Protein-water electrostatics and principles of bioenergetics

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I. MD SIMULATION AND ANALYSIS PROTOCOL

In order to simulate plastocyanin (PC) and the bacterial reaction center (RC), both electron transfer proteins, the following approach has been adopted. The interaction energy of the charges Δq_j of the protein's active site with waters of the solvent are calculated using the procedure suggested by Roberts and Schnitker.[1] The standard implementation of the Ewald sum techniques anticipates the tin-foil boundary at the dielectric surface enveloping the replicated cells of the Ewald sum. This approach is adopted within Amber 9.0 program suite and was used to generate the simulation trajectories. In order to speed up the analysis of electrostatic observables, the electrostatic interactions were cut off at half of the simulation cell size. Without correction, this approximation is prone to produce errors, although not dramatic ones given the large size of the simulated system. However, the simple cubic cutoff condition can be rigorously transformed to the standard tin-foil condition as was shown by Roberts and Schnitker.[1] The solute-water interaction potential V_{0s} then becomes

$$\begin{aligned} V_{0s} &= V_{0s}^{\text{cut}} + V_{\text{pol}} \\ V_{\text{pol}} &= -\frac{2\pi}{3V}\sum_j \Delta q_j \sum_n q_n(\mathbf{r}_n - \mathbf{r}_j)^2 \end{aligned} \tag{S1}$$

Here V_{0s}^{cut} is the Coulomb potential obtained with the cubic cutoff and V_{pol} is the correction term transforming the cubic cutoff into the standard tin-foil Ewald implementation. The second sum in V_{pol} runs over the partial charges q_n of the water molecules with coordinates $\mathbf{r}_n$ and V is the volume of the simulation cell. The distinction between the cubic cutoff and tin-foil condition thus lies in the fluctuations of the overall quadrupole moment of the simulation shell which can be substantial given that net ferroelectric dipole is produced in the solvation shells in our simulations. The relative effect of V_{pol} on the electrostatic parameters was investigated in the Supporting Information of Ref. 2. The details of the usual simulation parameters have been omitted here, but are given in detail in several references[2–4].

The simulations of both electron transfer proteins were performed in parallel using both the Saguaro supercomputer at ASU and the Ranger supercomputer at TACC. Ubiquitin (UB) and lysozyme (LY) were simulated in a similar fashion as RC and PC, with the major difference being the use of NAMD for the MD simulations and the CHARMM force field for the MD parameters. A graphical processing unit (GPU) accelerated NAMD, version 2.b2, was used in parallel on TACC's Longhorn GPU cluster. For both UB and LY, the details of the forcefield and simulation parameters can be found in the Supporting Information of Ref. 2.

Due to a large number of trajectory frames and compute-bound analysis, all MD trajectories generated for this study were analyzed using the Pretty Fast Analysis (PFA) parallel analysis program.[5] This includes all vertical energy gap calculations for PC and RC shown in various forms in Figures 3, 4, 5, 12 and Table 2; the water/protein dipole moments used in Figures 7 and 8 and Table 1; and the volume calculations required for the estimate of the distance-dependent dielectric constant in Figure 8. Trajectory analysis with PFA was performed at TACC's Ranger supercomputer as well as the Longhorn and Spur GPU clusters, at ASU's Saguaro supercomputer, as well as on our own local cluster. All molecular graphics, specifically those for Figures 5 and 9, as well as the journal's cover, were generated and rendered with VMD versions 1.8.6 and 1.8.7.[6]

II. TEMPERATURE AND PRESSURE DEPENDENCE OF THE RATE OF PRIMARY CHARGE SEPARATION

The rate of primary charge separation was calculated by iteratively solving the standard non-adiabatic equation for the electron-transfer rate in which the activation barrier is a function of the rate due to non-ergodic restrictions on the spectrum of nuclear fluctuations:[3,4,7]

$$k_{\text{ET}} = (V^2/\hbar)\sqrt{2\pi/\sigma^2}\exp\left[-X_{01}^2/2\sigma^2(k_{\text{ET}})\right]. \tag{S2}$$

In this equation, V is the electron-transfer matrix element, X_{01} is the average donor-acceptor energy gap for charge separation, and $\sigma^2 = \langle(\delta X)^2\rangle$ is the variance of the energy gap fluctuations. Both the average energy gap and the variance have contributions from non-polar induction interactions and Coulomb interactions. The Coulomb interaction is the interaction of the charges Δq_j, caused by charge separation, with the partial charges of the force-field water and protein. The induction interaction is given as a sum of inductive free energies produced by the electric field of the solute $\mathbf{E}_{0i}(\mathbf{r}_k)$ at the atoms of the medium with the positions $\mathbf{r}_k$ and polarizabilities α_k:

$$\Delta E^{\text{ind}}(Q) = -\frac{1}{2}\sum_k \left[E_{02}^2(\mathbf{r}_k) - E_{01}^2(\mathbf{r}_k)\right]\alpha_k. \tag{S3}$$

