# CHAPTER OVERVIEW

## 8: Rare-event sampling and free energy calculations

Our treatment of the classical ensembles makes clear that the free energy is a quantity of particular importance in statistical mechanics. Being related to the logarithm of the partition function, the free energy is the generator through which other thermodynamic quantities are obtained, via differentiation. In many cases, the free energy difference between two thermodynamic states is sought. Such differences tell, for example, whether or not a chemical reaction can occur spontaneously or requires input of work and is directly related to the equilibrium constant for the reaction. Thus, for example, from free energy differences, one can compute solvation free energies, acid ionization constants $K_a$ and associated $pK_a$ values, or drug inhibition constants $K_i$, that quantify the ability of a compound to bind to the active site of an enzyme. Another type of free energy often sought is the free energy as a function of one or more generalized coordinates in a system. An example might be the free energy surface as a function of a pair of Ramachandran angles $\phi$ and $\psi$ in an oligopeptide. Such a surface would provide a map of the stable conformations of the molecule, the relative stability of such conformations and the heights of barriers that need to be crossed in a conformational change.

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