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Conformational mobility of Trp125 in the EMAP II protein: molecular dynamics study

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Tryptophan fluorescence is one of the most widely used intrinsic probes of protein conformational dynamics, as the emission wavelength of a tryptophan residue is sensitive to its local environment. Although a red shift of the emission maximum is conventionally interpreted as an increase in solvent exposure of the indole ring, such interpretation may not always hold, particularly for tryptophans buried in the protein interior, where changes in the surrounding protein matrix can also modulate the emission.

Endothelial Monocyte-Activating Polypeptide II (EMAP II) contains a single tryptophan residue, Trp125, located within the functionally important tRNA-binding motif. Fluorescence measurements available in the literature indicate that its emission maximum shifts by 14 nm (from 335 to 349 nm) upon heating from 25 to 45 ℃, suggesting a major change in the residue's environment. However, the molecular mechanism behind this shift has remained unclear.

In this work, we carried out microsecond-long all-atom molecular dynamics simulations (CHARMM36m force field, at six temperatures, from 25 to 50 ℃) based on PDB 8ONG structure to investigate the conformational mobility of Trp125. The simulations reveal a temperature-driven coupled chi1/chi2 rotameric transition, confirmed by NMR data, with a midpoint matching the experimental fluorescence crossover at ˜42 ℃. Unexpectedly, the high-temperature flip-out state is more buried than the room-temperature flip-in state. Unbiased clustering of the residue's geometric environment shows that the rotameric switch repositions the indole between two distinct internal pockets. Based on the obtained data, an electrostatic emission model reproduces the experimental red shift trends, while the solvent-exposure model, based on solvent-accessible surface area (SASA), fails. The results establish a "buried flip-out" mechanism in which fluorescence is modulated by the protein matrix rather than by solvation, highlighting insightfulness of the molecular dynamics for the interpreting spectral signatures of tryptophan.

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