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Electrostatic effects on the folding stability of FKBP JYOTICA BATRA, HUAN-XIANG ZHOU, Institute of Molecular Biophysics and Department of Physics, Florida State University, Tallahassee, Fl-32306 — Charged residues play important roles in the folding of proteins and their interactions with biological targets. We have developed computational models for predicting electrostatic contributions to protein folding and binding stability. To rigorously test and further refine these models, we carried out experimental studies on the effects of charge mutations on the folding stability of FKBP. Two close homologues of FKBP, FKBP12 and FKBP12.6, differ in 18 of 107 positions, and 8 of which involve substitutions of charged residues. These 8 substitutions were introduced on FKBP12 and their effects on the folding stability were measured. The changes in unfolding free energy varied from -0.34 to 0.65 kcal/mol. A double and a triple mutation were introduced to accumulate the stabilization effect of individual substitutions, resulting an increase in stability of about 0.84 kcal/mol. On the other hand, neutralizing one or both partners of a conserved salt bridge reduced the stability by as much as 0.64 kcal/mol. These results suggest that charged residues can modulate the folding stability significantly. To further exploit stabilization effects of charged residues, experiments are now underway to introduce charge mutations that are modeled after a thermophilic FKBP.

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