Supporting Information for

Kinetic Isotope Effects of L-Dopa Decarboxylase

Yen-lin Lin and Jiali Gao

Department of Chemistry, Digital Technology Center and Supercomputing Institute,

University of Minnesota, Minneapolis, MN 55455

Email: gao@jialigao.org

This *Supporting Information* contains a list of the block averages of the computed kinetic isotope effects. Additional technical details have been published in a previous study of the intramolecular proton transfer equilibrium of the PLP cofactor in the Michaelis complex state in the enzyme L-dopa decarboxylase (DDC) and in water.[1] The initial structures used for the present potential of mean force (PMF) calculations for the decarboxylation of L-dopa in DDC were those that have been constructed in that study.[1] The input, topology, parameter and coordinate files for the simulation of the L-dopa decarboxylation reaction presented in this paper will be provided up on request since these files are too large to be included in the Supporting Information. These files can be directly used with CHARMM,[2] version c34a1.

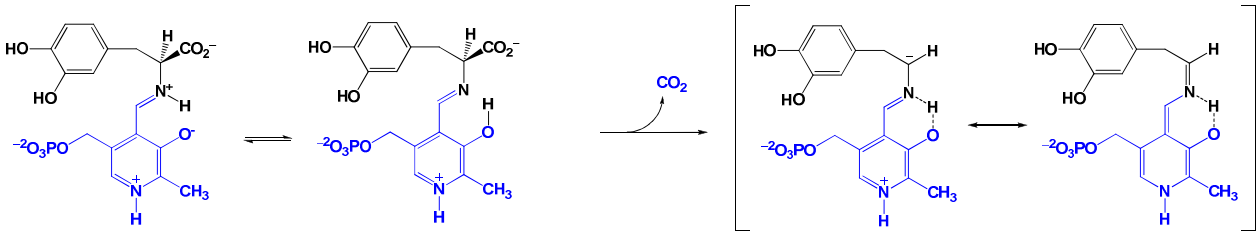

Figure 1. Schematic illustration of the keto and enol tautomerism of the PLP-L-dopa external aldimine, and its decarboxylation reaction product shown in two resonance structures.

Molecular Dynamics Simulations. Periodic boundary conditions along with the isothermal-isobaric (NPT) ensemble at 298.15 K and 1 atm were used, and long-range electrostatic effects are modeled using the particle-mesh Ewald method (PME–QM/MM). The leapfrog-Verlet integration scheme was used in all simulations with a time step of 1 fs, and the non-bonded interaction list was updated on every 25 integration steps using a cutoff of 14 Å for the real space calculation. The van der Waals energies were feathered to zero between 12 Å and 13 Å with a shift function. All bonds involving hydrogen atoms, except those in the QM region, were constrained to their equilibrium distances using the SHAKE algorithm during all dynamics simulations.

The initial enzyme system described above was embedded in a cubic box of water molecules about 93 × 93 × 93 Å^3 (Figure 3). The resulting system has a net charge of zero and no additional counterions were added. The final model of the enzyme system consists of 75514 atoms, including 20203 water molecules. The system has been thoroughly equilibrated during the study of keto-enol tautomeric equilibrium free energy simulations.[1] For the external aldimime reactions in water, the center of mass of the solute was solvated at the center of a cubic water box with a box length of 45 Å. Two sodium ions (Na^+) were added to neutralize the systems.

