Predicting Solvent Effects on Homogeneity and Kinetics of the Hydroaminomethylation: A Thermodynamic Approach Using PC-SAFT

Fabian Huxoll, Anna Kampwerth, Thomas Seidensticker, Dieter Vogt, and Gabriele Sadowski*

ABSTRACT: Solvents may significantly affect the phase behavior and kinetics of chemical reactions. Especially for complex reactions performed in mixtures of different solvents, it requires a high experimental effort to quantify these effects. This work focuses on a novel thermodynamic approach to predict solvent effects on both reaction rates and phase behavior. We applied this method to the homogeneously catalyzed hydroaminomethylation of 1-decene in a thermomorphic multiphase system of methanol and n-dodecane. For that purpose, the thermodynamic activities of the reactants and the liquid—liquid equilibrium of the multicomponent reaction system were successfully modeled using the Perturbed-Chain Statistical Associating Fluid Theory (PC-SAFT). An increasing concentration of n-dodecane in the solvent mixture was predicted not only to limit the working space for the reaction due to unwanted phase separation but also to massively reduce the reaction rate. These results were in good agreement with batch experiments and homogeneity tests performed in this work. The approach is applicable to a wide variety of liquid-phase reactions and thus is a valuable tool for reducing the experimental effort to a minimum.

1. INTRODUCTION

Solvents provide the reaction environment of all liquid-phase reactions in the chemical industry and can have an enormous impact on reaction rates, phase equilibria, and the phase behavior of complex reaction media. Especially for reactions performed in solvent mixtures, these effects are of major importance and need to be known to achieve high selectivities and reaction rates.

One example for complex reaction systems using solvent mixtures is the so-called thermomorphic multiphase system (TMS) proposed by Behr and Fängewisch. Using TMS is a promising strategy for homogeneously catalyzed reactions to enable efficient product separation and catalyst recycling, thus improving these processes from economic and ecological points of view. For this purpose, a polar solvent is combined with a nonpolar one to result in a strongly temperature-dependent miscibility gap. The reaction is performed at high temperatures in a homogeneous liquid without mass-transfer limitations, whereby the product separation takes place at a lower temperature, resulting in the formation of a product-rich, nonpolar phase and a catalyst-rich, polar phase.

To determine the most appropriate solvent composition for a given TMS, solvent effects on both reaction kinetics and the liquid—liquid equilibrium (LLE) of the multicomponent reaction mixture need to be considered. However, systematic experiments at all relevant reaction conditions and compositions of the reaction mixture are highly time consuming and therewith expensive. Consequently, thermodynamic modeling is a valuable tool to reduce this experimental effort to a minimum.

In this work, we propose a novel activity coefficient-based approach to predict solvent effects on the multicomponent phase behavior as well as on the reaction rate. For that purpose, the Perturbed-Chain Statistical Associating Fluid Theory (PC-SAFT) was used, which has already proven its ability to predict solvent effects on chemical reactions and, and, moreover, is able to model and extrapolate complex phase behavior over wide ranges of temperature and pressure.

The current study focuses on the eco-friendly, homogeneously catalyzed hydroaminomethylation (HAM) of 1-decene with diethylamine (DEA), combining the hydroformylation (HYFO) and the reductive amination (RA) to a one-pot auto tandem catalytic reaction (Figure 1). The RA can be divided into two distinct reactions, the N,N-diethyldecylenamine (enamine) condensation and the hydrogenation. In the

Received: September 28, 2021
Revised: December 19, 2021
Accepted: January 3, 2022
first step of the HAM, 1-decene reacts with syngas (H\textsubscript{2}/CO) to undecanal via the HYFO reaction, followed by the enamine condensation of undecanal and DEA to form \( N,N \)-diethylundec-1-en-1-amine (enameine) and water as a byproduct. The last step yields the final product, \( N,N \)-diethylundecan-1-amine (DEDA), via hydrogenation of the enamine. All reactions were investigated in a TMS of methanol and \( n \)-dodecane (DDC), which in recently published works\textsuperscript{14–18} was found to be a promising solvent system.

The pure-component PC-SAFT parameters and the binary interactions between all components involved in the HAM as well as between these and the solvents were investigated in detail in earlier works\textsuperscript{19,20}, providing an almost complete set of PC-SAFT parameters. In this work, the LLE of the multicomponent reaction system is predicted using PC-SAFT. Furthermore, solvent effects on the reaction kinetics are estimated based on reactant activity coefficients. Finally, these modeling results are compared to batch and homogeneity experiments performed in this work.

2. THEORETICAL BACKGROUND

2.1. Thermodynamic Estimation of Reaction Rates. According to Lemberg et al.\textsuperscript{21} the reaction rate \( r \) of an equilibrium reaction \( A + B \rightleftharpoons C + D \) is described in a thermodynamic-consistent way, as shown in eq 1.

\[
r = \frac{d\gamma_i}{dt} = \frac{k_{f1}^\text{eq} \gamma_i^\text{A} \gamma_i^\text{B} \gamma_i^\text{C} \gamma_i^\text{D}}{k_{f1}} - \frac{k_{r1}^\text{eq} \gamma_i^\text{A} \gamma_i^\text{C} \gamma_i^\text{D} \gamma_i^\text{D}}{k_{r1}} \tag{1}
\]

Herein, \( a_i \) are the thermodynamic activities of the components taking part in the reaction. These thermodynamic activities can be defined as the product of the mole fraction \( x_i \) and the mole fraction-based activity coefficient \( \gamma_i^\text{f} \) or as the product of the concentration \( c_i \) and the concentration-based activity coefficient \( \gamma_i^\text{c} \) (eq 2). \( \gamma_i^\text{f} \) and \( \gamma_i^\text{c} \) depend on the concentrations of all components in the mixture, including the solvents. Consequently, the apparent reaction rate constants of the forward reaction \( k_{f1} \) and of the backward reaction \( k_{r1} \) also depend on all concentrations as well as on the solvent system and its composition. Using thermodynamic activities instead of concentrations, the intrinsic reaction rate constants \( k_{f1}^\text{eq} \) and \( k_{r1}^\text{eq} \) no longer contain activity coefficients and thus are completely independent of the solvent as long as the transition state is not affected.\textsuperscript{23} As at the start of the reaction \( (t = 0) \), the backward reaction can be neglected, eq 1 then simplifies to

\[
r = \frac{k_{f1}^\text{eq} \gamma_i^\text{A} \gamma_i^\text{B}}{k_{r1}} \tag{3}
\]

This allows predicting the solvent effect on the reaction rate \( r \) solely based on the intrinsic reaction rate constant (determined in ANY solvent) and the thermodynamic activities of the reactants in the reaction mixture. This was successfully demonstrated in earlier works applying an activity coefficient-based solvent-selection approach using modified UNIFAC (Dortmund).\textsuperscript{18,22} Based on eq 3, doubling the thermodynamic activity of reactant results in a doubled reaction rate. Accordingly, the highest reaction rates and turnover frequencies are achieved in reaction mixtures that lead to the highest thermodynamic activities of the reactants.

