Transition State Stabilization or Ground State Destabilization: Study of the Most Proficient and Controversial Enzyme Orotidine Monophosphate Decarboxylase by First Principle Molecular Dynamics

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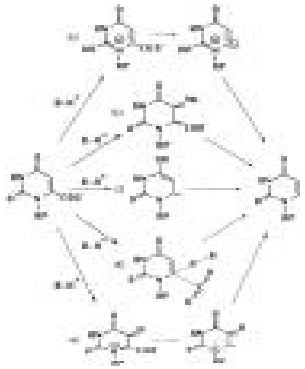
Enzymatic catalysis

The most proficient enzyme[1]

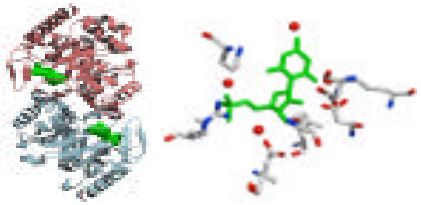
1. Miller, B. G.; Wolfenden, R. *Annu. Rev. Biochem.* **2002**, *71*, 847.

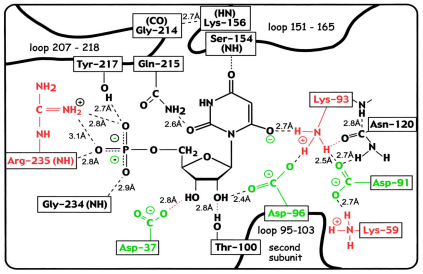
The most controversial enzyme[1]



a) Beak, P; Siegel, B. *J. Am. Chem. Soc.* **1973**, *95*, 7919.
b) Silverman, R. B.; Groziak, M. P. *J. Am. Chem. Soc.* **1982**, *104*, 6436.
c) (I) Lee, J. K.; Houk, K. N. *Science*, **1997**, *276*, 942; (II) Houk, K. N.; Lee, J. K.; Tantillo, D. J.; Bahmanyar, S.; Hiebrink, B. N. *ChemBiochem* **2001**, *2*, 113.
d) (I) Appleby, T. C.; Kinsland, C.; Begley, T.; Ealick, S. K. *Proc. Natl. Acad. Sci. USA* **2000**, *97*, 2005; (II) Miller, B. G.; Hassell, A. M.; Wolfenden, R.; Milburn, M. V. Short, S. A. *Proc. Natl. Acad. Sci. USA* **2000**, *97*, 2011; (III) Wu,N.; Mo, Y. R.; Gao, J.; Pai, E. F. *Proc. Natl. Acad. Sci. USA* **2000**, *97*, 2017.
e) Lee, T.-S.; Chong, L. T.; Kollman, P. A. *J. Am. Chem. Soc.* **2001**, *123*, 12837.

ODCase active site bounded with UMP





Circe: the black sorceress

"…Circe is best known for her role as enchantress and hostess in Homer's Odyssey. It was to her island, Aeaea, that Odysseus and his men sailed after escaping the Laestrygones…Circe welcomed them with all hospitality, serving them wine, women , and songs… and turned them into swine for good measure…With the aid of Hermes, Odysseus was able to resist Circe's magic and compel her to set his men free… It was Circe who advised Odysseus that in choosing between the twin perils of Scylla and Charybdis, he could avoid one or the other but not both…"

Ground state destabilization (Circe effect): ODCase allures the phosphate and ribose (nonreactive part) of orotidine 5´--monophosphate (OMP) to form tight binding while the orotate carboxylate group (reactive part) and a nearby aspartate group have strong repulsion resulting in the decarboxylation.

Transition state stabilization: The active site of ODCase is organized to stabilize the transition state more than the ground state mainly through electrostatic and hydrophobic interactions involving the polar and non polar residues with substrate OMP.

Car-Parrinello molecular dynamics[2]

Car-Parrinello Lagrangian

$$\mathbf{L}_{cp}[R_N, \dot{R}_N, \{\Phi_i\}, \{\dot{\Phi}_i\}] = \sum_I \frac{1}{2} M_I \dot{R}_I + \sum_i \frac{1}{2}\mu \langle \dot{\Phi} | \dot{\Phi} \rangle - \varepsilon^{KS}[\{\Phi_i\}, R^N]$$

Equations of motion

$$M_I \ddot{R}_I(t) = -\frac{\partial E^{KS}}{\partial R_I} + \sum_{ij} \Lambda_{ij} \frac{\partial}{\partial R_I} \langle \Phi_i | \Phi_j \rangle$$

$$\mu \ddot{\Phi}_i(t) = -\frac{\delta E^{KS}}{\delta \langle \Phi_i |} + \sum_j \Lambda_{ij} | \Phi_j \rangle$$

Position operator in periodic systems

$$\langle X \rangle = \frac{L}{2\pi} \mathrm{Im} \ln \left\langle \Psi | e^{i\frac{2\pi}{L}\hat{X}} | \Psi \right\rangle$$

Wannier function[3]: a unitary transformation performed on the occupied Bloch Orbitals; the total spread of the localized function is minimal.

The spread of the wavefunction

$$\Omega = \langle x^2 \rangle - \langle x \rangle^2$$

Resta equation

$$z = \int_L e^{i\frac{2\pi x}{L}} |\psi(x)|^2 dx$$

$$\Omega = \frac{1}{(2\pi)^2} \sum_n^{N_{states}} \sum_I \omega_I \log |z_{I,n}|^2$$

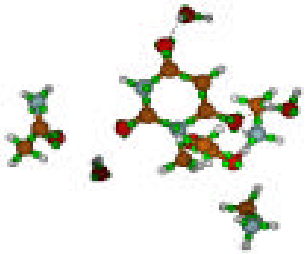
$$|\tilde{\psi}_n\rangle = \sum_i U_{in} |\psi_i\rangle \qquad \frac{\partial \Omega}{\partial U_{ij}} = 0$$

- Small system: *56 atoms* with modified Asp 91A-Lys 93A-Asp 96B and Gln 215A and four water molecules
- Big system: *109 atoms** with modified Asp 37A, Lys 59A-Asp 91A -Lys 93A -Asp 96B, Arg 235A, Gln 215A, Thr 100B, and four water molecules
- CPMD[4] with *Becke/Lee/Yang/Parr (BLYP) functional*; *Trouiller -Martins normconserving* pseudopotential for C, O, N, H

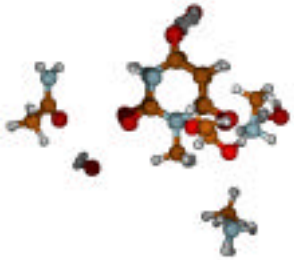
* These residues are proved to be critical to ODCase catalysis by varies mutation experiments.

2. (a) Car, R.; Parrinello, M. *Phy. Rev. Lett.* **1985**, *55*, 2471.
3. Berghold, G.; Mundy, C. J.; Romero, A. H.; Hutter, J.; Parrinello, M. *Phy. Rev.* B **2000**, *61*, 10040.
4. CPMD 3.5, J. Hutter et al., Copyright IBM Zurich Research Laboratory and MPI für Festkörperforschung **1995-2001**.

Snapshot of temperature controlled molecular dynamics with all heavy atoms constrained



Overlap of 1000 steps of constrained molecular dynamics at 100K



Conclusions and Future plans

- The small and big systems well represent the essential micro -environment of decarboxylation in ODCase
- Ab initio molecular dynamics of 100+ system is feasible with new Car-Parrinello code
- Molecular dynamics based on the minimum effective constraints
- Verify static quantum mechanical and classical molecular dynamics calculation results

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