ABSCHLUSSBERICHT

1 Allgemeine Angaben

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Projektnummer: 446436621

Titel des Projekts: MUST: MicroflUidik zur Bestimmung von Struktur-Reaktivitätsbeziehungen gestützt durch Thermodynamik & Kinetik

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Berichtszeitraum (gesamte Förderdauer): Förderung von 2020 bis 2025

Vorwort:

Dieses Projekt ist ein Kooperationsprojekt mit den Beteiligten Professoren Held, Leveneur und Legros im Rahmen des Programms DFG/ANR. Dieser Projektbericht umfasst den DFG-relevanten Teil bzgl. Phasengleichgewichte, Dissoziationsgleichgewichte sowie Kinetik und Gleichgewicht der Lävulinsäureveresterung und Nutzen von γ-Valerolacton als grünem Lösungsmittel für Veresterungsreaktionen.

2 Zusammenfassung / Summary

Dieses Projekt stellt einen neuartigen thermodynamischen Modellierungsansatz zur Vorhersage des Reaktionsgleichgewichts und der Reaktionskinetik von Veresterungsreaktionen von Lävulinsäure mit verschiedenen Alkoholen vor. Dabei wird Schwefelsäure als homogener Katalysator verwendet. Die Einflüsse von Temperatur, Lösungsmittel und Katalysatorkonzentration auf die Reaktionskinetik und das Gleichgewicht der Veresterung wurden systematisch bei Reaktionstemperaturen zwischen 303 K und 353 K untersucht. Ein wesentlicher Beitrag dieser Arbeit ist die Berechnung eines absoluten (d.h., nicht auf Wasser bezogen) Protonenaktivitätsterms, der die kinetische Modellierungsmethode erweitert und eine thermodynamische Beschreibung der Katalysatoreffekte auf die Reaktionskinetik ermöglicht. Für die präzise Vorhersage der absoluten Protonenaktivitäten war eine detaillierte Modellierung der freien Solvatisierungsenthalpie des Protons sowie der Säuredissoziationsgleichgewichte von Schwefelsäure in gemischten wässrig-organischen Reaktionssystemen erforderlich. Die Zustandsgleichung ePC-SAFT wurde genutzt, um die absoluten Protonenaktivitäten präzise vorherzusagen. Die experimentellen Ergebnisse verdeutlichten, dass sowohl der Katalysator als auch das Lösungsmittel einen signifikanten Einfluss auf Kinetik und Gleichgewicht der Veresterung ausüben. Dieses Verhalten konnte durch das neu entwickelte Berechnungsmodell präzise vorhergesagt werden. Insbesondere konnte der nachteilige Einfluss von Wasser auf die Kinetik quantitativ erklärt werden. Obwohl die Säuredissoziation in Wasser stark ist, bleibt die Protonenaktivität aufgrund einer stark negativen freien Solvatisierungsenthalpie sehr gering. Damit ein Lösungsmittel einen positiven Effekt auf die Reaktionskinetik ausübt, muss das Proton im Reaktionsgemisch möglichst reaktiv vorliegen, was eine geringere negative freie Solvatisierungsenthalpie des Protons bedingt. Zusätzlich ist eine ausreichend hohe Dissoziation von Vorteil, damit eine signifikante Menge an Protonen in der Lösung vorhanden ist. Das untersuchte Lösungsmittel γ-Valerolacton hatte nur einen minimalen Einfluss auf die Reaktionskinetik, da sich die genannten Effekte gegenseitig aufgehoben haben. Darüber hinaus konnte das Modell erfolgreich die Zusammenhänge zwischen kinetischen Reaktionsgeschwindigkeitskonstanten und Lösungsmitteleigenschaften beschreiben. Das entwickelte kinetische Modell reduziert den experimentellen Aufwand, indem es den Einfluss der wesentlichen Reaktionsbedingungen, einschließlich Katalysator- und Lösungsmittelkonzentrationen, zuverlässig vorhersagt.