All reactions investigated in this work (HYFO, RA, HAM) are liquid-phase reactions with the gases CO and/or H\textsubscript{2} as reactants. In the applied temperature and pressure range, the thermodynamic activity of these gases in the liquid phase was found to not depend on the solvent system and the composition of the liquid phase but only to depend on their mole fraction in the gas phase, which is in equilibrium with the liquid phase \((a_{\text{CO/H}_2} \approx x_{\text{CO/H}_2})\).\textsuperscript{18} Consequently, the thermodynamic activity of CO and/or H\textsubscript{2} in the liquid is constant and thus does not affect the reaction rate as long as the composition of the gas phase does not change and the gas phase is in equilibrium with the liquid phase. It is worth mentioning that while the thermodynamic activity of the gases does not depend on the solvent, their solubility in the liquid, of course, does.

2.2. PC-SAFT. The thermodynamic equation of state PC-SAFT\textsuperscript{23,24} calculates the residual Helmholtz energy \( A^{\text{res}} \) as a sum of different perturbation contributions, namely, the hard-chain repulsion \( A^\text{hc} \), dispersive attraction \( A^{\text{disp}} \), and associative interaction \( A^{\text{assoc}} \) (eq 4). Starting from \( A^{\text{res}} \), any other thermodynamic properties such as activity coefficients \( \gamma_i \) can be calculated.\textsuperscript{23,24}

\[
A^{\text{res}} = A^\text{hc} + A^{\text{disp}} + A^{\text{assoc}} \tag{4}
\]

Molecules are modeled as the chains of spherical segments, and each molecule is thus characterized by its segment diameter \( \sigma_i \) and segment number \( m_i^{\text{seg}} \). Dispersive interactions between two molecules are considered via the dispersion-energy parameter \( u_{ij}k_b^{-1} \) with \( k_b \) being the Boltzmann constant. Hence, three adjustable pure-component parameters are required to characterize a nonassociating component in PC-SAFT. In the case of associating components (e.g., methanol), two additional parameters, on the one hand, the association-volume parameter \( k_i^{\text{vol}} \) and on the other hand, the association-volume parameter \( k_i^{\text{vol}} \), are necessary to account for associative interactions like hydrogen bonding. Moreover, the numbers of electron donor and electron-acceptor sites of a molecule are described by association sites \( N_i^{\text{assoc}} \).

Combining rules as proposed by Berthelot\textsuperscript{25} and Lorentz\textsuperscript{26} are applied to calculate the segment diameter \( \sigma_i \) (eq 5) and the dispersion-energy parameter \( u_{ij} \) (eq 6) in mixtures of different components. Often, a binary interaction parameter \( k_{ij} \) is introduced to correct the cross-dispersion energy between two

---

**Figure 1.** Reaction scheme for the HAM of 1-decene with DEA.
Table 1. PC-SAFT Pure-Component Parameters’ Segment Number \( (m_{ij}^{seg}) \), Segment Diameter \( (\sigma_i) \), Dispersion-Energy Parameter \( (\epsilon_{iB}k_B^{-1}) \), Dipole Moment \( (\mu_i) \), Association-Energy Parameter \( (\epsilon_{iB}^{Aij}k_B^{-1}) \), Association-Volume Parameter \( (\kappa^{Aij}) \), and Number of Association Sites \( (N_i^{assoc}) \) Applied in This Work

| Component | \( M \) (g mol\(^{-1}\)) | \( m_{ij}^{seg} \) | \( \sigma_i \) (Å) | \( \epsilon_{iB}k_B^{-1} \) (K) | \( \epsilon_{iB}^{Aij}k_B^{-1} \) (K) | \( \kappa^{Aij} \) | \( N_i^{assoc} \) | Reference |
|-----------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------|
| 1-decene  | 140.266       | 4.3700         | 3.8908         | 250.35        | 864.80         | 0.015035       | 1/1            | 28       |
| DEA       | 73.138         | 3.3373         | 3.4017         | 218.64        | 2899.5         | 0.035176       | 1/1            | 19       |
| DDC       | 170.34         | 5.3060         | 3.8959         | 249.21        | 4127.1         | 0.080690       | 1/1            | 23       |
| methanol  | 32.042         | 1.5255         | 3.2300         | 188.90        | 1427.1         | 0.291220       | 2/2            | 20       |
| DEDA      | 227.434        | 5.7863         | 4.1204         | 255.09        | 1718.2         | 0.080690       | 1/1            | 20       |
| water     | 18.015         | 2.5472         | 2.1054         | 138.63        | 29             | 0.291220       | 2/2            | 20       |

\( ^aM \) is the molar mass of the pure component. \(^b\)Number of electron-donor sites/number of electron-acceptor sites.

Unlike molecules, generally, \( k_{ij} \) either is a constant or linearly depends on temperature.\(^5\)

\[
\kappa_{ij} = \frac{1}{2}(\sigma_i + \sigma_j)
\]

\[
\mu_{ij} = (1 - k_{ij}) \sqrt{\mu_i\mu_j}
\]

The mixing rules of Wolbach and Sandler\(^27\) are used to calculate the association-energy parameter \( \epsilon_{iB}^{Aij}k_B^{-1} \) (eq 7) and the association-volume parameter \( \kappa^{Aij} \) (eq 8) in a mixture of components \( i \) and \( j \).\(^24\)

\[
\epsilon_{iB}^{Aij} = \frac{1}{2}(\epsilon_{iB}^{AiBj} + \epsilon_{iB}^{Aij})
\]

\[
\kappa^{Aij} = \sqrt{\kappa_{iB}^{Aij}\kappa_{jB}^{Aij}} = \frac{\sqrt{\sigma_i\sigma_j}}{2(\sigma_i + \sigma_j)^3}
\]

Except for the enamine, all PC-SAFT pure-component parameters of compounds involved in the reactions investigated in this work were already available in the literature (Table 1). However, since the enamine is a chemically unstable intermediate product of the RA, PC-SAFT parameters could not be fitted to pure-component properties. For this reason, the pure-component parameters of the structurally comparable DEDA were used in this work to describe the enamine with PC-SAFT.

