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Thermodynamics and kinetics of protein folding on the ribosome: Alteration in energy landscapes, denatured state, and transition state ensembles EDWARD O'BRIEN, Dept. of Chemistry, University of Cambridge, MICHELE VENDRUSCOLO, Dept. of Chemistry University of Cambridge, CHRISTOPHER DOBSON, Dept. of Chemistry, University of Cambridge — *In vitro* experiments examining cotranslational folding utilize ribosome-nascent chain complexes (RNCs) in which the nascent chain is stalled at different points of its biosynthesis on the ribosome. We investigate the thermodynamics, kinetics, and structural properties of RNCs containing five different globular and repeat proteins stalled at ten different nascent chain lengths using coarse grained replica exchange simulations. We find that when the proteins are stalled near the ribosome exit tunnel opening they exhibit altered folding coopserativity, quantified by the van't Hoff enthalpy criterion; a significantly altered denatured state ensemble, in terms of R_g and shape parameters (R_g tensor); and the appearance of partially folded intermediates during cotranslation, evidenced by the appearance of a third basin in the free energy profile. These trends are due in part to excluded volume (crowding) interactions between the ribosome and nascent chain. We perform *in silico* temperature-jump experiments on the RNCs and examine nascent chain folding kinetics and structural changes in the transition state ensemble at various stall lengths.

Edward O'Brien
Chemistry

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