The most essential feature of living biological systems is their high degree of structural organization. An essential role in ordering these systems is played by two key biopolymers, proteins and nucleic acids. Under environmental conditions close to physiological these biopolymers are folded into unique native conformations but on deviating from these conditions their highly ordered structure breaks down cooperatively, i.e. they unfold. On restoring environmental conditions however, these polymers refold into their native conformation if their chemical structure has not been damaged and they did not aggregated. In their native conformation biological macromolecules recognize their partners and associate with them reversibly forming specific higher order complexes, the ‘molecular machines’. Thus the folding of biopolymers into their native conformation and their association with partners is in principle a reversible multistage thermodynamically driven process. Investigation of the thermodynamics of each individual step in their formation is essential for understanding their energetic base and mechanism of function. This requires recording each structural change of the macromolecules and measuring the accompanying heat effects. The main technical difficulties in realizing this program are the limited availability of the bio-macromolecules, their instability and the necessity of using highly dilute solutions for studying the folding and association of such strongly interacting objects. This demanded the development of super-sensitive calorimetric and optical methods for measuring the heat effects and structural changes of intra- and inter-molecular processes. Examples will be presented of thermodynamic studies of the unfolding/refolding of various proteins and their association with specific partners. Particular attention will be given to DNA-binding proteins associating with their recognition sequences, an aspect of transcriptional regulation now of special interest in view of the great success in genome decoding.