

# **Supporting Information: Double Proton Transfer in Hydrated Formic Acid Dimer: Interplay of Spatial Symmetry and Solvent-Generated Force on Reactivity**

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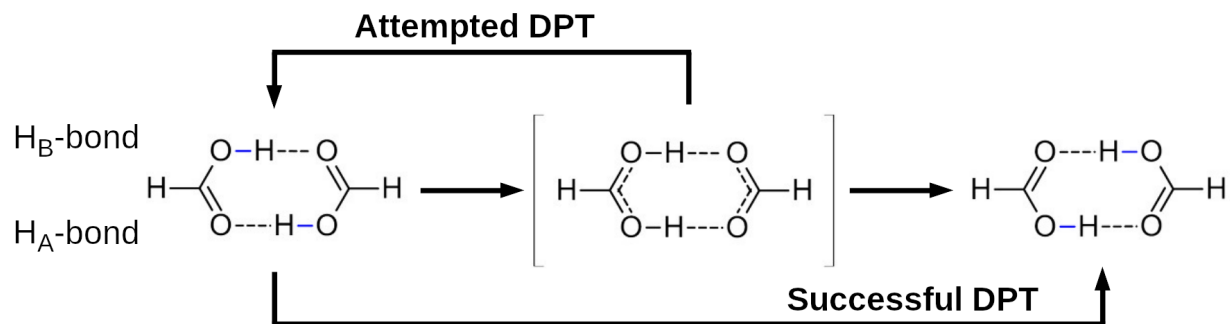


Figure S1: Schematic reaction profile of DPT in FAD. The intermediate ion-pair configuration after the first PT in the H<sub>A</sub>-bond is shown square brackets. The second PT occurs either in the H<sub>B</sub>-bond resulting in a successful DPT or in the H<sub>A</sub>-bond again labelled as attempted DPT. Note the inversion of the covalent O–H bonds (blue line) in a successful DPT where the attempted DPT leads to the original configuration.