3. MATERIALS AND METHODS

3.1. Materials. Diethylamine (99.5%, Roth), di-n-butylether (99%, Acros), H\(_2\) (99.999%, Messer Industriegase), methanol (99.8%, VWR Chemicals), n-dodecane (99%, Arcos Organics), and undecanal (97%, ABCR) were purchased from different suppliers. 1,1-Diethylundecan-1-amine (>98%) was synthesized according to Bianga et al.\(^3\). The purity of H\(_2\) was given in volume %, whereas all other purities are mass purities as provided by the suppliers. (Acrylamidoesters)-(1,5-cyclooctadienyl)-rhodium(I) [Rh(acac)(COD)] was donated from Umicro (99%), 4,5-Bis-(diphenylphosphino)-9,9-dimethylxanthene (Xantphos) (98%) was synthesized by Carbolution Chemicals. Water was purified using a Milli-Q device by Merck. All other chemicals were used as received.

3.2. Homogeneity Experiments. Optical investigations of the phase behavior of multicomponent systems were performed in a high-pressure variable-volume view cell (HPVVV) apparatus by New Ways of Analytics analytische Messgeräte GmbH (Lörrach, Germany), which was already used in previous works. The phase behavior of the system was observed during the experiments through two sapphire windows, one installed at the front and one at the back of the cell. The front sapphire is fixed, whereas the back sapphire is movable to vary the volume of the view cell between 30 and 60 mL. The pressure in the HPVVV was adjusted with a manual hydraulic-press M(O) 189 by Maximator (Zorge, Germany). A magnetically coupled stirrer ensured a quick homogenization. Two heating jackets were applied for temperature regulation (temperature stability: ±1 K).

At the beginning of each experiment, a sample of about 40 mL was transferred into the HPVVV and heated under continuous stirring to the desired temperature. Afterward, the volume of the HPVVV was reduced until a system pressure of 3 MPa was obtained. The mixture was equilibrated for an average of 30 min after which the stirrer was turned off, and the phase behavior was visually analyzed.

3.3. Reactor and Equipment. A 300 mL pressure autoclave was used for the RA experiments. To provide a constant H\(_2\) pressure of 3 MPa in the reactor, a pressure vessel \((V = 1 \text{ L}, p = 6 \text{ MPa})\) was used as a reservoir. To reduce the pressure to the desired reaction pressure, a pressure controller was used. A dropping funnel with pressure compensation was used for dosing of undecanal.

3.4. General Procedure of Reductive Amination. To carry out the RA reaction, the catalyst precursor Rh(acac)-(COD) (0.25 mol %), the ligand Xantphos (0.25 mol %), the solvents, and the DEA (molar DEA ratio \( \alpha_{DEA:Reactant} = 4 \)) were filled into the 300 mL pressure autoclave. The pressure autoclave was then closed and rinsed with argon. Afterward, it was supplied with 1 MPa H\(_2\). After the reaction temperature of 373.15 K had been reached, the H\(_2\) pressure was increased to 3 MPa. The reaction mixture was stirred for 1 h to achieve saturation of the solution with H\(_2\) and to form the active catalyst species. Undecanal (4 g) was then fed into the pressure autoclave via a valve using the dropping funnel. The total mass (without gaseous components) used in all experiments was 100 g. Over the course of the reaction, samples were taken manually via a valve and immediately quenched by rapid cooling to follow the reaction progress. These samples were analyzed via gas chromatography (GC).

3.5. Analytics via Gas Chromatography. The composition of the reaction mixture was determined via gas chromatography (Agilent 7890A, HP-5 column 30 m × 0.32 mm × 0.25 μm, 1 μL injection volume, split ratio 150:1, flame ionization detector). The internal standard method using di-n-butylether was applied. Detailed information regarding the heat profile of the GC and retention times as well as the response factors are listed in Tables S1 and S2 of the Supporting Information.

3.6. PC-SAFT Modeling of Homogeneity. To model the multicomponent phase behavior of the RA, HYFO, and HAM, common reaction conditions\(^14,30\) were applied (Table 2).
Accordingly, a temperature of 398.15 K and a pressure of 3.6 MPa were chosen for HYFO and HAM, whereas the phase behavior of the RA was investigated at 373.15 K and 3 MPa. The influence of dissolved gases (H₂ and CO) on the LLE is known to be negligible at these conditions and thus was not investigated in this work. Moreover, the formation of side products was neglected for the PC-SAFT modeling.

The possibility of unwanted phase separation depends on all of the components present in the reaction mixture and their concentration and may thus significantly change during the reaction. Therefore, the reaction medium should be monophase throughout the entire reaction to avoid mass-transfer limitations and the related formation of side products. Since undecanal (HYFO product) is expected to be a better phase mediator than 1-decene (HYFO reactant) between the polar and the nonpolar phase, phase separation is most likely to occur at the start of the HYFO reaction with a high amount of 1-decene in the reaction mixture. In the case of the RA and HAM, water is formed as a byproduct (see Figure 1), causing phase separation at the end of the reaction. Hence, the homogeneity of RA and HAM was investigated at the end of the reaction with the highest amount of water in the system, whereas for the HYFO reaction, the starting composition of the reaction mixture was considered.

3.7. PC-SAFT Modeling of Kinetics. In the case of HYFO, the thermodynamic activity of the reactant 1-decene is the only solvent-dependent property affecting the initial reaction rate (see Section 2.1). Hence, PC-SAFT was used to predict the initial reaction rate as a function of the solvent composition and the water content in the reaction mixture at different temperatures.

In contrast to the HYFO, the RA consists of two reactions (see Figure 1), whereby the latter is the rate-determining reaction. Consequently, the thermodynamic activity of the enamine is decisive for the initial reaction rate. The same applies to the HAM reaction. The influence of dissolved gases (H₂ and CO) on the thermodynamic activity of the reactants was found to be negligible for all investigated reactions and therefore was not taken into account.

