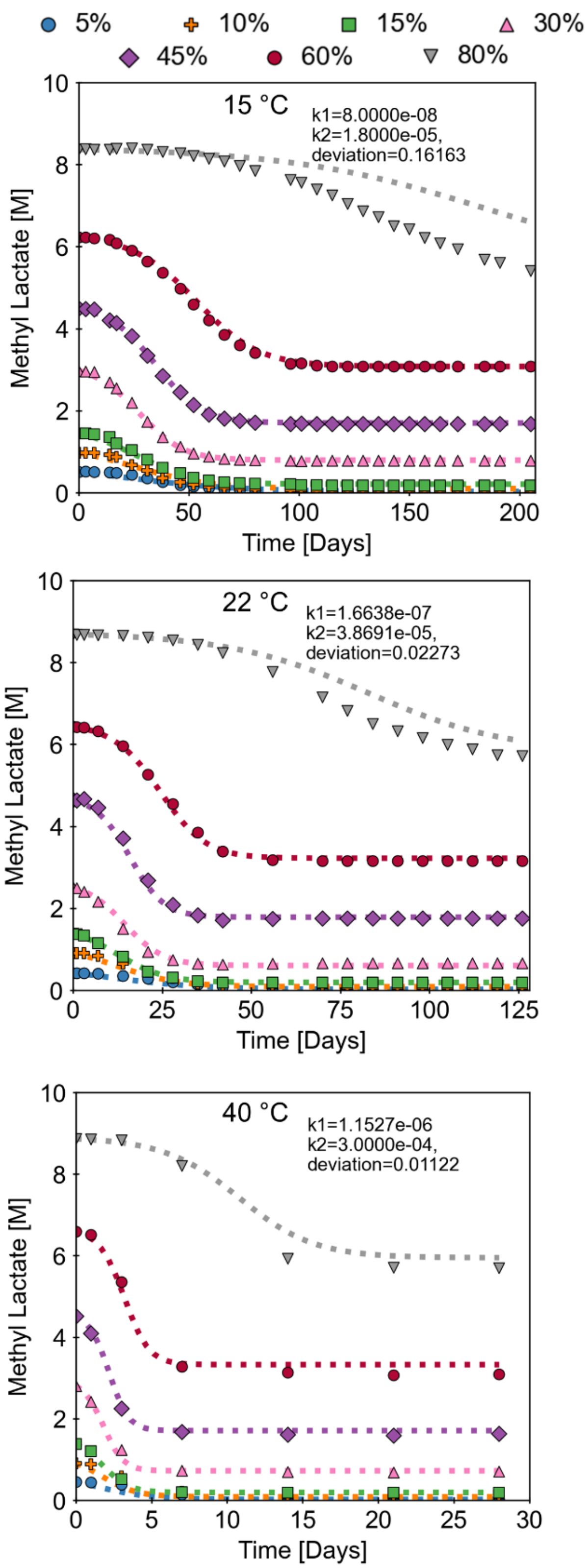

Figure 8. Model fit of Equation 8, the two-water molecular acid model, to concentrations ranging from 5-80wt% methyl lactate at 15ºC, 22ºC, and 40°C.

