

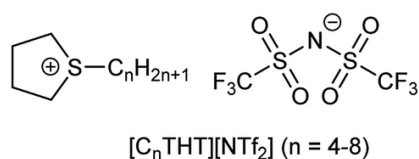
Self-Induced Odd-Even Effect in Enzyme-Catalyzed Reactions

Finding explanations through thermodynamic modeling of molecular interactions

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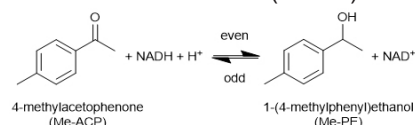
Enzyme-catalyzed reactions often take place in water. In this work, ionic liquids (ILs) were added to water to shift the reaction equilibrium of enzyme-catalyzed reactions with the goal to increase the reaction yield of the product methylated 1-phenylethanol (Me-PE). Tetrahydrothiophene-based ILs (THT-ILs) were used with varying IL-cation chain length and constant IL-anion. An odd–even effect of the IL-cation chain length on the yield was discovered. Beneficially, the addition of small amounts of THT-ILs with odd numbered chain length allowed very high yields, while adding THT-ILs with even numbered chain length caused lower yields. Reasoning behind this odd-even effect was found in molecular interactions of the IL cation and the reaction product Me-PE and, further, critical micellar concentration measurements validated the observations.

Tetrahydrothiophene-based ionic liquids (THT-ILs) are introduced in this work as a new IL class based on cyclic sulfonium (Scheme 1). Common ILs drastically decrease the activity of enzymes even at small concentration in the reaction medium. Additionally, the utilized enzyme alcohol dehydrogenase (ADH) needs dry storage at 18 °C. Remarkably, pure THT-ILs were found to stabilize the enzyme for over one month at ambient condition in liquid phase; a large benefit boosting the activity about 500 times. THT-ILs were thus found suitable to additives in bio reactions.



Scheme 1: Chemical structures of the tetrahydrothiophenium cation ($[C_nTHT]^+$; $3 < n < 9$) and bis(trifluoromethanesulfonyl)imide anion ($[NTf_2]^-$).

The investigated ADH-catalyzed reaction is visualized in Scheme 2. 4-methylacetophenone (Me-ACP) reacts to methylated 1-phenylethanol (Me-PE) using the co factor nicotinamide adenine dinucleotide (NADH).



Scheme 2: Reaction scheme of the alcohol dehydrogenase reaction from Me-ACP to Me-PE with the mandatory co-factor NADH.

The influence of THT-ILs on the percent conversion of the ADH reaction was monitored using UV/Vis spectroscopy. The resulting difference in experimental equilibrium conversions at 298 K are depicted in Figure 1 with the baseline showing the conversion in the neat buffer ($X = 87\%$).

While even numbered THT-ILs already at very small concentrations of 10 mmol/L largely decrease the conversion (-7%), the odd numbered THT-IL additives highly benefit the reaction ($+9\%$) to reach almost quantitative conversion. This odd even effect was never before reported for any (bio) reaction. One possible approach to find reasons for the odd even effect is thermodynamic modeling applying electrolyte models, which are required as the reacting agents are charged.

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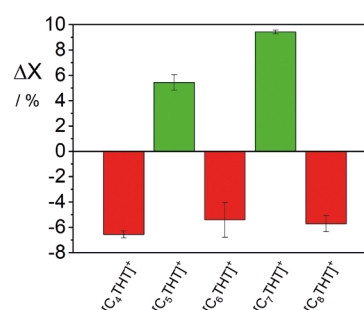


Figure 1: Difference in experimental conversion of the ADH reaction between buffer + 10 mmol/kg IL and neat buffer (base line) for THT-ILs at 298 K and 1 bar.

The thermodynamic model ePC-SAFT is suitable for this as it accounts for charges and hydrogen bonding. ePC-SAFT was used in this work to screen intermolecular forces that might explain the odd even effect. Therefore, the activity coefficients of reactants and products were modeled. Figure 2 shows the activity coefficients γ_i^{eq} for Me-ACP (blue bars) and Me-PE (orange bars). As expected, γ_{Me-ACP}^{eq} monotonically rises with increasing IL cation chain length. In contrast, γ_{Me-PE}^{eq} underlies an odd-even effect. That is, Me-PE beneficially interacts with the THT-IL with odd-number IL cation chain length, explaining the increased conversion from a theoretical point of view.

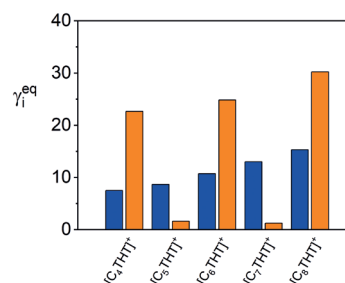


Figure 2: Activity coefficients γ_i^{eq} of the reactant Me-ACP (blue) and the product Me-PE (orange) in the reaction medium in presence of 10 mmol/L THT-IL with varied alkyl chain length n within the $[C_nTHT]$ cation.

The findings with ePC-SAFT were afterwards backed by measurements of the critical micellar concentration showing the same characteristic behavior favoring the odd numbered THT-ILs. That said, a high performance thermodynamic model like ePC-SAFT describing the reaction conditions is essential for deriving and screening of new co solvents and process variables.

Publications:

M. Bülow, A. Schmitz, T. Mahmoudi, D. Schmidt, F. Junglas, C. Janiak, C. Held, RSC Adv. 10, 28351-28354 (2020).