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## COMPUTATIONAL STUDY OF TEMPERATURE-DRIVEN TRYPTOPHAN SWITCHING IN THE CYTOKINE EMAP II

**Background/Aim.** Tryptophan fluorescence is a sensitive intrinsic probe of the local electrostatic field of the protein-water environment; in the cytokine EMAP II (the C-terminal domain of AIMP1/p43) the single Trp125 emission red-shifts from 335 to 349 nm on heating from 25 to 45 °C (transition near 42 °C), while NMR reveals an equilibrium between two conformational states of the indole ring. The molecular origin of this thermal switch is unresolved, and we investigate it computationally. **Methods.** We combined all-atom molecular dynamics and well-tempered metadynamics on the Trp125  $\chi_1/\chi_2$  dihedrals with unbiased Gaussian-mixture clustering of the local environment, and estimated the emission maximum by the López-Martínez model and by TD-DFT calculations. **Results.** The thermal switch is a coupled  $\chi_1/\chi_2$  “flip-in” ↔ “flip-out” rotamer transition that generalizes the NMR two-state picture. Unbiased Gaussian-mixture clustering of the indole environment recovers a few metastable pockets that, on heating, redistribute from a lysine-rich pocket (the buried “flip-in” state) toward a Gln129 pocket (the “flip-out” state). A Van’t Hoff analysis of the unbiased populations gives a switching temperature of 41.4 °C, consistent with four independent experimental markers within the 37–45 °C window. Crucially, the red shift develops with no increase of the indole solvent-accessible surface area, which even decreases (from 25.6 to 18.9 Å<sup>2</sup>): the “flip-out” state is more buried, and the surface conformation gives the bluest, not the reddest, emission. The decisive factor is the orientational ordering of pocket water by the side chain of Gln129, which forms about twice as many water-protein hydrogen bonds and builds a stronger coherent electrostatic field on the indole. Two independent methods – the López-Martínez model and TD-DFT – reproduce a statistically indistinguishable rotamer-only shift of +4.3 nm, showing that Trp125 senses local electrostatics rather than solvent exposure. **Conclusions.** The temperature-driven fluorescence switch of Trp125 is a transition between two buried environments with different electrostatic fields, governed by Gln129-coordinated water ordering rather than indole solvent exposure. The computed switching temperature coincides with the thermal transition of EMAP II, linking the local conformational switch to the physiologically relevant behaviour of the protein.

**Keywords:** EMAP II/AIMP1, tryptophan fluorescence, molecular dynamics, conformational switching, internal Stark effect.

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