**Model-based** **Solvent Screening for a Reductive Amination.**

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**Highlights**

* Application of an activity coefficient-based approach for a fast solvent screening.
* Solvent influence on reaction equilibrium and reaction rate can be predicted.
* No experimental reaction data needed.
* Promising solvents could be confirmed by experiments.

**1. Introduction**

Reaction equilibrium and reaction rate of chemical reactions are significantly influenced by the solvent used. Therefore, to optimize the equilibrium position, to increase the selectivity towards the product of interest and to enhance the reaction rate, it is important to consider the solvent influence on a reaction [1, 2]. State-of-the-art lab screening is highly time-consuming and therewith cost-intensive.

In this work, the RA (reductive amination) of undecanal and diethylamine to DEAU (1-diethylamino-undecan) and water was investigated. Appropriate solvents were identified using a thermodynamic approach and subsequently validated by experiments.

**2. Methods**

The thermodynamic equilibrium constant Ka, which does NOT depend on the solvent nor on the reactant concentrations, was used as the starting point of this approach. Ka is the product of Kx, which contains the equilibrium concentrations xi, and of Kγ, which contains the activity coefficients i.As the activity coefficients may strongly depend on the solvent whereas Ka does not, Kx is also strongly influenced by the solvent.

According to equation 1, increasing activity coefficients of the reactants lead to an increase of product concentrations at the reaction equilibrium. Moreover, high activity coefficients of the reactants imply a high reaction rate (2). Accordingly, the aim of this approach is to identify solvents which lead to high activity coefficients of the reactants.

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| $$K\_{a} =\frac{x\_{Product,1}∙ x\_{Product,2}}{x\_{Reactant,1}∙ x\_{Reactant,2}} ∙ \frac{γ\_{Product,1}∙ γ\_{Product,2}}{γ\_{Reactant,1}∙ γ\_{Reactant,2}}$$ | (1) |
| $$r =k ∙ x\_{Reactant,1}∙ γ\_{Reactant,1} ∙ x\_{Reactant,2}∙ γ\_{Reactant,2}$$ | (2) |

 For the solvent screening, a wide range of different solvents was investigated. Using the modified group contribution method UNIFAC [3], the activity coefficients were predicted without using any reaction data. Solvents were identified that lead to the highest possible reactant-activity coefficients. Afterwards, the most promising solvents of the screening were validated regarding reaction equilibrium and reaction rate.

**3. Results and discussion**

Based on the predicted activity coefficients, it could be shown that the applied solvents significantly influence the reaction rate and the reaction equilibrium. The activity coefficients of the reactants deviated from each other by a factor of up to 20. Out of 14 investigated solvents, methanol, DMF (*N,N*-dimethylformamide) and ACN (acetonitrile) turned out to be the most promising ones (see Figure 1).



**Figure 1.** RA-reactant activity coefficient for reaction mixtures in different solvents.

To validate these results, experiments were performed in these solvents at 30 bar and 100 °C. Results showed that the highest product concentrations and reaction rates were indeed achieved in the three top solvents of the screening. Furthermore, using this approach it was possible to qualitatively predict the influence of initial substrate concentrations on reaction yield and kinetics.

**4. Conclusions**

Applying a thermodynamic approach allows a fast solvent screening without the need of any experimental reaction data for parameter estimations. Predictions and experimental results were in very good agreement, showcasing the advantages of thermodynamic models in order to screen possible solvents over the experimental and thus time and cost consuming lab screening.

**References**

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