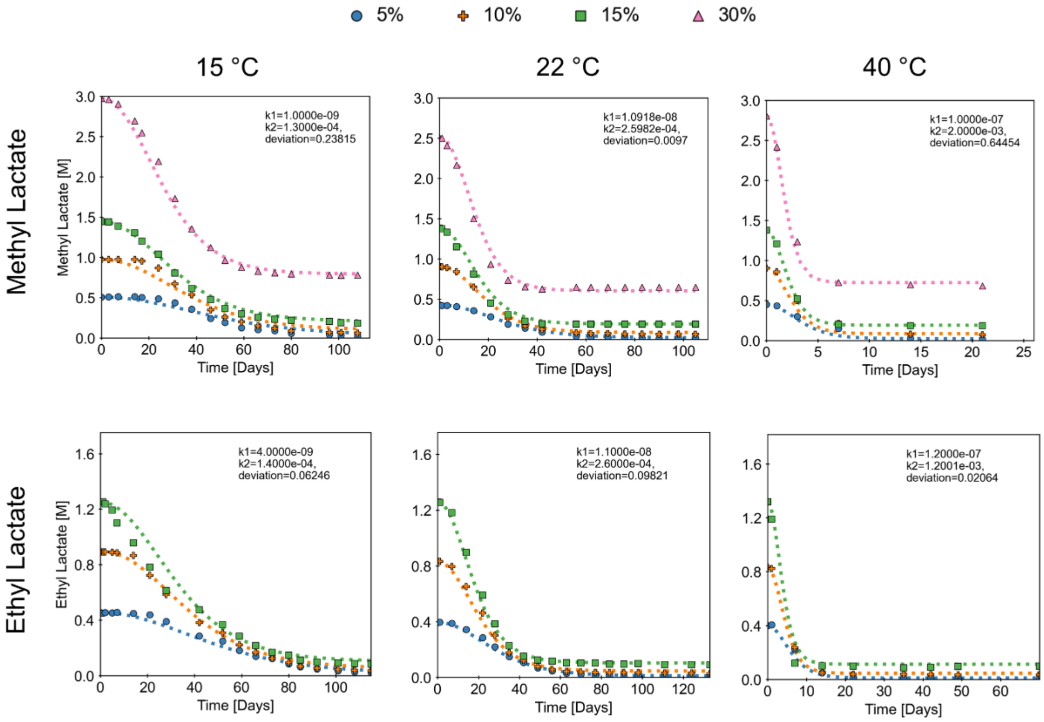

Figure 9. Model fit of Equation 9, the two-water dissociated acid model, to concentrations ranging from 5-30wt% methyl lactate and 5-15wt% ethyl lactate at 15ºC, 22ºC, and 40°C.

References

(1) Anastas, P.; Eghbali, N. Green Chemistry: Principles and Practice. *Chem. Soc. Rev.* **2010**, *39* (1), 301–312. https://doi.org/10.1039/B918763B.

(2) García-Serna, J.; Pérez-Barrigón, L.; Cocero, M. J. New Trends for Design towards Sustainability in Chemical Engineering: Green Engineering. *Chem. Eng. J.* **2007**, *133* (1), 7–30. https://doi.org/10.1016/j.cej.2007.02.028.

(3) Huang, K.; Peng, X.; Kong, L.; Wu, W.; Chen, Y.; Maravelias, C. T. Greenhouse Gas Emission Mitigation Potential of Chemicals Produced from Biomass. *ACS Sustain. Chem. Eng.* **2021**, *9* (43), 14480–14487. https://doi.org/10.1021/acssuschemeng.1c04836.

(4) Kohli, K.; Prajapati, R.; Sharma, B. K. Bio-Based Chemicals from Renewable Biomass for Integrated Biorefineries. *Energies* **2019**, *12* (2). https://doi.org/10.3390/en12020233.

(5) Hessel, V.; Tran, N. N.; Asrami, M. R.; Tran, Q. D.; Long, N. V. D.; Escribà-Gelonch, M.; Tejada, J. O.; Linke, S.; Sundmacher, K. Sustainability of Green Solvents–Review and Perspective. *Green Chem.* **2022**, *24* (2), 410–437.

(6) Zhenova, A. Challenges in the Development of New Green Solvents for Polymer Dissolution. *Polym. Int.* **2020**, *69* (10), 895–901. https://doi.org/10.1002/pi.6072.

(7) Jessop, P. G. Searching for Green Solvents. *Green Chem.* **2011**, *13* (6), 1391–1398. https://doi.org/10.1039/C0GC00797H.

(8) Naser, A. Z.; Deiab, I.; Darras, B. M. Poly (Lactic Acid)(PLA) and Polyhydroxyalkanoates (PHAs), Green Alternatives to Petroleum-Based Plastics: A Review. *RSC Adv.* **2021**, *11* (28), 17151–17196.

