Preface

This volume is the continuation in a series of Methods in Enzymology volumes which promotes thermodynamics as an important tool for the study of biological systems. One of the many examples of biological thermodynamics is the cooperative binding of oxygen by hemoglobin.

Hemoglobin is the quintessential example of a ligand-binding protein. Most biochemistry textbooks explain that the hemoglobin tetramer exists in two structural states, a low-affinity structure without oxygen bound and a high-affinity structure with oxygen bound. This is the classic two-state allosteric model as presented by Monod, Wyman, and Changeux (1965, *J. Mol. Biol.*, **12**, 88–118) and extended by Ackers and Johnson (1981, *J. Mol. Biol.* **147**, 559–582). Unfortunately, this model tells us nothing about the specific molecular interactions that are altered by the binding of oxygen, which force the hemoglobin to shift to the alternative structural state.

Investigating hemoglobin at this level is analogous to viewing only the first and last act of a tragedy by William Shakespeare (e.g., King Lear or Macbeth). The first act being a celebration and in the last act, the stage is full of dead bodies. While only the first and last acts are provocative, the truly wonderful part of a Shakespearean play is the character interactions in the intervening steps between the initial and final states, which force the last act to follow from the first act.

Thermodynamics provides a conceptual and mathematical framework, that is, a "logic tool," which allows the investigation of the specific molecular interactions and the concomitant energetics such as those that are altered by the binding of oxygen, which force the hemoglobin to shift to the alternative structural and/or association states.

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