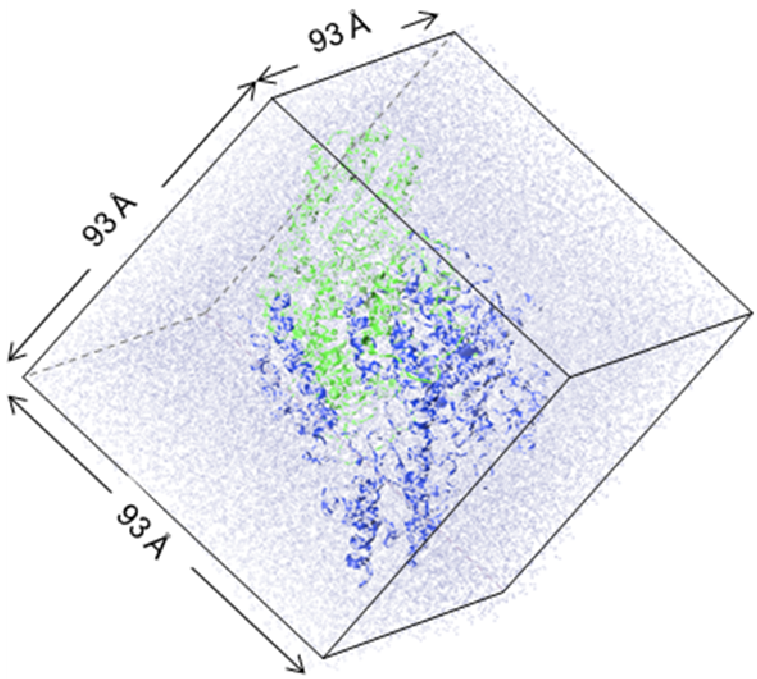

Figure 3. Simulation model of the fully solvated DDC dimeric protein in a box of water under periodic boundary conditions.

Computation of Kinetic Isotope Effects.

Table S1. Computed Kinetic Isotope Effects for the external aldimine complex of L-Dopa and PLP in aqueous solution at 25 ^{o}C. Enol is the O-protonated aldimine tautomer, and keto indicates the N-protonated configuration.

	C		C_α		H_α	
block	Enol	Keto	Enol	Keto	Enol	Keto
1	1.0529	1.0465	1.0281	1.0323	0.9795	1.1102
2	1.0559	1.0515	1.0350	1.0391	1.0389	1.0933
3	1.0511	1.0468	1.0295	1.0313	1.0083	1.1952
4	1.0539	1.0495	1.0328	1.0348	1.0036	1.1776
5	1.0486	1.0462	1.0310	1.0344	0.9387	1.1105
6	1.0548	1.0514	1.0291	1.0303	0.8620	1.0963
7	1.0486	1.0487	1.0248	1.0359	1.0092	1.0658
8	1.0551	1.0493	1.0318	1.0322	0.9905	1.1903
9	1.0536	1.0524	1.0254	1.0347	0.9352	1.1344
10	1.0545	1.0523	1.0293	1.0356	0.9904	1.2126
average	1.0529 ± 0.0026	1.0495 ± 0.0024	1.0298 ± 0.0031	1.0340 ± 0.0026	0.9746 ± 0.0509	1.1368 ± 0.0513

Table S2: Computed Kinetic Isotope Effects of the External Aldimine of L-Dopa and PLP in the Active Site of L-Dopa Decarboxylase. Enol is the O-protonated aldimine tautomer, and keto indicates the N-protonated configuration.

	Case (a)		Case (b)		Case (c)	
block	Enol	Keto	Enol	Keto	Enol	Keto
1	1.0567	1.0472	1.0265	1.0280	0.9913	1.0009
2	1.0514	1.0453	1.0390	1.0269	1.0387	1.1928
3	1.0517	1.0477	1.0335	1.0285	1.0313	1.1090
4	1.0514	1.0467	1.0355	1.0280	1.0943	1.2064
5	1.0528	1.0489	1.0431	1.0277	1.0626	1.1368
6	1.0556	1.0438	1.0406	1.0140	1.0555	1.0929
7	1.0570	1.0539	1.0431	1.0315	1.0276	1.2219
8	1.0530	1.0490	1.0470	1.0238	1.0705	1.1865
9	1.0521	1.0427	1.0297	1.0281	1.0776	1.1245
10	1.0493	1.0445	1.0342	1.0272	1.0920	1.1688
average	1.0530 ± 0.0025	1.0470 ± 0.0032	1.0372 ± 0.0065	1.0263 ± 0.0047	1.0528 ± 0.0323	1.1439 ± 0.0663

References

1. Lin, Y.-L.; Gao, J. *Biochemistry* **2010**, *49*, 84.
2. Brooks, B. R., Brooks III, C. L. , Mackerell Jr., A. D., Nilsson, L., Petrella, R. J., Roux, B., Won, Y., Archontis, G., Bartels, C., Boresch, S., Caflisch, A., Caves, L., Cui, Q., Dinner, A. R., Feig, M., Fischer, S., Gao, J., Hodoscek, M., Im, W., Kuczera, K., Lazaridis, T., Ma, J., Ovchinnikov, V., Paci, E., Pastor, R. W., Post, C. B., Pu, J. Z., Schaefer, M., Tidor, B., Venable, R. M., Woodcock, H. L., Wu, X., Yang, W., York, D. M., and Karplus, M. *J. Comput. Chem.* **2009**, *30***,** 1545-1614.