The average energy gap includes the gas-phase component, X_{01}^{gas}, the induction shift, $X_{01}^{\text{ind}} = \langle\Delta E^{\text{ind}}\rangle$, and the Coulomb shift, X_{01}^{C}:

$$X_{01} = X_{01}^{\text{gas}} + X_{01}^{\text{ind}} + X_{01}^{\text{C}}. \tag{S4}$$

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The variance is the sum of decoupled by symmetry Coulomb and induction variances

$$\sigma^2(k_{\rm ET}) = \sigma^2_{\rm ind} + 2k_{\rm B}T\lambda^{\rm var}(k_{\rm ET}). \quad \text{(S5)}$$

In this equation, the induction variance is not factored into the temperature and reorganization energy terms since this factorization does not arise for non-polar interactions generally producing a non-Arrhenius temperature dependence of the reaction rate.[8]

The dependence of the Coulomb component on the reaction rate is due to a slow portion of the corresponding Stokes shift correlation function arrested on the short time-scale of primary charge separation. The coulomb part of the Stokes shift correlation function obtained from MD trajectories is represented here by a sum of a Gaussian decay and two exponential functions

$$\langle \delta X^{\rm C}(t)\delta X^{\rm C}(0)\rangle = 2k_{\rm B}T\lambda^{\rm var}\left[A_G e^{-(t/\tau_G)^2} + \sum_{i=1,2} A_i e^{-t/\tau_i}\right]. \quad \text{(S6)}$$

Correspondingly, the non-ergodic reorganization energy depending on the reaction rate is obtained by integrating over frequencies in eqn 9 (main text)

$$\lambda^{\rm var}(k_{\rm ET}) = \lambda^{\rm var}\left[A_G + (2/\pi)\sum_i A_i \cot^{-1}(k_{\rm ET}\tau_i(T))\right]. \quad \text{(S7)}$$

The MD simulations of the hydrated reaction center resulted in the following fitting parameters for the Coulomb Stokes shift dynamics:[3] $A_G = 0.172$, $\tau_G = 0.1$ ps, $A_1 = 0.063$, $\tau_1 = 2.5$ ps, $\tau_2(T) = \tau_2^0 \exp[E_\tau/T]$ with $\tau_2^0 = 2.55$ ps and $E_\tau = 1212$ K. Equation S7 was used to produce the upper panel in Fig. 10.

The temperature dependence of the induction component of the average energy gap $X^{\rm ind}_{01}(T)$ caused by protein's contraction is the main source of the observed temperature dependence of the rate. An additional, less important, contribution comes from changes of $\lambda^{\rm var}(k_{\rm ET})$ caused by the temperature dependence of the relaxation time $\tau_2(T)$ in eqn S7. In order to model $k_{\rm ET}(T)$, equation S2 was solved iteratively at each temperature. The temperature variation of the induction shift $X_{01}(T) = 1.219 \times (1. - 3.25 * 10^{-4} \times (T - 300))$ eV was obtained from MD simulations. All other Coulomb energies were obtained from a long MD trajectory at 300 K and were kept constant: $X^{\rm gas}_{01} = 1.87$ eV, $X^{\rm C}_{01} = -0.473$ eV, $\sigma^2_{\rm ind} = 0.00615$ eV^2, $\lambda^{\rm var} = 1.564$ eV. In addition, the electron-transfer matrix element was obtained[3] from fitting the experimental[9] charge-separation rate at 300 K and fixed at the value of $V = 41.5$ cm^{-1}. The results of the rate calculation at different temperatures are given in the lower panel in Fig. 10.

The calculations of the pressure dependence of the rate of charge separation were again done by using eqn S2 in which now the electron-matrix element and the induction shift become dependent on the hydrostatic pressure. Increasing pressure changes the average donor-acceptor separation R and thus the matrix element $V(P)$ according to the equation[10]

$$V(P)^2 = V(1\text{ bar})^2 \exp[\kappa_T \gamma R P/3]. \quad \text{(S8)}$$

Here, $\kappa_T = 15$ Mbar^{-1} is the isothermal compressibility of the reaction center, $R = 11.3$ Å is the donor-acceptor separation from the X-ray structure, and $\gamma = 1.4$ Å^{-1} is the distance decay of the electron tunneling probability. Further, the variation of the induction shift with pressure is modeled by using eqn 13 and the experimental compressibility: $X^{\rm ind}_{01}(P) = -1.219 \times (1 + (P-1) * 15 * 10^{-6}\text{bar}^{-1})$ eV. All other parameters entering the rate were kept constant. The results of these calculations are given by the dashed line in the lower panel in Fig. 10. The variation of the Stokes shift dynamics with pressure is not known at this moment and was not included in the calculations.

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