Supporting Information

Hybrid Quantum/Classical Molecular Dynamics Simulations of the Proton Transfer Reactions Catalyzed by Ketosteroid Isomerase: Analysis of Hydrogen Bonding, Conformational Motions, and Electrostatics

Dhruva K. Chakravorty, Alexander V. Soudackov, and Sharon Hammes-Schiffer*

Department of Chemistry, 104 Chemistry Building, Pennsylvania State University, University Park, PA 16802; e-mail: shs@chem.psu.edu

Table S1

Rate constants[a]	Experimental[b]	k_{TST}[c]	k_{TST} with QCP[d,f]	k_{tot}[e,f]
k_1	1.7×10^5	1.5×10^5	9.2×10^5	2.4×10^5
k_{-1}	5.6×10^5	7.5×10^5	4.4×10^6	1.1×10^6
k_2	2.1×10^5	2.8×10^5	2.3×10^6	6.4×10^5
k_{-2}	40	30.6	290.6	81.4

Table S1: Rate constants[g] for the two proton transfer reactions catalyzed by KSI.

a) The EVB parameters used in all calculations for this table were V_{12} = 100.0 kcal/mol and Δ = 4.9 kcal/mol for the first step, and V_{12} = 93.8 kcal/mol and Δ = –15.8 kcal/mol for the second step.
b) The experimental rate constants were obtained from Ref. (*2*, *36*).
c) k_{TST} was calculated in terms of the PMF $W(\Lambda)$ for a general reaction coordinate Λ using the following expression:

$$k_{TST} = \left\{ \left(\frac{Z_\Lambda}{2\pi\beta} \right)^{1/2} \right\}_{\Lambda^\ddagger}^{\text{cond}} \frac{e^{-\beta W(\Lambda^\ddagger)}}{\int_{-\infty}^{\Lambda^\ddagger} d\Lambda e^{-\beta W(\Lambda)}} \quad , \tag{S1}$$

where

$$Z_\Lambda \equiv \sum_{i=1}^{3N} \frac{1}{M_i} \left(\frac{\partial \Lambda}{\partial R_i} \right)^2 , \tag{S2}$$

$$e^{-\beta W(\Lambda')} = \frac{\int d\mathbf{R} \delta(\Lambda - \Lambda') e^{-\beta V(\mathbf{R})}}{\int d\mathbf{R} e^{-\beta V(\mathbf{R})}} , \tag{S3}$$

and

$$\left\{ f(\mathbf{R}) \right\}_{\Lambda^\ddagger}^{\text{cond}} = \frac{\int d\mathbf{R} \delta(\Lambda - \Lambda^\ddagger) e^{-\beta V(\mathbf{R})} f(\mathbf{R})}{\int d\mathbf{R} \delta(\Lambda - \Lambda^\ddagger) e^{-\beta V(\mathbf{R})}} . \tag{S4}$$

Here N is the number of nuclei with masses M_i and coordinates R_i, $V(\mathbf{R})$ is the potential energy of the system, and $\Lambda = \Lambda^\ddagger$ at the dividing surface. In our calculations, $\Lambda^\ddagger = 0$.
d) The QCP method includes the nuclear quantum effects of the transferring H.
e) k_{tot} was calculated with Eq. (3) and includes nuclear quantum effects and barrier recrossings.
f) QCP corrections and κ values presented in Section III.A were used to calculate 'k_{TST} with QCP' and k_{tot}. Test calculations with different V_{12} and Δ parameters indicated that the QCP corrections and κ values are not sensitive to these types of minor changes in V_{12} and Δ.
g) Rate constants given in s^{-1}.