This project aimed to investigate the thermodynamic and kinetic properties of esterification reactions, focusing on the role of solvent effects, catalyst behavior, and reaction equilibria. The study introduced an advanced thermodynamic model using ePC-SAFT to predict reaction kinetics and equilibrium states. Experimental and computational methodologies were integrated to validate model predictions, ultimately providing a framework for optimizing reaction conditions. This project presents a novel thermodynamic modeling approach to predict the kinetics and equilibrium of esterification reactions, focusing on levulinic acid esterification using various alcohols and sulfuric acid as a homogeneous catalyst. The effects of temperature, solvent, and co-solvent on the reaction kinetics and equilibrium were systematically studied under at reaction temperatures ranging from 323 K to 353 K. A key innovation in this work is the calculation and incorporation of an absolute proton activity term, which extends the kinetic modeling framework and enables a thermodynamic description of catalyst effects on reaction kinetics. Accurate predictions of proton activities required detailed modeling of Gibbs energies of solvation and acid dissociation equilibria in mixed aqueous-organic reaction systems. The equation of state ePC-SAFT was utilized to calculate fugacity coefficients and absolute proton activities, with model parameters adjusted to literature-based data on proton Gibbs energies of solvation and on acid dissociation equilibria. The novel approach achieved high accuracy in proton Gibbs energies of solvation, acid dissociation equilibria, and absolute proton activity in mixed-solvent systems. The experimental results revealed that the catalyst, solvent, and co-solvent significantly impact reaction kinetics and equilibrium. This behavior was accurately predicted by the developed computational model. Additionally, the model successfully explained the relationships between kinetic reaction rate constants and solvent properties. In order to positively affect reaction kinetics, the proton must exhibit high reactivity within the reaction mixture, which requires a less negative Gibbs energy of solvation of the proton in the chosen solvent. Additionally, sufficiently high acid dissociation is desired to ensure the presence of a significant amount of protons in the solution. In particular, this work could quantitatively explain the disadvantageous effect of water on kinetics although acid dissociation in water is strong, the proton activity remains very low due to the very negative Gibbs energy of proton solvation in water solvent. In contrast, the studied co-solvent γ-valerolactone showed minimal influence on the reaction kinetics. The resulting kinetic model reduces experimental efforts by reliably predicting the influence of key reaction conditions, including catalyst and solvent concentrations. The framework enables a priori identification of optimal reaction conditions and provides a foundation for extending the methodology to other acid-catalyzed reactions.

3 Wissenschaftlicher Arbeits- und Ergebnisbericht

3.1 Key Questions

The main questions of this project from a thermodynamic perspective are as follows:

1. Is ePC-SAFT suitable to predict the thermodynamics (phase behavior, reaction equilibrium) and kinetics of various chemical systems based on activities?
2. How accurate are the activity-based ePC-SAFT predictions for equilibrium and kinetics under homogeneous reaction conditions?
3. What are the most critical properties responsible for the reaction medium effects on reaction profiles?
4. How effective can GVL serve as a meaningful green reaction medium?
5. Are the current Taft substituent parameters reliable across different operating conditions, and if not, how can they be re-estimated using activity values instead of concentrations (➔ not included in this report, WP France Universities)?
6. What is the influence of solvent on polar & steric effects in a reaction calculated using concentrations/activities (➔ not included in this report, WP France Universities)?

3.2 Thermodynamic Properties and Phase Behavior (WP1)

Calculating thermodynamic properties in electrolyte systems or non-ideal mixtures in different phases presents a significant challenge due to the complex interactions between components and the deviations from ideal behavior. The electrolyte Perturbed-Chain Statistical Associating Fluid Theory (ePC-SAFT) was applied in this project. The original PC-SAFT model calculates the residual Helmholtz free energy a^{res} of the system at given conditions (temperature T, volume V, and composition x) as the sum of three contributions. ePC-SAFT was first introduced to extend PC-SAFT for modeling aqueous electrolyte solutions by incorporating a Debye-Hückel (DH) term to account for electrostatic long-range interactions. Later, pure ion parameters were reassessed to improve predictive accuracy, and an altered Born term was added to capture electrostatic interactions between charged species and their surrounding medium. The resulting residual Helmholtz energy a^{res} is finally given as the sum of five contributions according to equation (1).

$$a^{res} = a^{hc} + a^{disp} + a^{assoc} + a^{DH} + a^{Born} \tag{1}$$

Hereby, a^{hc} accounts for the hard-chain repulsion in a system. The dispersive van der Waals forces between molecules are captured by a^{disp}, while a^{assoc} accounts for the associative forces, specifically hydrogen bonding.

