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Understanding the Thermostability and Activity of *Bacillus subtilis* Lipase mutants: Insights from Molecular Dynamics Simulations

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Abstract

Improving thermostability of industrial enzymes is an important protein engineering challenge. Point mutations, induced to increase thermostability, affect the structure and dynamics of the target protein in several ways and thus can also affect its activity. There appears to be no general rules for improving thermostability of enzymes, without adversely affecting their enzymatic activity. We report MD simulations, of wild type *Bacillus subtilis* lipase (WT) and its six progressively thermostable mutants (2M, 3M, 4M, 6M, 9M and 12M), performed at different temperatures, to address this issue. Less thermostable mutants (LTMs), 2M - 6M, show WT-like dynamics at all simulation temperatures. However, the two more thermostable mutants (MTMs), show required flexibility at appropriate temperature ranges and maintain conformational stability at high temperature. They show deep and rugged free-energy landscape, confining them within a near-native conformational space by conserving non-covalent interactions, and thus protecting them from possible aggregation. In contrast, the LTMs having marginally higher thermostabilities than WT show greater probabilities of accessing non-native conformations, which, due to aggregation, have reduced possibilities of reverting to their respective native states under refolding conditions. Our analysis indicates the possibility of non-additive effects of point mutations on the conformational stability of LTMs.