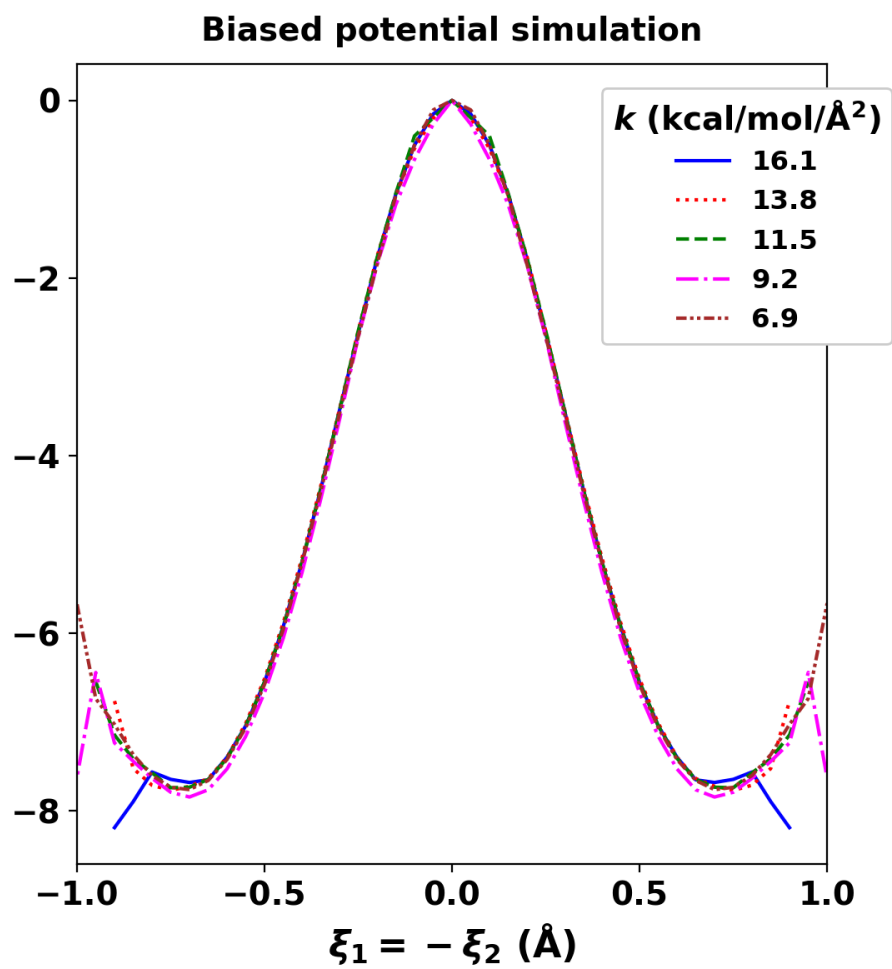


Figure S2: 1-dimensional free energy profiles from the 2-dimensional free energy surfaces at different force constants for the artificial harmonic potential in biased simulation of FAD in solution to constraint FAD around the TS conformation.

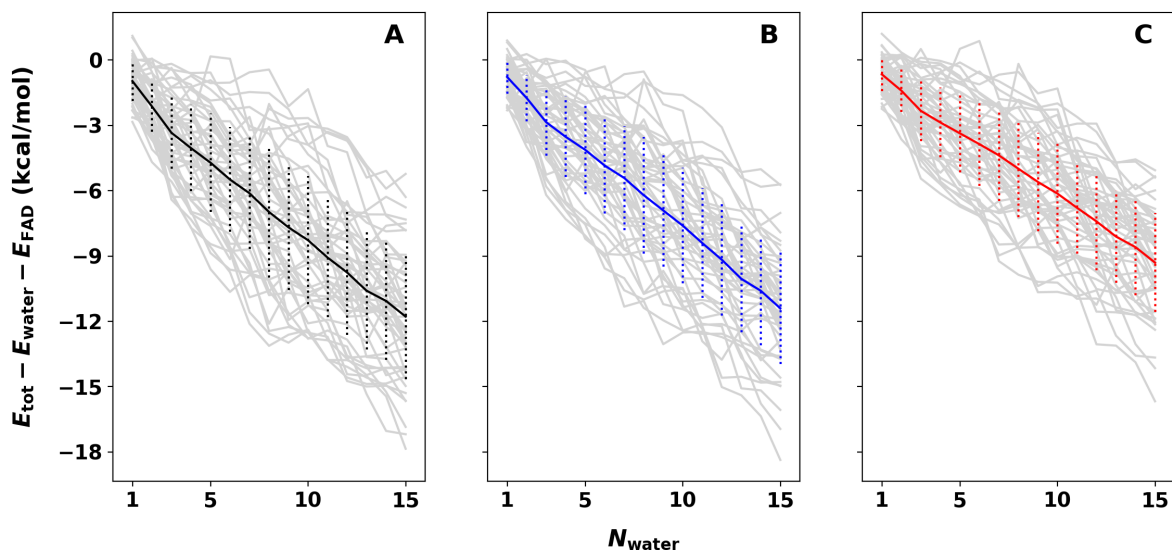


Figure S3: Average interaction energy and fluctuation around it between FAD and increasing number of closest water molecules  $N_{\text{water}}$  from 50 randomly chosen snapshots from a 2 ns simulation at 300 K. The standard deviation is given by the dashed error bars and the light grey lines shows the hydration energy of the chosen snapshots. The interaction energies are determined by (left panel) DFT (B3LYP+D3/aug-cc-pVTZ, BSSE corrected), (center panel) the current ML/MM model and (right panel) with the CHARMM program package with the CGenFF force field.