The goal of WP1 was to characterize the thermodynamic properties of levulinic acid esterification systems by modeling phase behavior and obtaining reaction-independent model parameters. To apply ePC-SAFT the pure-component parameters are required. According to the reaction schemes, these are the parameters for: levulinic acid, levulinate esters, gamma-valerolactone (GVL), alcohols as well as the catalyst, H_3O^+. The parameters of the compounds were partly available in the literature. As an example, Figure 1 presents experimental vapor pressure data for propyl levulinate, with ePC-SAFT parameters fitted accordingly.

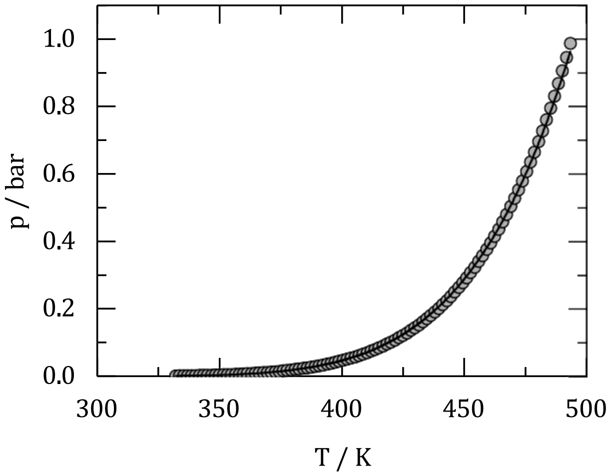

Figure 1: Vapor pressure of propyl levulinate. Circles show calculated vapor pressures using the Antoine equation with parameters from the literature (A = 7.18953, B = 2385.63, C = 238.831). The line represents the PC-SAFT modeling.

Furthermore, we validated the ePC-SAFT parameters for non-reactive subsystems to identify solvent-dependent behavior. To improve the accuracy of mixture predictions, we applied the combining rules of Berthelot, Lorenz, and Wolbach-Sandler. A single binary interaction parameter (k_{ij}) was used. If necessary, binary parameters were be adjusted based on phase equilibrium data. The experimental determination of solubilities and vapor-liquid equilibria provided essential data for calibrating the ePC-SAFT model. Key findings include the measured equilibrium solubilities of levulinic acid, alcohols, and catalysts in various solvents, as well as the validation of ePC-SAFT parameters for accurately predicting phase equilibria and solubility limits. Figure 2 presents the ternary liquid-liquid equilibrium of ethyl levulinate, methanol, and water, where binary interaction parameters were fitted to describe the phase behavior of the main solvents in the reaction mixture.

These data were instrumental for WP2, where they were utilized to refine reaction thermodynamic models.

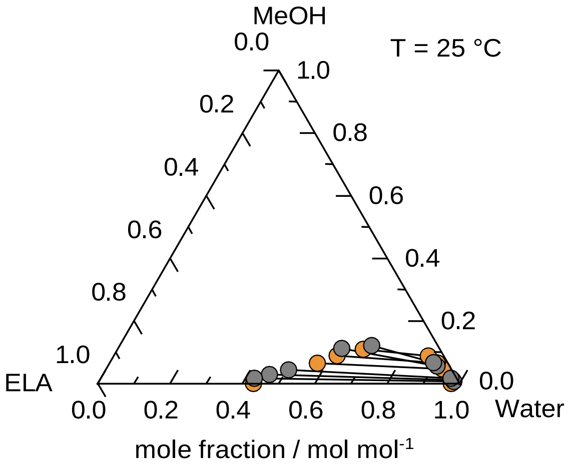

Figure 2: Ternary liquid-liquid equilibrium of ethyl levulinate (ELA), methanol, and water at 298 K. Orange symbols represent literature data, while gray symbols denote ePC-SAFT modeling results.