4. RESULTS AND DISCUSSION

4.1. Binary Interaction Parameters. All PC-SAFT binary interaction parameters (\(k_{ij}\)) used in this work are summarized in Table 3. Most of them were already available in the literature. The remaining \(k_{ij}\) were fitted to VLE data in this work (for detailed information, see Figures S1 and S2 of the Supporting Information). As can be seen in Table 3, the \(k_{ij}\) sometimes depend on temperature, but the \(k_{ij}\) determined in this work do not.

4.2. PC-SAFT Modeling Results. To prove that the published PC-SAFT parameters are able to describe the phase behavior of the ternary system methanol/DDC/water, PC-SAFT modeling results were compared to experimental literature data. It is worth mentioning that the \(k_{ij}\) (methanol/DDC, methanol/water, and DDC/water) were fitted to phase equilibria (LLE or VLE) of the binary subsystems only, and no ternary data was used for the \(k_{ij}\) fitting. As shown in Figure 2, the PC-SAFT predictions at 398.15 K are in perfect accordance with the experimental data. The ternary system forms an open miscibility gap since both DDC and water as well as DDC and methanol demix. Even the smallest amounts of water in a solvent mixture of DDC and methanol were found to cause phase separation in an initially homogeneous DDC/methanol system with a high DDC content. Moreover, the predicted LLE at 373.15 K reveals that methanol/DDC solvent mixtures with DDC mass...
fractions between 0.17 and 0.68 are already biphasic in the absence of water (Figure 2). This demonstrates the importance of considering the multicomponent reaction system for obtaining reliable information about the homogeneity during the reaction.

Based on the presented and validated approach, the solvent effects on both homogeneity and reaction rate are evaluated in the following. Representing these effects in one chart enables a condensed and fast identification of the most favorable working space for the investigated reactions. The PC-SAFT modeling results are shown in Figures 3, 4, and 6 for HYFO, RA, and HAM, respectively. Predicted binodal curves separate single-phase regions from two-phase regions. Due to mass-transfer limitations in the two-phase region, these areas should be avoided for all reactions. Besides the binodal curve, a mapping of reactant thermodynamic activities in single-phase regions as a function of the methanol/DDC composition on the one hand and of water content, on the other hand, was performed (Figures 3, 4, and 6). The higher the thermodynamic activity of the reactant, the higher is the expected reaction rate (see Section 2.1).

4.2.1. Hydroformylation (HYFO). As a first example, the HYFO reaction was investigated. The PC-SAFT modeling results for 373.15 and 398.15 K are shown in Figure 3, left and right, respectively. As the HYFO could be combined with the RA to the one-pot HAM, the water tolerance of the HYFO reaction mixture was also investigated, although no water is formed during the HYFO (see Figure 1).

As expected, the water tolerance of the HYFO reaction medium against demixing (LLE) decreases with the increasing DDC content of the solvent. Using pure methanol as a solvent, the system is predicted to be homogeneous up to a water weight fraction of $w_{\text{water}} = 0.12$ at 373.15 K ($w_{\text{water}} = 0.16$ at 398.15 K). However, if pure DDC is used as a solvent, phase separation is already expected for much lower water contents ($w_{\text{water}} > 0.0007$ at 373.15 K and $w_{\text{water}} > 0.0015$ at 398.15 K). The binodal curves show a strong curvature. For DDC contents in the solvent mixture lower than 30 wt %, the water tolerance of the reaction mixture is very low ($w_{\text{water}} < 2.3 \times 10^{-3}$) at 373.15 K, whereas for higher DDC contents, the water tolerance strongly increases. This behavior is in very good accordance with the LLE of the ternary system methanol/DDC/water (see Figure 2).

An increasing thermodynamic activity of 1-decene $a_{1\text{-decene}}$ and thereby an increased reaction rate was predicted for decreasing DDC contents in the solvent mixture. Moreover, the temperature dependence of $a_{1\text{-decene}}$ was found to be negligible in the investigated temperature range. In a water-free system with pure DDC as the solvent, the thermodynamic activity of 1-decene was calculated to be $a_{1\text{-decene}} = 0.12$ at
398.15 K, while using pure methanol as solvent, $a_{\text{decene}} = 0.26$ was obtained. This corresponds to an increase of the initial reaction rate by a factor of 2.2 caused by solvent effects only (see eq 3). High amounts of water in the reaction system were predicted to increase the reaction rate further, while small water contents only little effect $a_{\text{decene}}$.

Based on these findings, methanol would be the preferred solvent for HYFO to reach the best reaction performance. Increasing the DDC content of the solvent mixture was found to significantly reduce both the initial reaction rate and the water tolerance of the reaction medium.

### 4.2.2. Reductive Amination (RA)

As a second example, the RA reaction was investigated at 373.15 and 398.15 K. The modeling results are shown in Figure 4, left and right, respectively. Using pure methanol as the solvent, the reaction medium was predicted to be homogeneous up to water contents of $w_{\text{water}} = 0.34$ at 373.15 K ($w_{\text{water}} = 0.39$ at 398.15 K). If pure DDC is used instead, phase separation occurs at water weight fractions higher than 0.001 at 373.15 K and higher than 0.002 at 398.15 K. Hence, the water tolerance of the RA is greater than that of the HYFO (Figure 3), which can be attributed to the increased amount of DEA in the system and its strong solubilizing effect compared to alkenes and aldehydes. 19,35

As a result of the water formed during the reaction (see Figure 1), it is not possible to perform the RA in pure DDC without the occurrence of phase separation (Figure 4). At 373.15 K, a homogeneous liquid at the end of the reaction can only be obtained at contents in the solvent mixture of up to 50 wt % DDC. This DDC content is directly obtained from Figure 4 by determining the DDC content on the binodal curve, which belongs to the amount of water formed during the reaction. By increasing the reaction temperature to 398.15 K, the working space for a homogeneous reaction medium is enlarged to up to 86 wt % DDC in the solvent mixture.