(9) Castro-Aguirre, E.; Iñiguez-Franco, F.; Samsudin, H.; Fang, X.; Auras, R. Poly(Lactic Acid)—Mass Production, Processing, Industrial Applications, and End of Life. *PLA Biodegrad. Polym.* **2016**, *107*, 333–366. https://doi.org/10.1016/j.addr.2016.03.010.

(10) Maki-Arvela, P.; Simakova, I. L.; Salmi, T.; Murzin, D. Y. Production of Lactic Acid/Lactates from Biomass and Their Catalytic Transformations to Commodities. *Chem. Rev.* **2014**, *114* (3), 1909–1971.

(11) Zhai, Z.; Li, X.; Tang, C.; Peng, J.; Jiang, N.; Bai, W.; Gao, H.; Liao, Y. Decarbonylation of Lactic Acid to Acetaldehyde over Aluminum Sulfate Catalyst. *Ind. Eng. Chem. Res.* **2014**, *53* (25), 10318–10327. https://doi.org/10.1021/ie500988q.

(12) Murphy, B. M.; Letterio, M. P.; Xu, B. Catalytic Dehydration of Methyl Lactate: Reaction Mechanism and Selectivity Control. *J. Catal.* **2016**, *339*, 21–30. https://doi.org/10.1016/j.jcat.2016.03.026.

(13) Noda, Y.; Zhang, H.; Dasari, R.; Singh, R.; Ozmeral, C.; Román-Leshkov, Y.; Rioux, R. M. Importance of Dimer Quantification for Accurate Catalytic Evaluation of Lactic Acid Dehydration to Acrylic Acid. *Ind. Eng. Chem. Res.* **2017**, *56* (20), 5843–5851. https://doi.org/10.1021/acs.iecr.7b00864.

(14) Paul, S.; Pradhan, K.; R Das, A. Ethyl Lactate as a Green Solvent: A Promising Bio-Compatible Media for Organic Synthesis. *Curr. Green Chem.* **2016**, *3* (1), 111–118.

(15) Pereira, C. S. M.; Silva, V. M. T. M.; Rodrigues, A. E. Ethyl Lactate as a Solvent: Properties, Applications and Production Processes – a Review. *Green Chem.* **2011**, *13* (10), 2658–2671. https://doi.org/10.1039/C1GC15523G.

(16) Karthika, S.; Radhakrishnan, T.; Kalaichelvi, P. Crystallization and Kinetic Studies of an Active Pharmaceutical Compound Using Ethyl Lactate As a Green Solvent. *ACS Sustain. Chem. Eng.* **2019**, *8* (3), 1527–1537.

(17) Kim, Y. J.; Hong, W. H.; Wozny, G. Effect of Recycle and Feeding Method on Batch Reactive Recovery System of Lactic Acid. *Korean J. Chem. Eng.* **2002**, *19* (5), 808–814. https://doi.org/10.1007/BF02706972.

(18) Kumar, R.; Mahajani, S.; Nanavati, H.; Noronha, S. Recovery of Lactic Acid by Batch Reactive Distillation. *J. Chem. Technol. Biotechnol.* **2006**, *81*, 1141–1150. https://doi.org/10.1002/jctb.1444.

(19) Barve, Prashant Purushottam; Kulkarni, Bhaskar Dattatreya; Nene, Sanjay Narayan; Shinde, Ravindra William; Gupte, Milind Yashwant; Joshi, Chandrashekar Narayan; Thite, Gandhali Arun; BHIKU Chivan, Vilas Bhiku; Deshpande, Tushar Ramchandra. Process for Preparing L- (+) -Lactic Acid. US 7820859 B2, October 26, 2010. https://lens.org/069-019-967-071-292.

(20) Miller, Dennis J; Navinchandra, Asthana; Kolah, Aspi; Lira, Carl T. Process for Production of Organic Acid Esters. US7652167B2, January 26, 2010. https://patents.google.com/patent/US7652167B2/en.