3.3 Reaction Thermodynamics (WP2), TU Dortmund

Major achievements of this work include the development of an extended thermodynamic framework that incorporates absolute proton activity and the refinement of a kinetic model to account for solvent effects on reaction rates and equilibrium shifts. By implementing activity-based kinetic modeling, we achieved a more accurate representation of reaction behavior compared to conventional concentration-based approaches. This advancement enhances the predictive capability of the model, allowing for better optimization of reaction conditions and improved understanding of complex chemical systems. WP2 focused on applying ePC-SAFT to determine activity-based equilibrium and kinetic constants independent of solvent effects. The goal of this WP was to develop thermodynamic models based on ePC-SAFT, and this allowed to evaluate activity values instead of concentrations for the different chemical systems, cf. DOI: 10.1016/j.ces.2022.117928 and DOI: 10.1021/acs.iecr.5c00115. This way, intrinsic (activity-based) kinetic parameters could be provided to our partners from ANR.

3.3.1 Reaction Equilibrium

In a first step, we predicted reaction equilibrium constants across different temperatures and reaction equilibria at different solvent compositions, and we did the experimental validation thereof. The study considered a range of solvents, including GVL (a polar aprotic solvent), water (a polar protic solvent), and alcohol in excess (polar protic solvent), across varying reactant ratios, catalyst concentrations, and temperatures. To calculate the equilibrium constant K_{th} for each temperature, the equilibrium mole fraction (K_x) and the equilibrium activity coefficient (K_γ) of all reactants had to be known (equation (2)).

$$K_{th}(T,p) = \prod_{i=1}^{N} x_{i,EQ} \cdot \prod_{i=1}^{N} \gamma_{i,EQ} = K_x\ (T,p,x_i) \cdot K_\gamma\ (T,p,x_i) \tag{2}$$

Therefore, experiments were performed in order to measure equilibrium concentrations with the GC-FID analysis. Activity coefficients were determined with ePC-SAFT to determine activities based on the measured equilibrium concentrations. Based on the activity-based equilibrium constant, ePC-SAFT was applied to predict the influences of the reactant ratio, initial GVL and water concentration, and temperature on the reaction equilibrium. Considering the levulinic acid (LA) esterification reaction (of interest in this work), the activity-based equilibrium constant for the reaction between LA and each alcohol were determined. Each alcohol requires its own K_{th}, resulting in five specific activity-based equilibrium constants according to the following reaction equations.

$$LA + MeOH \rightleftharpoons MLA + H_2O \tag{3}$$

$$LA + EtOH\ (+GVL) \rightleftharpoons ELA + H_2O \tag{4}$$

$$LA + 1\text{-}PrOH \rightleftharpoons PLA + H_2O \tag{5}$$

$$LA + 1\text{-}BuOH\ (+GVL) \rightleftharpoons BLA + H_2O \tag{6}$$

Figure 3 summarizes the natural logarithmic function of K_{th} according to the van't Hoff equation for all in this work studied esterification reactions of LA. We published an overview article with thermodynamic standard data (i.e., activity-based) on 16 different esterification reactions in an open-access journal (https://doi.org/10.1021/acsengineeringau.5c00002).

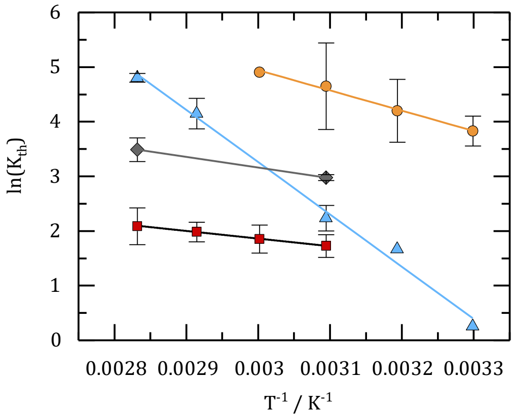

Figure 3: Natural logarithmic function of K_{th} of all experiments. Corresponding activity coefficients were predicted by ePC-SAFT). The solid line represents the regression according to the van't Hoff equation. The data is color-coded as follows: orange for LA + MeOH (y = - 3712.63x + 16.08, R^2 = 0.993), red for LA + EtOH (y = -1397.75x + 6.05, R^2 = 0.999), blue for LA + 1-PrOH (y = -9561.61x + 31.94, R^2 = 0.992), and gray for LA + 1-BuOH (y = -1942.10x + 8.988, R^2 = 1).