The thermodynamic activity of enamine $a_{\text{enamine}}$ was found to be the crucial quantity for affecting the RA reaction rate (Section 3.7). As can be seen in Figure 4, $a_{\text{enamine}}$ increases with increasing methanol content in the solvent mixture. Due to strong interactions between methanol and DDC, the lowest value of $a_{\text{enamine}}$ was not obtained in pure DDC, but for 65 wt % DDC in the solvent mixture. In a water-free system with pure methanol as a solvent, the thermodynamic activity of enamine was calculated to be $a_{\text{enamine}} = 0.019$ at 398.15 K, while for 65 wt % DDC content in the solvent mixture, an enamine activity of $a_{\text{enamine}} = 0.007$ was obtained. Thus, the initial reaction rate is expected to increase by a factor of 2.7 if pure methanol is used as the solvent. Small amounts of water in the reaction system again were predicted to have a negligible effect on $a_{\text{enamine}}$.

To gain further insights on how temperature affects the phase behavior of the RA, the water tolerance of the multicomponent system (containing methanol, DDC, water, DEA, and DEDA) was modeled as a function of temperature and water content in the system for varying methanol/DDC solvent compositions. Figure 5 reveals an almost linearly increasing water tolerance with rising temperatures for all solvent mixtures investigated. In this case, the intersection of the line representing the amount of water formed during the reaction and the one of the DDC content in the solvent mixture indicates the lowest temperature required for a homogeneous reaction system (Figure 5). According to the modeling results, the reaction temperature should be at least 330 K for homogeneous reaction systems when using 20 wt % DDC in the solvent mixture. For 50 wt % DDC content of the solvent mixture, this temperature increases to 376 K.

Again, methanol would be the preferred solvent for the RA to reach the best reaction performance and to avoid phase separation during the reaction. DDC was found to significantly decrease both the thermodynamic reactant activity and the water tolerance of the reaction medium. As a result, higher reaction temperatures are required to keep the reaction mixture homogeneous for high DDC contents in the solvent mixture.

### 4.2.3. Hydroaminomethylation (HAM)

Third, we applied our approach to the one-pot HAM. As shown in Figure 6, the predicted binodal curve is quite similar to the one of the RA (Figure 4). In pure methanol, the reaction medium is expected to be a homogeneous liquid up to a water content of $w_{\text{water}} = 0.22$ at 373.15 K ($w_{\text{water}} = 0.26$ at 398.15 K) and in addition to that exceeding the water tolerance of the HYFO. This is certainly caused by the fact that DEDA is a stronger mediator between the polar and the nonpolar phase than 1-decene. Nevertheless, the water tolerances of the HAM and RA are very similar, although the DEDA content in the HAM reaction system is higher than that in the RA system. This is caused by the lower amount of DEA in the HAM reaction system, which is performed without a molar excess of DEA (Table 2). The strong solubilizing effects of DEA were already described in the literature. 14,40 As a result, the positive effect of DEDA on the water tolerance of the system is counterbalanced by the absence of DEA, keeping the water tolerance of the HAM in the same range as that of the RA.

At 373.15 K, the reaction system is predicted to be homogeneous up to 33 wt % DDC in the solvent mixture for all compositions occurring during the reaction. By increasing the reaction temperature to 398.15 K, the working space for the reaction is enlarged to up to 55 wt % DDC content in the solvent mixture. Due to higher initial reactant concentration (HAM: 10 wt %, RA: 4 wt %), more water is formed during the HAM, requiring a higher methanol content in the solvent to avoid phase separation.

The thermodynamic activity map of the reactant shown in Figure 5 reveals an almost linearly increasing water tolerance with rising temperatures for all solvent mixtures investigated.
found for 65 wt % DDC in the solvent mixture. These results are in very good agreement with the RA findings and emphasize the importance of simultaneously investigating the reactant thermodynamic activity and the homogeneity of the reaction system. Based on the predicted thermodynamic activity of the reactants at 398.15 K (Figure 6 (right)) only, pure DDC would be suitable as a solvent. However, since it is expected to cause phase separation during the reaction (increasing water content), pure DDC as a solvent should be avoided. The thermodynamic activity of enamine can be increased by a factor of 2.5 using pure methanol compared to 65 wt % DDC in the solvent mixture, which is consistent with the predicted solvent effects on the initial reaction rate for the RA. The higher absolute values of enamine were caused by the higher reactant concentrations in the HAM reaction mixture (see Table 2).

Overall, these findings are in line with the results for the previously analyzed HYFO and RA. Again, methanol was found to be the preferred solvent, distinctly increasing the initial reaction rate and the water tolerance of the reaction medium.

4.3. Experimental Validation. To validate the PC-SAFT modeling results on homogeneity, samples were visually analyzed at reaction conditions using the HPVVV apparatus.

Figure 6. PC-SAFT predictions of enamine thermodynamic activities (a_enamine) at 373.15 K (left) and 398.15 K (right) at 3.6 MPa as a function of the methanol/DDC solvent composition and the water content in the HAM reaction mixture (see Section 3.6) (highest a_enamine is green; lowest a_enamine is red). The solid lines represent binodal curves, and the white areas mark two-phase zones. PC-SAFT modeling results were obtained using the parameters from Tables 1 and 3. The dashed lines represent the amount of water formed during the HAM.

Figure 7. View through the front sapphire into the HPVVV: a heterogeneous mixture at ambient conditions (left) and a homogeneous liquid at reaction conditions (373.15 K, 3 MPa) (right).

Figure 8. PC-SAFT predictions of enamine thermodynamic activities (a_enamine) at 373.15 K at 3 MPa as a function of the methanol/DDC solvent composition and the water content in the RA reaction mixture (see Section 3.6) (highest a_enamine is green; lowest a_enamine is red). HPVVV homogeneity experiments (1)–(6) and experimental product yield of DEDA Y_DEDA after t = 2 min (diamonds) are compared to the PC-SAFT modeling results for the RA at 373.15 K and 3 MPa. The solid line represents the predicted binodal curve separating the single-phase region (white area) from the two-phase region (colored area). Empty stars are homogeneous samples; half-filled stars are heterogeneous samples. The PC-SAFT modeling results were obtained using the parameters from Tables 1 and 3. The detailed reaction conditions are presented in Section 3.4.
For that purpose, samples of known compositions were prepared. Chemical reactions were not performed in the HPVVV to avoid deviations due to incomplete conversion or due to the formation of byproducts.

