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## Thermodynamic Analysis of Human Hemoglobins in Terms of the Perutz Mechanism: Extensions of the Szabo–Karplus Model To Include Subunit Assembly<sup>†</sup>

Michael L. Johnson\* and Gary K. Ackers

**ABSTRACT:** The stereochemical postulates of Perutz for the mechanism of hemoglobin [Perutz, M. F. (1970) *Nature (London)* 228, 726–739] have been formulated into a statistical thermodynamic model. The model is based on that of Szabo and Karplus [Szabo, A., & Karplus, M. (1972) *J. Mol. Biol.* 72, 163–197] but has been extended to include the properties of dissociated dimers in equilibrium with tetramers. The dissociation eliminates the  $\alpha_1\beta_2$  intersubunit contact which is the major site of ligand-linked structure change. The model quantitatively describes the coupling between binding of oxygen and protons in dimers and tetramers, the change in quaternary structure, and the breaking of salt bridges which are assumed to stabilize the deoxy quaternary structure. The extended model has been tested against an extensive series of recent experimental data from our laboratory and elsewhere

on the ligand-linked dimer–tetramer assembly in normal human hemoglobin A and in the variant hemoglobin Kansas ( $\beta 102 \text{ Asp} \rightarrow \text{Asn}$ ). Two versions of the model were used which differ in the properties of the dissociated dimers. For both hemoglobins, the models were found capable of simultaneously describing the data on the ligand-linked dimer–tetramer assembly and predicting the tetramer Bohr effect. However, neither model predicted reasonable values for the tetramer Bohr effect without simultaneously predicting unreasonable values for the affinities of individual chains. Both models incorrectly predict preferential binding of oxygen to the  $\alpha$  or  $\beta$  chains within the tetramer. These results argue against the Perutz mechanism for the molecular processes of hemoglobin.