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Understanding alcohol dehydrogenase catalysis and enzyme-substrate-binding in non-conventional reaction media

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PURPOSE OF THE ABSTRACT

Understanding the enzymatic behavior of alcohol dehydrogenase (ADH) in non-conventional reaction media is vital to establish its catalysis in these systems and overcome the limitations of aqueous solutions. Those include a limited solubility of hydrophobic reactants and water-induced side effects. Solvent selections for ADH catalysis are pivotal to optimize the biotransformation in non-conventional reaction media. In this context, the hydration of ADHs is crucial to maintain its activity in non-aqueous media and is difficult to access experimentally. However, molecular dynamics (MD) simulations can shed light on the hydration of ADHs in different solvents and their influence on the enzyme behavior. Moreover, in conjunction with experimental analysis, MD simulations offer a much deeper understanding of the underlying phenomena on the atomistic level.

In this work, we present the investigation of horse liver alcohol dehydrogenase (HLADH) as a model enzyme in different organic solvents [1] and deep eutectic solvents (DESs) [2,3] – a novel solvent class, which recently got attention in biocatalysis. With the help of MD simulations, the solvation effects of DESs, individual DES components and organic solvents and their impact on the specific activity and stability of HLADH in these systems could be identified. For example, a high affinity of the HLADH surface towards glycerol could be linked to a drastically improved enzymatic stability in ChCl-Gly (1:2)-water mixtures. This could even be improved by shifting the molar ratio of glycerol in ChCl-Gly from 1:2 to 1:9 (Fig. 1) [3]. Moreover, the spatial distribution of the organic solvent and DES molecules around HLADH could identify the regions on the enzyme surface that are strongly affected by a specific solvent [1,3]. This helps to unravel the solvent impact on the molecular flexibility and regional/global structural changes of HLADH [2,3]. In addition, for an organic-aqueous phase boundary, the MD simulations could identify the position and orientation of HLADH at this interface and highlighted the usage of methyl tert-butyl ether (MTBE) and cyclopentyl methyl ether (CPME) as suitable organic solvents for ADH catalysis [1].

A particular focus is laid on the active center of HLADH and its structural changes in different reaction environments. The MD simulations can hereby help to unravel the enzyme substrate interactions in different solvent environments and can even quantify them by calculating free energy profiles of a substrate molecule along the substrate-binding tunnel from the bulk phase to the active center.

Understanding the enzyme behavior in non-conventional reaction media and its underlying phenomena on the atomistic level is crucial for guiding solvent selection for biocatalysis. Thereby, MD simulations provide deep

insights into the enzyme-solvent interactions and enzyme-substrate binding in non-conventional reaction media, which can ultimately help to guide solvent engineering and the necessary addition of water to maintain enzymatic activity.

FIGURES

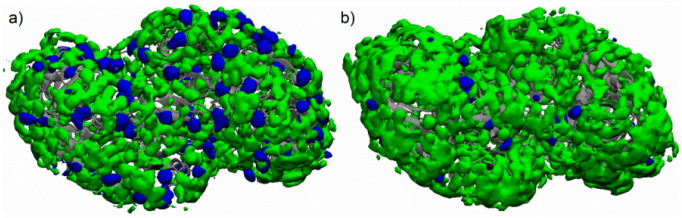

FIGURE 1

Figure 1.

Spatial distribution function of glycerol molecules (green) and choline ions (blue) in the proximity of horse liver alcohol dehydrogenase (gray) in the MD simulations of (a) ChCl-Gly (1:2, mol:mol) and (b) ChCl-Gly (1:9, mol:mol) in mixtures with 20 vol.%

FIGURE 2

KEYWORDS

molecular dynamics simulations | alcohol dehydrogenase | deep eutectic solvents | experimental analysis

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