The mechnanochemical coupling in F1-ATPase: How electrostatics play the crucial role in the rotary mechanism

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Abstract

F1-ATPase is a remarkable molecular motor that generate or hydrolyze ATP in the α/β catalytic subunits as the rotor y rotates in a specific direction. Single molecule experiments have observed the coupling of y rotation with chemical events on the α/β catalytic subunits. Although there are many theoretical attempts, the occurrence of 80° and 40° rotational substates and its precise nature of coupling with the chemistry could not be understood without incorporating any prior information about such intermediate states in the simulation procedure. We use a coarse-grained model with specialized electrostatics treatment and generate a structure-based free energy landscape that reproduces the rotational substates. We also generate an effective simplified free energy surface using multisiminima EVB approach and run Langevin Dynamics to demonstrate the catalytic dwell.

The landscape along the rotary path is determined by the electrostatic free energy and not by steric effects. The generated surface and the corresponding Langevin dynamics simulations identify a hidden conformational barrier that provides a new fundamental interpretation of the catalytic dwell and illuminate the nature of the energy conversion process (Ref 1).

Single Molecule experiments: Coupling of y and α/β dimers

Time-course of y rotation observed from a 40nm bead attached to y at 2mM ATP (Ref 3)

The stalling after each 120° rotation is the catalytic dwell

The binding dwell is only visible at lower substrate concentration

Schematic representations of ATP hydrolysis cycle during 120° rotation of y

Results

Electrostatic free energy surface for the conformational cycle of y rotation and α/β subunit alterations

The least energy path shows the 80° and 40° substeps for y rotation

The 80° rotation has small barriers but there is significant barrier for the β subunit changes and 40° rotation

Phenomenological treatment of ATP binding, ADP release, ATP → ADP+P and P release steps

Simplified surface show the chemistry after 80° y rotation

Calculated using the multi-minima EVB approach (Ref 4)

Simplified surface show the chemistry after 80° y rotation

The CG Model

The CG model describes the main chains explicitly and represents the side chains as a simplified united atom model (details in Ref 6,7). It expresses the overall free energy as,

\[ \Delta G_{\text{free}} = \Delta G_{\text{energetic}} + \Delta G_{\text{steric}} + \Delta G_{\text{el}} \]

The most relevant part of our treatment comes from the \( \Delta G_{\text{steric}} \) part. Now,

\[ \Delta G_{\text{steric}} = -2.3RT \sum_i \Delta(pK_i) \langle \mu^e \rangle_{i\text{ion}} \]

where \( i \) runs over the protein ionized residues, \( \mu^e_i \) is the electrostatic potential at the \( i \)th residue in water and \( Q_i \) is the charge of the \( i \)th residue in the given ionization state.

The charge-charge interaction is given by,

\[ \Delta G_{\text{interaction}} = \sum_{i \neq j} U_i \nabla_i \cdot \nabla_j \]

A key element of our treatment is the self energy of ionizable residues, \( \Delta G_{\text{self}} \), which is associated with charging each ionized group in its specific environment.

References