The selection of an appropriate solvent for chemical reactions is a key factor in optimizing reaction performance. When choosing solvents, the focus may be on improving catalyst recycling or replacing existing solvents with greener alternatives. Determining the optimal solvent often requires expensive laboratory experiments. However, the activity-based thermodynamic equilibrium constant K_{th} calculated in Figure 3 can be used to efficiently screen various solvents. Notably, the addition of a solvent to the reaction medium does not change K_{th}. Solvents can significantly influence the activity coefficients of the reacting species, thereby affecting their equilibrium concentrations. This enables solvents manipulate K_x values and reaction yields, but also reaction kinetics and acid dissociation, which is presented next.

3.3.2 Dissociation equilibria of H_2SO_4 and proton activity coefficient

As the catalyst of several reactions considered in MUST project is H_3O^+ and thus, it is ionic, the ionic interactions have to be accounted for modeling, since such interactions might influence the activity of the reaction species. Here, acid dissociation is considered. The esterification kinetics is highly affected by the amount of dissociated catalyst (H_2SO_4). Therefore, knowledge of the degree of dissociation of H_2SO_4 is crucial for the determination of H_3O^+ (will be denoted $H^+$from now on) concentration. The key to predict dissociation equilibria (expressed as pK_a^c) in non-aqueous solutions is the activity-based equilibrium constant K_a^{th}. We used the proton's Gibbs energy of solvation infinitely diluted in solvents ($\Delta^{solv} g^{\infty}_{H^+}$) to fit ePC-SAFT parameters between H^+ and each solvent. These results served as a basis to model pK_a^c values and absolute proton activity. Accurate modeling of $\Delta^{solv} g^{\infty}_{H^+}$ in pure solvents and in mixtures were achieved especially for mixtures relevant for the sulfuric-acid catalyzed esterification of levulinic acid with various alcohols, cf. [10.1021/acs.iecr.5c00115].

3.3.3 Reaction kinetics

Using the ePC-SAFT predicted $\Delta^{solv} g^{\infty}_{H^+}$ values and sulfuric acid dissociation equilibria, absolute proton activities were accurately quantified and integrated into the kinetic model:

$$r = \left(k_1 \cdot a_A \cdot a_B - \frac{k_1}{K_{th}} \cdot a_C \cdot a_D\right) \cdot a^*_{H^+,\text{abs}} \tag{7}$$

Here, k_1 denotes the “intrinsic” kinetic reaction rate constant, which is not a function of catalyst. Previous activity-based kinetic models did not account for catalyst interactions [10.1002/cphc.201700507]. An essential element in calculating the reaction rate *r* is the absolute proton activity $a^*_{H^+,\text{abs}}$. The implementation of $a^*_{H^+,\text{abs}}$ in the modeling of reaction velocity *r* also allows predicting any change in reactants, catalyst concentrations, or co-solvent addition on *r*.

