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A summary of a research performed under a DOE contract

Principal Investigator: Ron Elber

Empirical potentials for recombination reactions of photo-dissociated ligands

The aim of the above mentioned research was to design an appropriate potential and simulation methodology to describe the effect of radiation on ligands bound to metal-proteins. As model systems we investigated myoglobin, hemoglobin and their mutants. The great advantage of the globins as a target for theoretical studies is the wealth of experimental data available for them. We focused on studies that combine fast spectroscopy with mutation experiments. The mutations make it possible to examine detailed changes in the kinetic curves with atomically detailed information. The fast spectroscopy, which is in the same time scale as of ordinary molecular dynamics (sub nanoseconds), makes it possible to compare the results of the computations to "raw" experimental data.

Experiments were performed by the groups of John Olson from Rice, and Quentin Gibson from Cornell. The geminate recombination of nitric oxide to myoglobin and myoglobin mutants was affected profoundly by site directed mutations in the heme pocket and beyond. For example, in contrast to expectation (and to textbooks), mutation of Leu B10 to Phe B10, shorten the lifetime of the dissociated ligand and enhanced the recombination yield in the sub nanosecond time scale.

We combined molecular dynamics simulations of proteins using well-established energy functions (AMBER/OPLS), with a model for the photo-dissociation and ligand recombination process. The initial photon is assumed to bring the electrons to an excited state, leaving the nuclei frozen at their positions. Then the ligand, and the atoms coupled to it, move (classically) on the excited state until they reach the neighborhood of the crossing interface between the ground and the excited states. Near the crossing interface a transition to the ground state might occur following the Landau-Zener semi-empirical theory.

The missing pieces to make the above scheme into a useful computational model were the parameters of the excited state and the coding of the semi-empirical theory in a molecular dynamics program for biomolecules. Parameters for electronically excited states and crossing points are hard to come by even for small molecular systems. They are obviously difficult to get for proteins and for proteins with additional groups such as a heme. The approach we took was empirical. We assumed a functional form for the ground and the excited states and used some of the experimental data available to us to check that the functional form is flexible enough to accommodate the data and to fit the parameters to the observations.

The two potential energy surfaces that are used to model photo-dissociation consist of two parts: (a) The interaction potential of the nitric oxide ligand (NO) with the iron and (b) A modified heme potential that provides the correct asymptotic heme properties for iron with six and five ligands. The iron-NO interactions were modeled by an angle term, a Morse potential for the ground state, and a repulsive exponent function for the excited state. The two potential curves were shifted with respect to each other to fit the position of the crossing point and the approximate excitation energy. The heme potential was interpolated (using a switching function) between the two energy surfaces - one with a bound ligand and one without it.

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The observation we fitted is the recombination yield for the different mutants at the sub-nanosecond time scale. The fitting procedure was far from trivial. For example, the position of the crossing point determines its accessibility to the diffusing diatom and strongly influenced the relative recombination rate in the mutants of the protein. Four different variants of myoglobin (ala/val/leu/phe B10) were used in the fit (the leucine is the native) providing what we considered to be an adequate model.

The model was tested on numerous (different) heme-pocket mutations of myoglobin as well as on hemoglobin. The hemoglobin molecule has quite different recombination properties compared to myoglobin. The adequate results for the hemoglobin molecule were therefore encouraging. The complete results are summarized in the Ph.D. thesis of the student that worked on this project (Dr. Haiying Li [1]). The code and the parameterization are available in our (public domain) molecular dynamics code [2]. All the sub-projects we set for ourselves at the beginning of the research were completed.

[1] Haiying Li, Ph.D. thesis, University of Illinois at Chicago, 1992

[2] R. Elber, A. Rothberg, C. Simmerling, R. Goldstein, H. Li, G. Verkhivker, C. Kester, J. Zhang and A. Ulitsky "MOIL: A program for simulations of macromolecules", Computer Physics Communications, 91,159-189(1995)