(21) Sanz, M. T.; Beltrán, S.; Calvo, B.; Cabezas, J. L.; Coca, J. Vapor Liquid Equilibria of the Mixtures Involved in the Esterification of Lactic Acid with Methanol. *J. Chem. Eng. Data* **2003**, *48* (6), 1446–1452. https://doi.org/10.1021/je034028c.

(22) Vu, D. T.; Lira, C. T.; Asthana, N. S.; Kolah, A. K.; Miller, D. J. Vapor−Liquid Equilibria in the Systems Ethyl Lactate + Ethanol and Ethyl Lactate + Water. *J. Chem. Eng. Data* **2006**, *51* (4), 1220–1225. https://doi.org/10.1021/je050537y.

(23) Filachione, E. M.; Fisher, C. H. Purification of Lactic Acid. *Ind. Eng. Chem.* **1946**, *38* (2), 228–232. https://doi.org/10.1021/ie50434a029.

(24) Su, C.-Y.; Yu, C.-C.; Chien, I.-L.; Ward, J. D. Control of Highly Interconnected Reactive Distillation Processes: Purification of Raw Lactic Acid by Esterification and Hydrolysis. *Ind. Eng. Chem. Res.* **2015**, *54* (27), 6932–6940. https://doi.org/10.1021/ie5039133.

(25) Komesu, A.; Martins Martinez, P. F.; Lunelli, B. H.; Oliveira, J.; Wolf Maciel, M. R.; Maciel Filho, R. Study of Lactic Acid Thermal Behavior Using Thermoanalytical Techniques. *J. Chem.* **2017**, *2017*, 4149592. https://doi.org/10.1155/2017/4149592.

(26) Kamble, S. P.; Barve, P. P.; Joshi, J. B.; Rahman, I.; Kulkarni, B. D. Purification of Lactic Acid via Esterification of Lactic Acid Using a Packed Column, Followed by Hydrolysis of Methyl Lactate Using Three Continuously Stirred Tank Reactors (CSTRs) in Series: A Continuous Pilot Plant Study. *Ind. Eng. Chem. Res.* **2012**, *51* (4), 1506–1514. https://doi.org/10.1021/ie200642j.

(27) Filachione, E. M.; Lengel, J. H.; Fisher, C. H. Preparation of Methyl Lactate. *Ind. Eng. Chem.* **1945**, *37* (4), 388–390. https://doi.org/10.1021/ie50424a024.

(28) Sanz, M. T.; Murga, R.; Beltrán, S.; Cabezas, J. L.; Coca, J. Autocatalyzed and Ion-Exchange-Resin-Catalyzed Esterification Kinetics of Lactic Acid with Methanol. *Ind. Eng. Chem. Res.* **2002**, *41* (3), 512–517. https://doi.org/10.1021/ie010454k.

(29) Troupe, R. A.; Kobe, K. A. Kinetics of Methanol–Lactic Acid Reaction - Reactions with 85% Acid. *Ind. Eng. Chem.* **1950**, *42* (5), 801–810. https://doi.org/10.1021/ie50485a020.

(30) Troupe, R. A.; Kobe, K. A. Kinetics of Methanol–Lactic Acid Reaction. *Ind. Eng. Chem.* **1950**, *42* (7), 1403–1409. https://doi.org/10.1021/ie50487a040.

(31) Delgado, P.; Sanz, M.; Beltrán, S. Kinetic Study for Esterification of Lactic Acid with Ethanol and Hydrolysis of Ethyl Lactate Using an Ion-Exchange Resin Catalyst. *Chem. Eng. J.* **2007**, *126*, 111–118. https://doi.org/10.1016/j.cej.2006.09.004.

(32) Seo, Y.; Hong, W. H. Kinetics of Esterification of Lactic Acid with Methanol in the Presence of Cation Exchange Resin Using a Pseudo-Homogeneous Model. *J. Chem. Eng. Jpn.* **2000**, *33* (1), 128–133. https://doi.org/10.1252/jcej.33.128.

