

# **Effect of Thermal Perturbations and chemical denaturants on the Folding of Trp-cage miniprotein via Free Energy Calculations**

by

K Koushik, U Deva Priyakumar

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Centre for Computational Natural Sciences and Bioinformatics  
International Institute of Information Technology  
Hyderabad - 500 032, INDIA  
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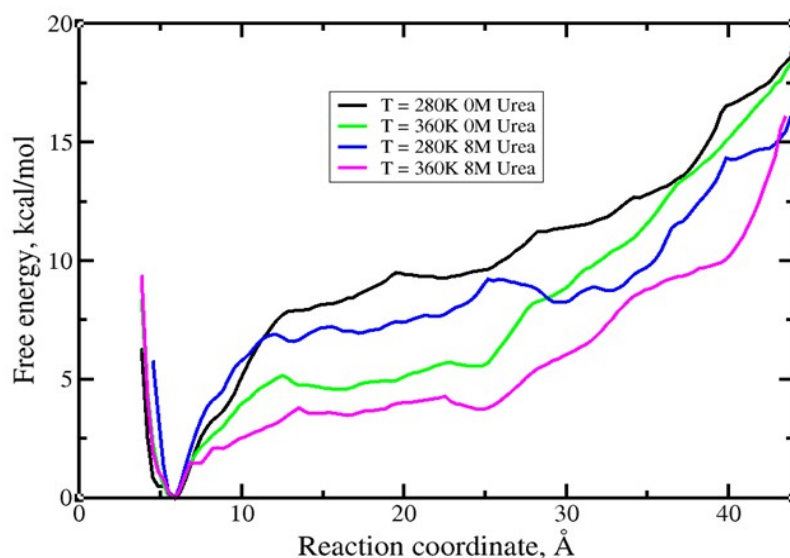
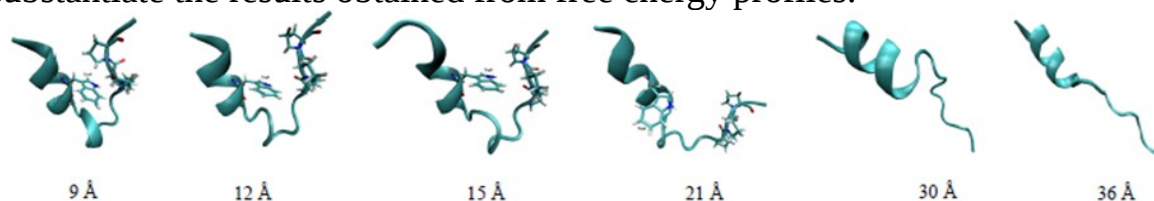
K. Koushik and U. Deva Priyakumar

Center for Computational Natural Sciences and Bioinformatics, International Institute of Information Technology, Hyderabad 500032.

Email: [deva@iiit.ac.in](mailto:deva@iiit.ac.in)

Understanding protein folding thermodynamics and kinetics is a central issue in molecular biology. Molecular dynamics (MD) simulations are being extensively used for this purpose. However, direct comparison between simulations and experiments requires both, an accurate description of the system and extensive sampling of the conformational space. Variants of MD have been developed to overcome sampling issues. Here, we use umbrella sampling technique to quantitatively compute the differences in thermodynamic quantities of the unfolding process of Trp-cage miniprotein TC5b (PDB ID: 1L2Y) due to changes in temperature as well as the presence/absence of chemical denaturants. Urea at a concentration of 8M has been used as the chemical denaturant. WHAM was used to obtain the unbiased free energy profiles.

The free energy profile can be categorised into three parts – the opening of the Trp-cage, separation of secondary structure elements and distortion of alpha-helix. An increase in temperature or presence of urea effects only the opening of the Trp-cage while the separation of the secondary structure elements and distortion of alpha-helix is independent of temperature and urea. Contour plots were constructed to substantiate the results obtained from free energy profiles.



The free energy profiles constructed using umbrella sampling simulations at 280K and 360K in the presence/absence of urea. The structures of the Trp-cage along the reaction coordinate are shown.