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Predicting the solvent effect on esterification kinetics

Max Lemberg and Gabriele Sadowski*

Abstract: It is well-known that solvents influence reaction kinetics. The classical concentration-based kinetic modeling is unable to describe these effects. In this work, the reaction kinetics was studied for the esterifications of acetic acid and of propionic acid with ethanol at 303.15 K. It was found that the reactant ratio as well as the applied solvents (acetonitrile, tetrahydrofurane, dimethylformamide) significantly affect the reaction rate. The thermodynamic model PC-SAFT was applied to account for the interactions between the reacting species and the solvents via activity coefficients. This allowed the identification of solvent-independent kinetic constants and the prediction of the solvent effect on reaction kinetics in almost quantitative agreement with the experimental data. The presented approach shows the importance of taking into account thermodynamic non-idealities and significantly reduces experimental effort for finding the best solvent candidate for a given target reaction.

Solvents are known to have a significant influence on both, reaction equilibria and reaction kinetics. A comprehensive overview of related studies was given by Reichardt and Welton^[1]. Besides experimental results, they presented a theoretical framework based on the Gibbs energy of solvation that allowed for correlating experimentally-obtained apparent equilibrium constants and rate constants with the solvent polarity scale $E_T(30)$. However, as these correlations are empirical and specific for a given reaction, they cannot be used to predict solvent effects on other reactions than the ones used for obtaining the correlations.

A predictive approach for describing solvent effects on reaction equilibria was presented in a previous work of our group by Riechert et al.^[2] who investigated the esterification equilibrium of acetic acid (HAc) and of propionic acid (HProp) with ethanol (EtOH) at different reactant ratios and in different solvents. The proposed thermodynamic approach considers the interactions between the reacting species and the different solvents via activity coefficients predicted using the Perturbed-Chain Statistical Associating Fluid Theory (PC-SAFT). This allowed predicting the solvent effects once the thermodynamic equilibrium constants were determined from experimental data for the solvent-free reaction equilibrium.

Works that account for activity coefficients of reactants/products when modeling the kinetics of liquid-phase reactions were published by several groups applying *g*^E-models like UNIFAC^[3], UNIQUAC^[4] and NRTL^[5]. These works mostly investigated the effects of temperature, catalyst concentration and reactant ratio on the reaction kinetics whereas the effect of solvents on the reaction kinetics has not been examined. The parameters of the kinetic models were fitted to the entire experimental data obtained in these works and there was no focus on predicting

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any solvents effects.

Jannsen et al.^[6] investigated an enzyme-catalyzed esterification reaction in different solvents and modeled the experimental data comparing the performance of two different kinetic models. Thereby one of the models accounted for the activity coefficients of reactants/products and the other did not. As they observed a significant solvent effect, they fitted a completely new set of kinetic parameters for every solvent. They found that the model parameters obtained when accounting for the activity coefficients were less solvent-dependent than the ones obtained when not accounting for the activity coefficients. This shows that the solvent effect on the kinetics of enzyme reactions can at least partly be explained by the solvent-influenced activity coefficients of the reactants/products. For those reactions, the solvent effect is usually also partly attributed to solvent-enzyme interactions which cannot be accounted for by the activity coefficients for the reactants/products.

Kiviranta-Pääkkönen et al.^[7] investigated the kinetics of the tertiary amyl methyl ether (TAME) synthesis and also applied two models for the correlation of the experimental data. They found that the model which accounted for the activity coefficients was able to describe the experimental data over a wider range of conditions than the other model which did not.

In this work we investigated the reaction kinetics of the esterification of HAc with EtOH (R1) and of HProp with EtOH (R2) at 303.15 K using Raman spectroscopy. The reactions were performed in solvent-free reaction mixtures at different initial mole ratios $n_{acid}^0: n_{EtOH}^0$ (1:1, 3:1, 1:3) on the one hand and in the solvents acetonitrile (ACN), tetrahydrofurane (THF) and N,N-dimethylformamide (DMF) at an initial reactant concentration of $c_{acid}^0 = c_{EtOH}^0 = 3.5188$ mol/L on the other hand. Fuming hydrochloric acid (HCI) was used as catalyst at constant concentration of $c_{HCI}^0 = 0.1506$ mol/L in all reaction mixtures. Further details for the reaction-kinetics measurements are presented in the supporting information S4.

The experimental data of the solvent-free systems with equimolar reactant ratio was modeled by fitting the intrinsic rate constants while accounting for the activity coefficients of the reactants/products using PC-SAFT. Based on this, the esterification kinetics at the other reactant ratios and in the different solvents were purely predicted via PC-SAFT using the solvent–dependent activity coefficients of the reactants/products and compared with the experimental data. Details concerning the PC-SAFT model and the used model parameters are presented in the supporting information S1.