Figure 7 (left), for example, shows a heterogeneous sample that was transferred into the HPVVV at ambient conditions. After heating up and pressurizing the system, the behavior of the mixture was examined under RA reaction conditions at 373.15 K and 3 MPa (Figure 7 (right)). The difference between the cloudy heterogeneous system at ambient conditions and the homogeneous liquid at reaction conditions becomes visible.

4.3.1. Reductive Amination (RA). Homogeneity experiments for the RA were performed at 373.15 K and 3 MPa for six mixtures of different compositions (Figure 8 (1)−(6)) that were chosen to cover a wide range of conditions close to the predicted binodal curve. The detailed compositions of the samples are listed in Table S3 of the Supporting Information. Based on the PC-SAFT predictions, samples (1)−(3) were expected to form one homogeneous liquid at reaction conditions, while samples (4)−(6) should be heterogeneous mixtures. In addition, the water content of the sample (5) was chosen to be equal to the amount of water generated during the RA. Figure 8 shows the comparison of these validation experiments with the modeling results.

It turned out that the experiments were in perfect accordance with the modeling results. For samples (1)−(3), a homogeneous liquid was observed at reaction conditions, allowing a clear view through the cell to the sapphire piston in the back. In contrast, samples (4)−(6) show strong turbidity of the sample caused by a finely dispersed second liquid phase refracting the light. As a result, the back sapphire piston is no longer visible.

Furthermore, RA reaction experiments were performed at 373.15 K and 3 MPa in methanol/DDC solvent mixtures of different compositions. Moreover, the initial water concentration was varied. The obtained molar yield of the product DEDA (Y_DEDA) after t = 2 min is shown in Figure 8. For detailed results, see Table S5 of the Supporting Information. The highest product yield Y_DEDA = 94.1% was obtained in pure methanol, revealing very good accordance with the PC-SAFT predictions (highest enamine activity in pure methanol). Forty weight percent DDC content in the solvent mixture resulted in a reduction of the product yield to Y_DEDA = 86.6%, confirming the predicted negative effect of DDC on the initial reaction rate.

4.3.2. Hydroaminomethylation (HAM). Further, homogeneity experiments were performed for the HAM. Compared to the RA experiments, no DEA was present in the mixture, and the HPVVV was heated up to 398.15 K instead of 373.15 K. Three samples of different compositions were prepared. Two of them were expected to form a heterogeneous mixture at reaction conditions; the third was expected to form a homogeneous liquid according to the PC-SAFT predictions. The detailed compositions of the samples are listed in Table S4 of the Supporting Information.

As can be seen in Figure 9, again all experimental results perfectly agree with the predictions. Sample (1) formed one homogeneous liquid phase at reaction conditions. In contrast, two distinguishable liquid phases with a sharp phase boundary were formed in samples (2) and (3).

5. CONCLUSIONS

In this work, we applied a thermodynamic-activity-based approach built on PC-SAFT to predict solvent effects on both phase behavior and reaction rates of chemical reactions. The presented workflow applies to a wide variety of liquid-phase reactions. It was used to the example reactions hydroformylation (HYFO), reductive amination (RA), and hydroaminomethylation (HAM) in a solvent mixture of methanol and n-dodecane. The thermodynamic activities of the reactants in the multicomponent reaction systems and the liquid−liquid equilibrium (LLE) were predicted using PC-SAFT and compared to batch and homogeneity experiments performed in this work.

For all reactions, the water tolerance against demixing and therewith the working space of the reaction increased with increasing temperature. However, it dramatically decreased with increasing n-dodecane (DDC) content in the solvent mixture. Moreover, DDC was found to significantly lower the thermodynamic reactant activity and thus the reaction rate. This fact results in the formation of more byproducts, thus reducing the product yield. As a result, performing the considered reactions in a solvent system of methanol/DDC should be critically evaluated. The best reaction performance was predicted and experimentally validated in the absence of DDC. The modeling results agree very well with the experimental findings and clearly emphasize the positive effect of high methanol contents in the solvent on both the reaction rates and the homogeneity during the reaction. It is worth mentioning that alternatively, DDC could be added only after the reaction to form a second liquid phase, thus enabling an efficient product separation and catalyst recycling.

The main advantage of the presented approach is the ability to predict the LLE of the multicomponent system and initial reaction rates just based on experimental phase equilibrium data used for estimating binary model parameters. This provides in-depth process insights and the opportunity to identify the most promising solvent compositions for the investigated reaction system so that the liquid remains one homogeneous phase during the reaction and high reaction rates are achieved. As no experimental reaction data is required for the parameter fitting, promising solvent compositions and
working spaces can be identified fast and reliably, reducing time-consuming experiments to a minimum.

■ ASSOCIATED CONTENT

Supporting Information
The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.iecr.1c03891.

Detailed information on the GC procedure, compositions of the homogeneity samples, and VLEs (water/DEDAs and DEA/DEDA) (PDF)

■ AUTHOR INFORMATION

Corresponding Author
Gabriele Sadowski – Laboratory of Thermodynamics, Department of Biochemical and Chemical Engineering, TU Dortmund University, 44227 Dortmund, Germany;
orcid.org/0000-0002-5038-9152; Phone: +49 231-7552635; Email: gabriele.sadowski@tu-dortmund.de

Authors
Fabian Huxoll – Laboratory of Thermodynamics, Department of Biochemical and Chemical Engineering, TU Dortmund University, 44227 Dortmund, Germany;
Anita Kampwerth – Laboratory of Thermodynamics, Department of Biochemical and Chemical Engineering, TU Dortmund University, 44227 Dortmund, Germany
Thomas Seidensticker – Laboratory of Thermodynamics, Department of Biochemical and Chemical Engineering, TU Dortmund University, 44227 Dortmund, Germany
Dieter Vogt – Laboratory of Thermodynamics, Department of Biochemical and Chemical Engineering, TU Dortmund University, 44227 Dortmund, Germany;
orcid.org/0000-0002-8514-5326

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.iecr.1c03891

Notes
The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Gefördert durch die Deutsche Forschungsgemeinschaft (DFG)—TRR 63 “Integrierte chemische Prozesse in flüssigen Mehrphasensystemen” (Teilprojekte A4 und A11)—S6091768. Funded by the Deutsche Forschungsgemeinschaft (DFG, German Research Foundation)—TRR 63 “Integrated Chemical Processes in Liquid Multiphase Systems” (subprojects A4 and A11)—S6091768. The authors thankfully acknowledge Umicore for the donation of rhodium precursors. Special thanks go to Jonas Bianga for the synthesis of N,N-diethylundecan-1-amine.