(33) Hawkins, J. E. *Hydrolysis of Esters in Weak Acid-Neutral Salt Solutions*; University of Pennsylvania, 1927.

(34) Ballara, A.; Verdu, J. Physical Aspects of the Hydrolysis of Polyethylene Terephthalate. *Polym. Degrad. Stab.* **1989**, *26* (4), 361–374.

(35) Kallies, B.; Mitzner, R. Models of Water-Assisted Hydrolyses of Methyl Formate, Formamide, and Urea from Combined DFT-SCRF Calculations. *Mol. Model. Annu.* **1998**, *4* (6), 183–196. https://doi.org/10.1007/s0089480040183.

(36) Day, J.; Ingold, C. K. Mechanism and Kinetics of Carboxylic Ester Hydrolysis and Carboxyl Esterification. *Trans. Faraday Soc.* **1941**, *37*, 686–705.

(37) Jogunola, O.; Salmi, T.; Eränen, K.; Wärnå, J.; Kangas, M.; Mikkola, J.-P. Reversible Autocatalytic Hydrolysis of Alkyl Formate: Kinetic and Reactor Modeling. *Ind. Eng. Chem. Res.* **2010**, *49* (9), 4099–4106. https://doi.org/10.1021/ie902031d.

(38) Bánsági, T.; Taylor, A. F. Ester Hydrolysis: Conditions for Acid Autocatalysis and a Kinetic Switch. *Tetrahedron Lett.* **2017**, *73* (33), 5018–5022. https://doi.org/10.1016/j.tet.2017.05.049.

(39) Radell, J.; Brodman, B.; Hirshfeld, A.; Bergmann, E. Acidity and Autocatalysis of Esterification of Acetylenic and Fluoro Acids. *J. Phys. Chem.* **1965**, *69* (3), 928–932.

(40) Jogunola, O.; Salmi, T.; Wärnå, J.; Mikkola, J.-P.; Tirronen, E. Kinetics of Methyl Formate Hydrolysis in the Absence and Presence of a Complexing Agent. *Ind. Eng. Chem. Res.* **2011**, *50* (1), 267–276. https://doi.org/10.1021/ie101045k.

(41) Pang, Y.; Ardagh, M. A.; Shetty, M.; Chatzidimitriou, A.; Kumar, G.; Vlaisavljevich, B.; Dauenhauer, P. J. On the Spatial Design of Co-Fed Amines for Selective Dehydration of Methyl Lactate to Acrylates. *ACS Catal.* **2021**, *11* (9), 5718–5735. https://doi.org/10.1021/acscatal.1c00573.

(42) Pang, Y.; Lee, C.; Vlaisavljevich, B.; Nicholas, C. P.; Dauenhauer, P. J. Multifunctional Amine Modifiers for Selective Dehydration of Methyl Lactate to Acrylates. *JACS Au* **2023**, *3* (2), 368–377. https://doi.org/10.1021/jacsau.2c00513.

(43) Jiang, S.; Liu, M.; Pan, L. Kinetic Study for Hydrolysis of Methyl Lactate Catalyzed by Cation-Exchange Resin. *J. Taiwan Inst. Chem. Eng.* **2010**, *41* (2), 190–194. https://doi.org/10.1016/j.jtice.2009.06.006.

(44) Pereira, C. S. M.; Pinho, S. P.; Silva, V. M. T. M.; Rodrigues, A. E. Thermodynamic Equilibrium and Reaction Kinetics for the Esterification of Lactic Acid with Ethanol Catalyzed by Acid Ion-Exchange Resin. *Ind. Eng. Chem. Res.* **2008**, *47* (5), 1453–1463. https://doi.org/10.1021/ie071220p.

(45) Yates, Keith.; McClelland, R. A. Mechanisms of Ester Hydrolysis in Aqueous Sulfuric Acids. *J. Am. Chem. Soc.* **1967**, *89* (11), 2686–2692. https://doi.org/10.1021/ja00987a033.