Figure S1

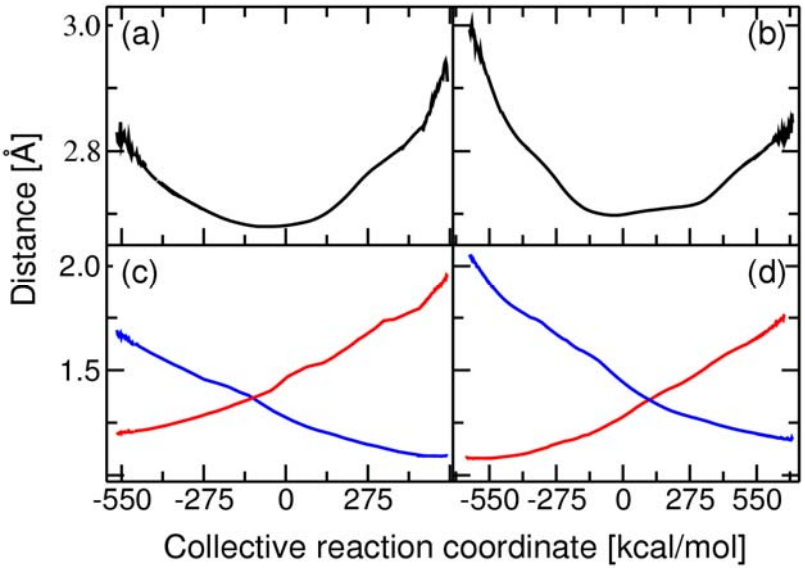

Figure S1: Thermally averaged distances within the proton transfer interface calculated along the collective reaction coordinate for the two proton transfer reactions catalyzed by KSI for the second data set. For the first proton transfer step, the substrate C4 atom is the donor and the Asp38 OD2 atom is the acceptor. For the second proton transfer step, the Asp38 OD2 atom is the donor and the substrate C6 atom is the acceptor. The donor-acceptor distance is depicted for the first step in (a) and the second step in (b). The donor-hydrogen (red) and acceptor-hydrogen (blue) distances are depicted for the first step in (c) and the second step in (d).

Figure S2

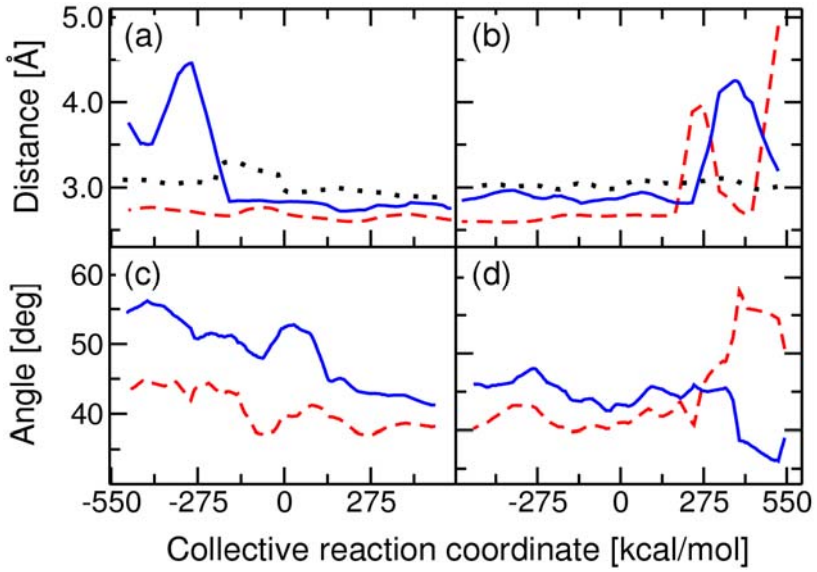

Figure S2: Thermally averaged distances and angles within the active site calculated along the collective reaction coordinate for the two proton transfer reactions catalyzed by KSI for the second data set. The hydrogen bond donor-acceptor distances between the substrate O3 atom and Tyr14 (solid blue), between the substrate O3 atom and Asp99 (dashed red), and between Tyr14 and Tyr15 (dotted black) are depicted for the first step in (a) and the second step in (b). The angles Tyr14-Asp99-SubstrateO3 (solid blue) and Asp99-Tyr14-SubstrateO3 (dashed red) are depicted for the first step in (c) and the second step in (d). These angles are defined in terms of the heavy atoms involved in the hydrogen bonds between the substrate and both Tyr14 and Asp99.