■ ABBREVIATIONS

| Abbreviation | Definition                        |
|--------------|----------------------------------|
| DDC          | n-dodecane                       |
| DEA          | diethylamine                     |
| DEA          | N,N-diethylundecan-1-amine       |
| enamine      | N,N-diethyldicyclemamine         |
| HAM          | hydroaminomethylation            |
| HPVVV        | high-pressure variable-volume view cell |
| HYFO         | hydroformylation                 |
| LLE          | liquid-liquid equilibrium        |
| PC-SAFT      | Perturbed-Chain Statistical Associating Fluid Theory |
| RA           | reductive amination               |
| Rh(acac)(COD) | (acetylacetonato)-(1,5-cyclooctadienyl)-rhodium(I) |
| TMS          | thermomorphic multiphase system  |
| VLE          | vapor-liquid equilibrium         |
| Xanthos      | 4,5-bis-(diphenylphosphino)-9,9-dimethyl-xanthene |

■ LIST OF SYMBOLS

| Symbol | Definition                        |
|--------|----------------------------------|
| A      | Helmholtz energy (J mol⁻¹)       |
| a      | thermodynamic activity           |
| c      | concentration (mol L⁻¹)          |
| k_i    | apparent reaction rate constant (mol L⁻¹ min⁻¹) |
| k_i²   | intrinsic reaction rate constant (mol L⁻¹ min⁻¹) |
| k_B    | Boltzmann constant (K⁻¹)        |
| k_i,j  | binary interaction parameter     |
| M      | molar mass (g mol⁻¹)             |
| m_{seg} | segment number                   |
| N_{assoc} | number of association sites     |
| p      | pressure (Pa)                    |
| r      | reaction rate (mol L⁻¹ min⁻¹)    |
| T      | temperature (K)                  |
| t      | time (min)                       |
| u      | standard uncertainty             |
| u_k_B | dispersion energy parameter (K) |
| V      | volume (mL)                      |
| w_i    | mass fraction                    |
| x_i    | mole fraction                    |

■ GREEK SYMBOLS

| Symbol | Definition                        |
|--------|----------------------------------|
| α      | molar ratio                      |
| γ_{i,c} | concentration-based activity coefficients |
| γ_{i,m} | mole fraction-based activity coefficients |
| ϵ_{k_B} | association-energy parameter (K) |
| κ_{k_B} | association-volume parameter     |
| σ_i    | segment diameter (Å)             |

■ SUBSCRIPT

| Subscript | Meaning                         |
|-----------|---------------------------------|
| i         | component index                 |
| j         | component index                 |
| r         | relative                        |

■ SUPERSCRIPT

| Superscript | Meaning                   |
|-------------|---------------------------|
| assoc       | associating               |
| disp        | dispersion                |
| hc          | hard chain                |
| L           | liquid                    |
| res         | residual                  |
| seg         | segment                   |
| V           | vapor                     |

■ REFERENCES

(1) Reichardt, C.; Welton, T. Solvents and Solvent Effects in Organic Chemistry; Wiley: Weinheim, 2011.
(2) Riechert, O.; Husham, M.; Sadowski, G.; Zeiner, T. Solvent effects on esterification equilibria. AIChE J. 2015, 61, 3000–3011.
(3) Behr, A.; Fängewisch, C. Rhodium-catalysed synthesis of branched fatty compounds in temperature-dependent solvent systems. J. Mol. Catal. A: Chem. 2003, 197, 115–126.
(4) Bianga, J.; Künneke, K. U.; Gaide, T.; Vorholt, A. J.; Seidensticker, T.; Dreimann, J. M.; Vogt, D. Thermomorphic
Multiphase Systems: Switchable Solvent Mixtures for the Recovery of Homogeneous Catalysts in Batch and Flow Processes. Chem.—Eur. J. 2019, 25, 11586–11608.

(5) Behr, A.; Vorholt, A. J.; Ostrowski, K. A.; Seidensticker, T. Towards resource efficient chemistry: tandem reactions with renewables. Green Chem. 2014, 16, 982–1006.

(6) Tumakaka, F.; Gross, J.; Sadowski, G. Thermodynamic modeling of complex systems using PC-SAFT. Fluid Phase Equilib. 2005, 228–229, 89–98.

(7) Lemberg, M.; Sadowski, G.; Gerlach, M.; Kohls, E.; Stein, M.; Hamel, C.; Seidel-Morgenstern, A. Predicting solvent effects on the 1-dodecene hydroformylation reaction equilibrium. AIChE J. 2017, 63, 4576–4585.

(8) Knieberin, M.; Wangler, A.; Luong, T. Q.; Winter, R.; Held, C.; Sadowski, G. Combined co-solvent and pressure effect on kinetics of a peptide hydrolysis: an activity-based approach. Phys. Chem. Chem. Phys. 2019, 21, 22224–22229.

(9) Lemberg, M.; Sadowski, G. Predicting the Solvent Effect on Esterification Kinetics. ChemPhysChem 2017, 18, 1977–1980.

(10) Wangler, A.; Held, C.; Sadowski, G. Thermodynamic Activity-Based Solvent Design for Bioreactions. Trends Biotechnol. 2019, 37, 1038–1041.

(11) Schäfer, E.; Sadowski, G.; Enders, S. Calculation of complex phase equilibria of DMF/alkane systems using the PCP-SAFT equation of state. Chem. Eng. Sci. 2014, 115, 49–57.

(12) Ahmed, M.; Seayad, A. M.; Jackstell, R.; Beller, M. Amines made easily: a highly selective hydroaminomethylation of olefins. J. Am. Chem. Soc. 2003, 125, 10311–10318.

(13) Kalick, P.; Urrutigoity, M. Tandem Hydroaminomethylation Reaction to Synthesize Amines from Alkenes. Chem. Rev. 2018, 118, 3833–3861.

(14) Schlüter, S.; Künneemann, K. U.; Freis, M.; Roth, T.; Vogt, D.; Dreimann, J. M.; Skiborowski, M. Continuous co-product separation by organic solvent nanofiltration for the hydroaminomethylation in a thermomorphic multiphase system. Chem. Eng. J. 2021, 409, No. 128219.