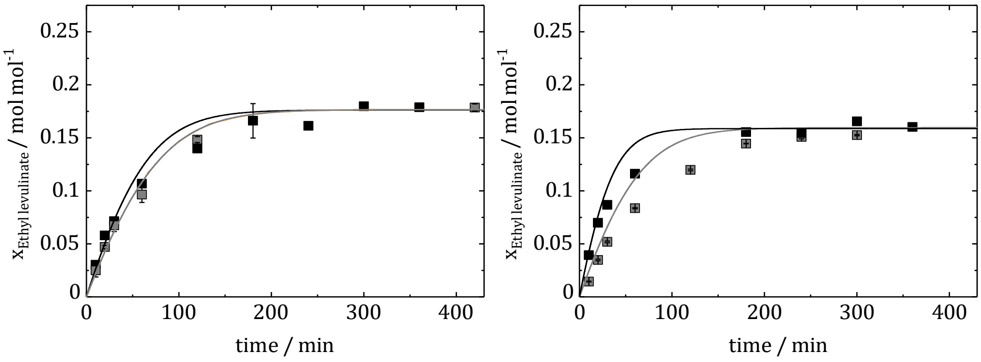

Figure 4: Mole fraction of ethyl levulinate plotted against the reaction time at temperatures of 323.15 K (left) and 333.15 K (right), at a pressure of 1.013 bar. Symbols represent experimental mole fractions measured by INSA (Left: black squares (EtOH 1), $x_{H_2SO_4} = 0.0062$ mol mol^{-1}, gray squares (EtOH 2), $x_{H_2SO_4} = 0.0048$ mol mol^{-1}; Right: black squares (EtOH 3), $x_{H_2SO_4} = 0.0067$ mol mol^{-1}, gray squares (EtOH 4), $x_{H_2SO_4} = 0.0032$ mol mol^{-1}). The lines represent ePC-SAFT predictions. For the exact conditions cf. also phd thesis of Dr. Marcel Klinksiek.

Figure 4 shows four chosen experimental kinetic plots of the esterification of LA + EtOH, which differ in catalyst concentration. As expected, a lower catalyst concentration results in decreased reaction kinetics. The intrinsic kinetic reaction rate constant (k_1) was fitted to the experiments EtOH 1 (323.15 K) and EtOH 2 (333.15 K) using Eq. 7. Hence, the kinetic curves of reactions EtOH 2 and EtOH 4 (at comparatively lower catalyst concentrations than EtOH 1 and EtOH 3) were predicted with ePC-SAFT and Eq. 7. Although the differences in catalyst concentration are not very pronounced, ePC-SAFT predictions show good agreement with the experimental data. A key challenge for successful modeling of reaction kinetics was to correctly account for the influence of the initial water concentration on the kinetic curves. Water, which is a product of the esterification reaction, significantly reduces both the equilibrium conversion and the reaction rate of the esterification reaction. Figure 5 compares the experimental results of LA esterification with EtOH at T = 323.15 K (left) and T = 353.15 K (right) with the respective ePC-SAFT predictions.

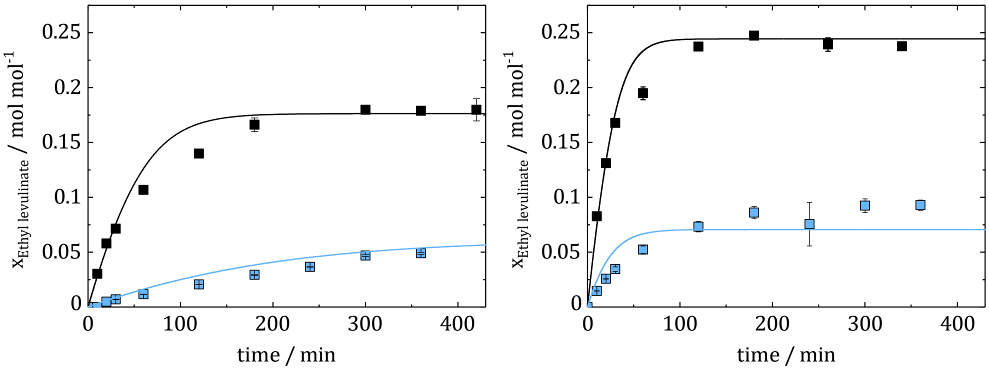

Figure 5: Mole fraction of ethyl levulinate plotted against the reaction time at temperatures of 323.15 K (left) and 353.15 K (right), at a pressure of 1.013 bar. Symbols represent experimental mole fractions measured by INSA (black squares (Left: EtOH 1, Right: EtOH 6) show experiments with no initial water concentration. Blue squares (Left: EtOH 5, Right: EtOH 7) show experiments with a significant initial water amount. The corresponding experimental data are listed in Table A6 (Appendix). The lines represent ePC-SAFT predictions.

Once again, only a single intrinsic kinetic reaction rate constant was used to predict the effect of water on the reaction kinetics. The gray squares in Figure 5 (left) represent the same experiment as in Figure 4, using the same k_1. It can be clearly seen that the kinetic approach developed in this work accurately predicts the reaction kinetics at different conditions. This success is due to the use of absolute proton activity in the model provided by ePC-SAFT. This shows the superiority of our new approach cf. [10.1021/acs.iecr.5c00115], over relative proton activity in predicting esterification kinetics across different solvent conditions, which was the state-of-the-art before we started our project (10.1002/cphc.201700507).