Figure S3

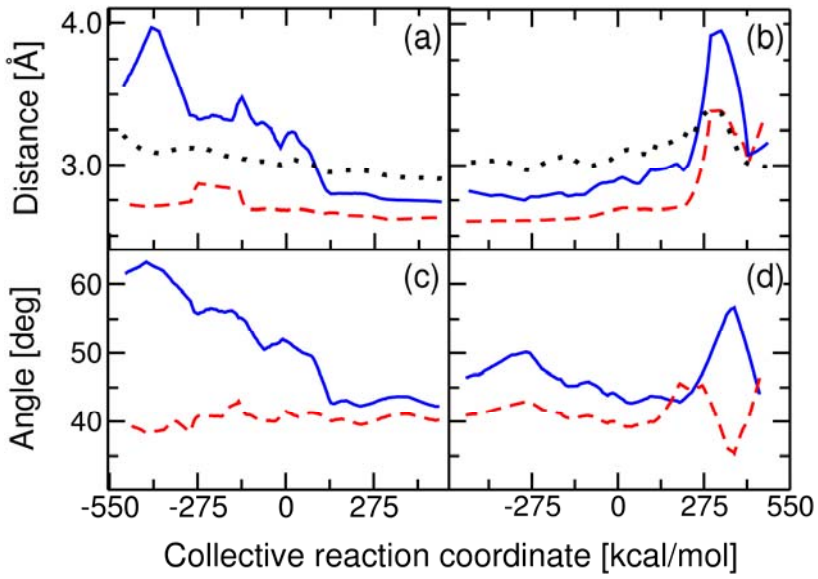

Figure S3: Thermally averaged distances and angles within the active site calculated along the collective reaction coordinate for the two proton transfer reactions catalyzed by KSI using the set of EVB parameters from k_{TST} calculated from Eq. (S1) for the first data set. The hydrogen bond donor-acceptor distances between the substrate O3 atom and Tyr14 (solid blue), between the substrate O3 atom and Asp99 (dashed red), and between Tyr14 and Tyr15 (dotted black) are depicted for the first step in (a) and the second step in (b). The angles Tyr14-Asp99-SubstrateO3 (solid blue) and Asp99-Tyr14-SubstrateO3 (dashed red) are depicted for the first step in (c) and the second step in (d). These angles are defined in terms of the heavy atoms involved in the hydrogen bonds between the substrate and both Tyr14 and Asp99.

Figure S4

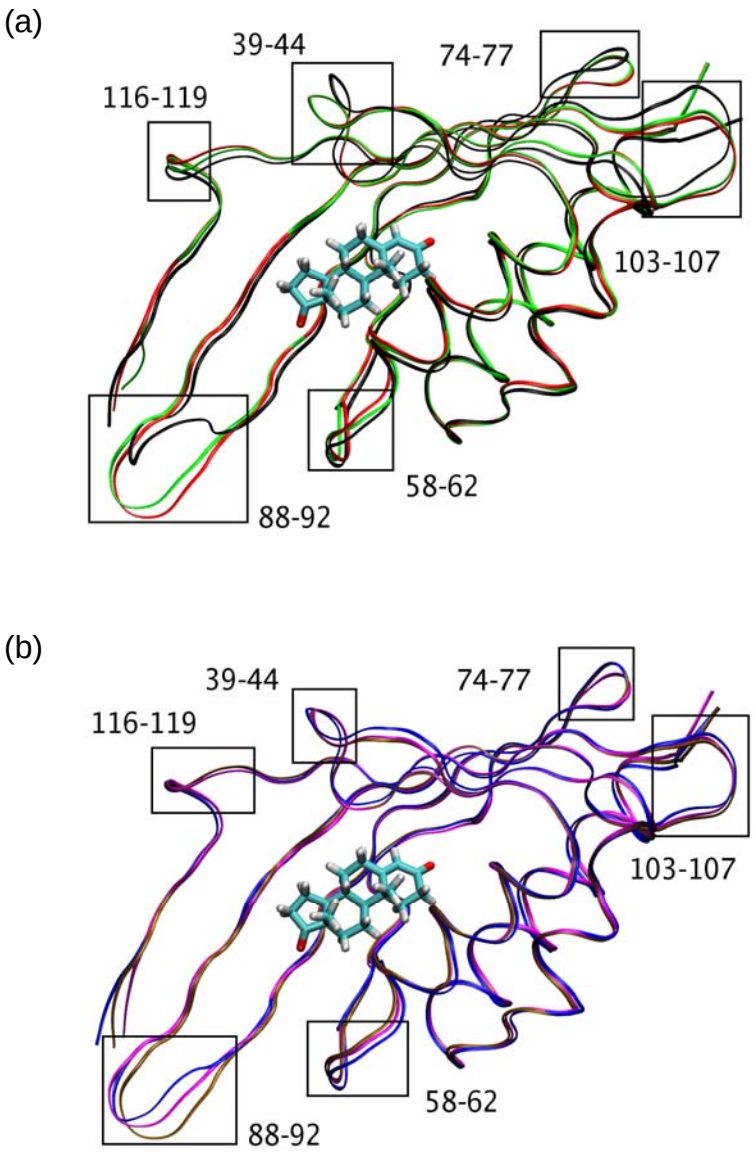

Figure S4: Thermally averaged structures of KSI along the reaction pathway for (a) the first proton transfer step and (b) the second proton transfer step. The reactant state (black), transition state (red) and product state (green) for the first proton transfer step and the reactant state (brown), transition state (magenta) and product state (blue) for the second proton transfer step are presented. The loop regions exhibiting significant structural changes are labeled.