(15) Kirschtowski, S.; Jameel, F.; Stein, M.; Seidel-Morgenstern, A.; Hamel, C. Kinetics of the reductive amination of 1-undecanediol in thermomorphic multicomponent system. Chem. Eng. Sci. 2021, 230, No. 116187.

(16) Kirschtowski, S.; Kadar, C.; Seidel-Morgenstern, A.; Hamel, C. Kinetic Modeling of Rhodium-Catalyzed Reductive Amination of 1-Undecanol in Different Solvent Systems. Chem. Ing. Tech. 2020, 92, 582–588.

(17) Bianga, J.; Künneemann, K. U.; Goclik, L.; Schurm, L.; Vogt, D.; Seidensticker, T. Tandem Catalytic Amine Synthesis from Alkenes in Continuous Flow Enabled by Integrated Catalyst Recycling. ACS Catal. 2020, 10, 6463–6472.

(18) Huxoll, F.; Jameel, F.; Bianga, J.; Seidensticker, T.; Stein, M.; Sadowski, G.; Vogt, D. Solvent Selection in Homogeneous Catalysis—Optimization of Kinetics and Reaction Performance. ACS Catal. 2021, 11, 590–594.

(19) Huxoll, F.; Schlüter, S.; Budde, R.; Skiborowski, M.; Petzold, M.; Böhm, L.; Kraume, M.; Sadowski, G. Phase Equilibria for the Hydroaminomethylation of 1-Decene. J. Chem. Eng. Data 2021, 66, 4484–4495.

(20) Huxoll, F.; Heyng, M.; Andreeva, I. V.; Verevkin, S. P.; Sadowski, G. Thermodynamic Properties of Biogenic Amines and their Solutions. J. Chem. Eng. Data 2021, 66, 2822–2831.

(21) Lemberg, M.; Schomäcker, R.; Sadowski, G. Thermodynamic prediction of the solvent effect on transesterification reaction. Chem. Eng. Sci. 2018, 176, 264–269.

(22) Gmehlings, J.; Li, J.; Schiller, M. A modified UNIFAC model. 2. Present parameter matrix and results for different thermodynamic properties. Ind. Eng. Chem. Res. 1993, 32, 178–193.

(23) Gross, J.; Sadowski, G. Perturbed-Chain SAFT: An Equation of State Based on a Perturbation Theory for Chain Molecules. Ind. Eng. Chem. Res. 2001, 40, 1244–1260.

(24) Gross, J.; Sadowski, G. Application of the Perturbed-Chain SAFT Equation of State to Associating Systems. Ind. Eng. Chem. Res. 2002, 41, 5510–5515.

(25) Berthelot, D. Sur le m’elange des gaz. C. R. Acad. Sci. 1898, 126, 1703–1706.

(26) Lorentz, H. A. Ueber die Anwendung des Satzes vom Virial in der kinetischen Theorie der Gase. Ann. Phys. 1881, 248, 127–136.

(27) Woballah, J. P.; Sandler, S. I. Using Molecular Orbital Calculations to Describe the Phase Behavior of Cross-associating Mixtures. Ind. Eng. Chem. Res. 1998, 37, 2917–2928.

(28) Ghosh, A.; Chapman, W. G.; French, R. N. Gas solubility in hydrocarbons—a SAFT-based approach. Fluid Phase Equilib. 2003, 209, 229–243.

(29) Kiesow, K.; Tumakaka, F.; Sadowski, G. Experimental investigation and prediction of oiling out during crystallization process. J. Cryst. Growth 2008, 310, 4163–4168.

(30) Bianga, J.; Kopplin, N.; Hülsmann, J.; Vogt, D.; Seidensticker, T. Rhodium-Catalysed Reductive Amination for the Synthesis of Tertiary Amines. Adv. Synth. Catal. 2020, 362, 4415–4424.

(31) Göhrnt, M.; Sadowski, G. Phase-equilibrium measurement and modeling of the PMMA/MMA/carbon dioxide ternary system. J. Supercrit. Fluids 2008, 46, 218–225.

(32) Brandenbusch, C.; Sadowski, G. Supercritical phase behavior for biotransformation processing. J. Supercrit. Fluids 2010, 55, 635–642.

(33) Vogelpohl, C.; Brandenbusch, C.; Sadowski, G. High-pressure gas solubility in multicomponent solvent systems for hydroformylation. Part I: Carbon monoxide solubility. J. Supercrit. Fluids 2013, 81, 23–32.

(34) Lemberg, M.; Sadowski, G. Phase Equilibria for the Hydroesterification of 10-Undecenoic Acid Methyl Ester. J. Chem. Eng. Data 2016, 61, 3317–3325.

(35) Schäfer, E.; Brunsch, Y.; Sadowski, G.; Behr, A. Hydroformylation of 1-Dodecene in the Thermomorphic Solvent System Dimethylformamide/Decane. Phase Behavior—Reaction Performance—Catalyst Recycling. Ind. Eng. Chem. Res. 2012, 51, 10296–10306.

(36) Fuentes, J. A.; Wawrzyniak, P.; Roff, G. J.; Bühl, M.; Clarke, M. L. On the rate-determining step and the ligand electronic effects in rhodium catalysed hydrogenation of enamines and the hydroaminomethylation of alkenes. Catal. Sci. Technol. 2011, 1, 431.

(37) Altunetepe, E. Thermodynamics of Enzyme-Catalysed Reactions in Organic Media. Ph.D. Thesis, TU Dortmund University, Dr. Hüt: München, 2018.

(38) Haarmann, N.; Enders, S.; Sadowski, G. Modeling binary mixtures of n-alkanes and water using PC-SAFT. Fluid Phase Equilib. 2018, 470, 203–211.

(39) Lasich, M.; Moodley, T.; Bhownath, R.; Naidoo, P.; Ramjugernath, D. Liquid—Liquid Equilibria of Methanol, Ethanol, and Propan-2-ol with Water and Dodecane. J. Chem. Eng. Data 2011, 56, 4139–4146.

(40) Künneemann, K. U.; Bianga, J.; Scheel, R.; Seidensticker, T.; Dreimann, J. M.; Vogt, D. Process Development for the Rhodium-Catalyzed Reductive Amination in a Thermomorphic Multiphase System. Org. Process Res. Dev. 2020, 24, 41–49.