3.4 Microreactor-Based Kinetic Studies (WP3), INSA Rouen & COBRA Laboratory

In WP3, kinetic experiments were conducted in a continuous microreactor setup under isothermal conditions to eliminate concentration and temperature gradients. Key outcomes:

- Esterification reactions in a microreactor at controlled residence times.
- Real-time monitoring of reaction progress using Raman spectroscopy.
- Identification of optimal microreactor configurations for scaling reaction processes.

3.5 Estimation of Taft Substituent Parameters (WP4), INSA Rouen

In WP4 Taft substituent parameters were re-estimated to generalize kinetic models.

- Determination of steric and polar substituent effects on reaction rates.
- Correlation of intrinsic rate constants with solvent properties using Taft parameters.
- Bayesian framework for parameter estimation, ensuring robust model predictions.

3.6 Kinetics & Structure-reactivity (WP5), INSA Rouen

In WP5 the knowledge gained before was applied to three different test reactions.

- Kinetic models were developed with help of WP3
- Taft equation was used to evaluate different molecular mechanism on the reaction kinetics.
- The method developed was applied to three reactions, glucose solvolysis, enzymatic esterification, and hydrogenation.
- All results were published.

4 Veröffentlichte Projektergebnisse

4.1 Publikationen mit wissenschaftlicher Qualitätssicherung

1. Baco, S., Klinksiek, M., Zakaria, R. I. B., Garcia-Hernandez, E. A., Mignot, M., Legros, J., Held, C., Leveneur, S., Solvent effect investigation on the acid-catalyzed esterification of levulinic acid by ethanol aided by a Linear Solvation Energy Relationship. Chem. Eng. Sci., **2022**, 260, 117928. DOI: 10.1016/j.ces.2022.117928

2. Capecci, S., Wang, Y, Moreno, VC, Held, C., Leveneur, S., Solvent effect on the kinetics of the hydrogenation of n-butyl levulinate to γ-valerolactone, Chemical Engineering Science 231, **2020**, 116315. DOI: https://doi.org/10.1016/j.ces.2020.116315

2. Klinksiek, M., Baco, S., Leveneur, S., Legros, J., & Held, C., Activity-based models to predict kinetics of levulinic acid esterification. ChemPhysChem, **2023**, 24(4), e202200729. DOI: 10.1016/j.ces.2022.117928

3. Cordier A., Klinksiek M., Held C., Legros J., Leveneur S, Biocatalyst and continuous microfluidic reactor for an intensified production of n-butyl levulinate: Kinetic model assessment. J. Chem. Eng. **2023**, 451, 138541. DOI: 10.1016/j.cej.2022.138541

4. Baco, S., Klinksiek, M., Mignot M., Leveneur, S., Legros, J., & Held, C., Temperature effect on the steric and polar Taft substituent parameter values. React. Chem. Eng., **2024**, 9, 833-841. DOI: 10.1039/D3RE00500C

5. Klinksiek, M., Baco, S., Leveneur, S., Legros, J., & Held, C., Predicting proton activity and acid dissociation equilibria in mixed-solvent systems, and their impact on esterification kinetics of levulinic acid. Ind. Eng. Chem. Res., **2025**, DOI: 10.1021/acs.iecr.5c00115

6. Jovein, I.B., Baco, S., Sadowski, G., Doghieri, F., Baschetti, M.G., Yu, G., Leveneur, S., Legros, J., Held, C. Comprehensive Compilation on Esterification Reactions and Predicting Reaction Kinetics and Equilibrium Using PC-SAFT, ACS AU, **2025**, https://doi.org/10.1021/acsengineeringau.5c00002

7. Baco, S., Mignot, M., Held, C., Legros, J., Leveneur, S. Dissecting steric and polar substituent effects in linear free energy Relationships: Re-Assessment of the Taft equation with Temperature-Dependent kinetic modeling, Chemical Engineering Science, **2025**, 122700

4.2 Weitere Publikationen und öffentlich gemachte Ergebnisse

The work has been presented in various formats at both national and international conferences, including an oral presentation at the „Thermodynamik Kolloquium 2023“ in Garbsen, Germany, and oral and poster presentations at “ESAT 2024” in Edinburgh, UK.

4.3 Patente (angemeldete und erteilte)

- keine