For an equilibrium reaction of the type $A + B \rightleftharpoons C + D$, the reaction rate *r* can be expressed as

 $r = \frac{dc_C}{dt} = k_1 \cdot c_A \gamma_A \cdot c_B \gamma_B - k_{-1} \cdot c_C \gamma_C \cdot c_D \gamma_D \quad (1)$

whereby c_i denotes the concentration of component *i* in mol/L and γ_i is the activity coefficient of component *i*. k_1 and k_{-1} are the intrinsic rate constants of the forward and backward reaction, respectively. The activity coefficients γ_i account for the interactions of the reacting agents among themselves and with other components present in the reaction mixture (e.g. solvents). COMMUNICATION

In contrast to the intrinsic rate constants k_1 and k_{-1} which depend on temperature only, the activity coefficients γ_i depend on reactant concentrations as well as on the solvent. Using them in Eq.(1) thus allows for predicting the effects of reactant ratio and solvents on the reaction kinetics.

As the reaction kinetics leads to the reaction equilibrium (eq) at infinite time (where r = 0), k_1 and k_{-1} are connected via the thermodynamic equilibrium constant K_a according to:

$$\frac{k_1}{k_{-1}} = K_a = \frac{c_{C,eq}\gamma_{C,eq}\cdot c_{D,eq}\gamma_{D,eq}}{c_{A,eq}\gamma_{A,eq}\cdot c_{B,eq}\gamma_{B,eq}}$$
(2)

This means, that once the thermodynamic equilibrium constant K_a is known, only one kinetic parameter k_1 - or k_{-1} - needs to be adjusted for modeling the reaction kinetics.

The K_a -values for the reactions R1 and R2 at 303.15 K were determined from literature data to 20.4 and 10.0, respectively. Details can be found in the supporting information S5. The rate constants $k_{1,R1}$ and $k_{1,R2}$ were fitted to the reaction kinetics of the solvent-free system with equimolar reactants (1:1 system) of the respective reaction. The resulting values are $k_{1,R1}$ =2.45·10⁻⁵ L/(mol·s) and $k_{1,R2}$ =1.45·10⁻⁵ L/(mol·s). Using K_a and k_1 for both reactions, the reaction kinetics of the remaining solvent-free systems (1:3, 3:1) and for the reactions in different solvents were predicted via Eqs. 1 and 2. The activity coefficients γ_i were predicted using PC-SAFT without fitting any model parameters to reaction data.

The experimental and modeling/prediction results for the reaction kinetics of the solvent-free reactions R1 and R2 are presented in Figure 1.

Comparing the experimental results for R1 and R2, it can be seen that R1 is approximately twice as fast as R2. For both, R1 and R2, the reaction with an initial reactant-ratio 1:1 and the highest initial reactant concentrations was the fastest one. This was expected according to Eq. 1 even when neglecting the activity coefficients γ_i . What was unexpected is the difference in the reaction rates of the 1:3 and the 3:1 reactions as the rate law (Eq. 1) is symmetric with respect to the concentrations of the two reactants when not accounting for their activity coefficients. This discrepancy is obviously caused by the (concentration dependent) activity coefficients of the reactants/products and could never be accounted for when they were neglected.

Thus, using the activity coefficients of the reactants/products in Eq. 1 obtained from the thermodynamic model PC-SAFT and the intrinsic rate constants k_1 , fitted to the reaction kinetics of the solvent-free 1:1 systems, the reaction kinetics of the 1:3 and 3:1 systems were purely predicted as shown in Fig. 1. In case of R1 (Fig. 1 left) it can be seen that the reaction kinetics for the 3:1 system was predicted to be much faster than the one for the 1:3 system which is in very good agreement with the experimental findings. Only for longer times, the prediction slightly overestimates the concentration of ethyl acetate (EtAc) for the 1:3 system. For R2, the effect of the reactant ratio on the reaction rate is predicted to be opposite to the one of R1 as the 1:3 system reacts faster than the 3:1 system, which is again in very good agreement with the experimental data (Fig.1 right). The concentration of ethyl propionate (EtProp) is slightly underestimated for the 3:1 system at the beginning of the reaction but again in very good agreement with the experiment at longer times.





For a qualitative prediction of the solvents effect on the reaction kinetics. binarv equilibrium vapor-liquid (VLE) data from reactant/solvent systems was used. This VLE data allows to identify and to evaluate the interactions between a reactant and a solvent and therewith to determine the activity coefficients of the γi

in

solvents. These activity coefficients are of particular interest for a qualitative prediction of the solvent effect on the initial part of the reaction kinetics as at this point the concentration of the products is still small (Eq. 1).

reactants

The equilibrium pressure *p* of a binary mixture is related to the activity coefficients γ_i of the components in the mixture as described in Eq. 3:

$$p = x_1 \gamma_1 p_{01}^{LV} + x_2 \gamma_2 p_{02}^{LV}$$
(3)