(46) Gunaydin, H.; Houk, K. N. Molecular Dynamics Prediction of the Mechanism of Ester Hydrolysis in Water. *J. Am. Chem. Soc.* **2008**, *130* (46), 15232–15233. https://doi.org/10.1021/ja8050525.

(47) O'Neil, M. J.; Royal Society of Chemistry (Great Britain). *The Merck Index : An Encyclopedia of Chemicals, Drugs, and Biologicals*, Fifteenth edition.; Royal Society of Chemistry: Cambridge, UK, 2013.

(48) Virtanen, P.; Gommers, R.; Oliphant, T. E.; Haberland, M.; Reddy, T.; Cournapeau, D.; Burovski, E.; Peterson, P.; Weckesser, W.; Bright, J.; van der Walt, S. J.; Brett, M.; Wilson, J.; Millman, K. J.; Mayorov, N.; Nelson, A. R. J.; Jones, E.; Kern, R.; Larson, E.; Carey, C. J.; Polat, İ.; Feng, Y.; Moore, E. W.; VanderPlas, J.; Laxalde, D.; Perktold, J.; Cimrman, R.; Henriksen, I.; Quintero, E. A.; Harris, C. R.; Archibald, A. M.; Ribeiro, A. H.; Pedregosa, F.; van Mulbregt, P.; SciPy 1.0 Contributors. SciPy 1.0: Fundamental Algorithms for Scientific Computing in Python. *Nat. Methods* **2020**, *17*, 261–272. https://doi.org/10.1038/s41592-019-0686-2.

(49) Pöpken, T.; Götze, L.; Gmehling, J. Reaction Kinetics and Chemical Equilibrium of Homogeneously and Heterogeneously Catalyzed Acetic Acid Esterification with Methanol and Methyl Acetate Hydrolysis. *Ind. Eng. Chem. Res.* **2000**, *39* (7), 2601–2611. https://doi.org/10.1021/ie000063q.

(50) Venkatasubban, K. S.; Davis, K. R.; Hogg, J. L. Transition-State Structure for the Neutral Water-Catalyzed Hydrolysis of Ethyl Trifluorothiolacetate. *J. Am. Chem. Soc.* **1978**, *100* (19), 6125–6128. https://doi.org/10.1021/ja00487a026.

(51) Venkatasubban, K. S.; Bush, M.; Ross, E.; Schultz, M.; Garza, O. Transition State Structure for the Water-Catalyzed Hydrolysis of p-Nitrophenyl Trifluoroacetate in Acetonitrile. *J. Org. Chem.* **1998**, *63* (18), 6115–6118. https://doi.org/10.1021/jo972027f.

(52) Shi, Z.; Hsieh, Y.; Weinberg, N.; Wolfe, S. The Neutral Hydrolysis of Methyl Acetate — Part 2. Is There a Tetrahedral Intermediate? *Can. J. Chem.* **2009**, *87* (4), 544–555. https://doi.org/10.1139/V09-011.

(53) da Silva, P. L.; Guimarães, L.; Pliego, J. R. Jr. Revisiting the Mechanism of Neutral Hydrolysis of Esters: Water Autoionization Mechanisms with Acid or Base Initiation Pathways. *J. Phys. Chem. B* **2013**, *117* (21), 6487–6497. https://doi.org/10.1021/jp311504d.

(54) Mata-Segreda, J. F. Spontaneous Hydrolysis of Ethyl Formate: Isobaric Activation Parameters. *Int. J. Chem. Kinet.* **2000**, *32* (1), 67–71. https://doi.org/10.1002/(SICI)1097-4601(2000)32:1<67::AID-JCK8>3.0.CO;2-M.

(55) Sanz, M. T.; Murga, R.; Beltrán, S.; Cabezas, J. L.; Coca, J. Kinetic Study for the Reactive System of Lactic Acid Esterification with Methanol: Methyl Lactate Hydrolysis Reaction. *Ind. Eng. Chem. Res.* **2004**, *43* (9), 2049–2053. https://doi.org/10.1021/ie034031p.