Thereby x_i denotes the mole fraction and p_{0i}^{LV} the vapor pressure of component i Neglecting the activity coefficients γ_i , Eq. 3 becomes the Raoult's law. lf the activity coefficients are not unity, a system has either a positive deviation ($\gamma_i > 1$) or a negative deviation $(\gamma_i < 1)$ from Raoult's law. This deviation is associated with



repulsive and attractive interactions between the components. Deviations from the Raoult's law may also lead to the formation of azeotropes with a pressure maximum (p_{max}) or pressure minimum (p_{min}) , corresponding to activity coefficients greater than one (repulsion) or smaller than one (attraction), respectively. Table 1 gives an overview of binary azeotropes of the reactants and solvents of the two reactions considered in this work. This already allows to qualitatively estimate the solvent effect on the esterification kinetics.

Table 1. Binary p_{\min}/p_{max} azeotropes of HAc, HProp, EtOH with the solvents used in this work

azeotrope	ACN	THF	DMF
HAc	no ^[8]	no ^[9]	p _{min} ^[10]
HProp	no ^[8]	no ^[a]	$p_{min}^{[a]}$
EtOH	<i>p_{max}</i> ^[11]	no ^[12]	no ^[13]

[a] VLE data measured within this work. Details are provided in the supporting information S3

As it can be seen from Table 1, the carboxylic acids HAc and HProp behave similarly as they both only show a pressureminimum azeotrope with the solvent DMF. This corresponds to attractive interactions and acid activity coefficients in DMF smaller than one. EtOH on the other hand shows a pressuremaximum azeotrope with the solvent ACN, which corresponds to repulsive interactions and EtOH activity coefficients greater than one. As can be seen in Eq. 1, the product $\gamma_{acid}\gamma_{EtOH}$ determines the solvent effect on the reaction rate. It can therefore be qualitatively concluded from Table 1 that the reaction rates $r_{solvent}$ in a solvent are expected in the order $r_{ACN} > r_{THF} > r_{DMF}$ for both, R1 and R2.

Quantitative predictions of the reaction kinetics of the systems with equimolar reactants in ACN, THF and DMF were performed in the same way as for the solvent-free 1:3 and 3:1 systems using Eq. 1 and the same intrinsic rate constants as before while accounting for the reactant/product activity coefficients in the reaction mixtures obtained from PC-SAFT. The predicted results compare with experimental data as shown in Figure 2.

Figure 2. Concentration of EtAc (left) and EtProp (right) for R1 (left) and R2 (right) at 303.15 K over time. The symbols are experimental data for systems with an initial reactant concentration of $c_{acid}^0 = c_{EtOH}^0 = 3.5188$ mol/L in the solvents ACN (circles), THF (triangles) and DMF (squares). The error bars lie within the symbols and are therefore not shown. The lines are purely predicted with PC-SAFT for the solvents ACN (drawn through), THF (dashed) and DMF (dotted).

It can be seen that the reaction rate strongly depends on the solvent, whereby the effects of the solvents on R1 and R2 are comparable. Both reactions are fast in ACN and slow in DMF. This is in agreement with the qualitative discussion above without using any calculation based on VLE data only.

Concerning the quantitative prediction, it has to be mentioned that the solvent effect in principle cannot be predicted using concentration-based kinetic model as the initial reactant concentration did not change. Thus, using the same rate constants would lead to exactly the same reaction rates for every solvent. However, by accounting for the activity coefficients for the reactants/products which strongly depend on the solvent, the solvent effect on the reaction rate of R1 could be predicted using the above-determined intrinsic rate constant in very good agreement with the experimental data (Fig. 2 left). For R2, the prediction is also in good agreement with the experimental data for the solvents ACN and DMF, whereby the concentration of the ester is slightly underestimated in both cases (Fig. 2 right). The prediction for R2 in THF is still qualitatively correct as it lies between the predictions for R2 in DMF and in ACN.

Concluding, it was shown that the reactant concentration/ratio and solvents can affect the rate of reactions significantly due to interactions of the reactants/products among themselves as well as with the solvent(s). For a quick assessment of different solvents, a strategy was presented solely based on binary reactant/solvent VLE data. Using a kinetic model accounting for the interactions between reactants/products and the presence of solvents via activity coefficients even allowed for quantitatively predicting the influence of solvents and reactant concentrations on the reaction kinetics in very good agreement with the

DMF

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effort for finding the best solvent candidate for a given reaction.

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experimental data. This significantly reduces the experimental

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Predict the best reaction solvent.

For the esterifications of acetic acid and of propionic acid with ethanol in different solvents, a thermodynamic model was applied to account for solvent/reactant interactions. Using only one intrinsic kinetic constant for all solvent systems, the proposed new activitybased kinetic modeling approach allowed for predicting the solvent effects on reaction kinetics in very good agreement with the experimental data.