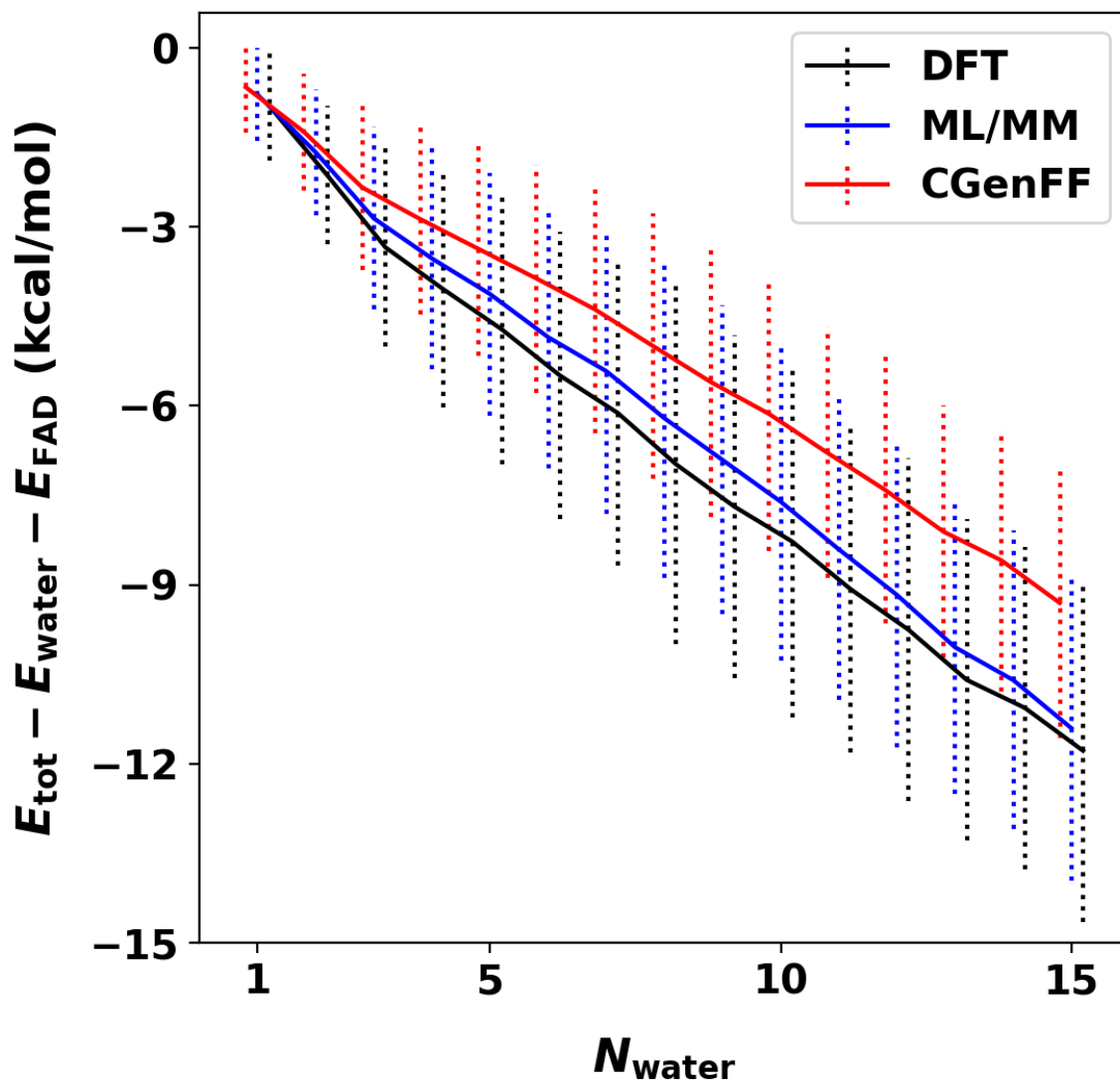


Figure S4: Average interaction energy and fluctuation around it between FAD and increasing number of closest water molecules  $N_{\text{water}}$  in 50 randomly chosen snapshots from 300 K simulations. The standard deviation is given by the dashed error bars which are slightly shifted for better visualization. The interaction energies are determined by DFT (B3LYP+D3/aug-cc-pVTZ, BSSE corrected), the current ML/MM model and with the CHARMM program package with the CGenFF force field.

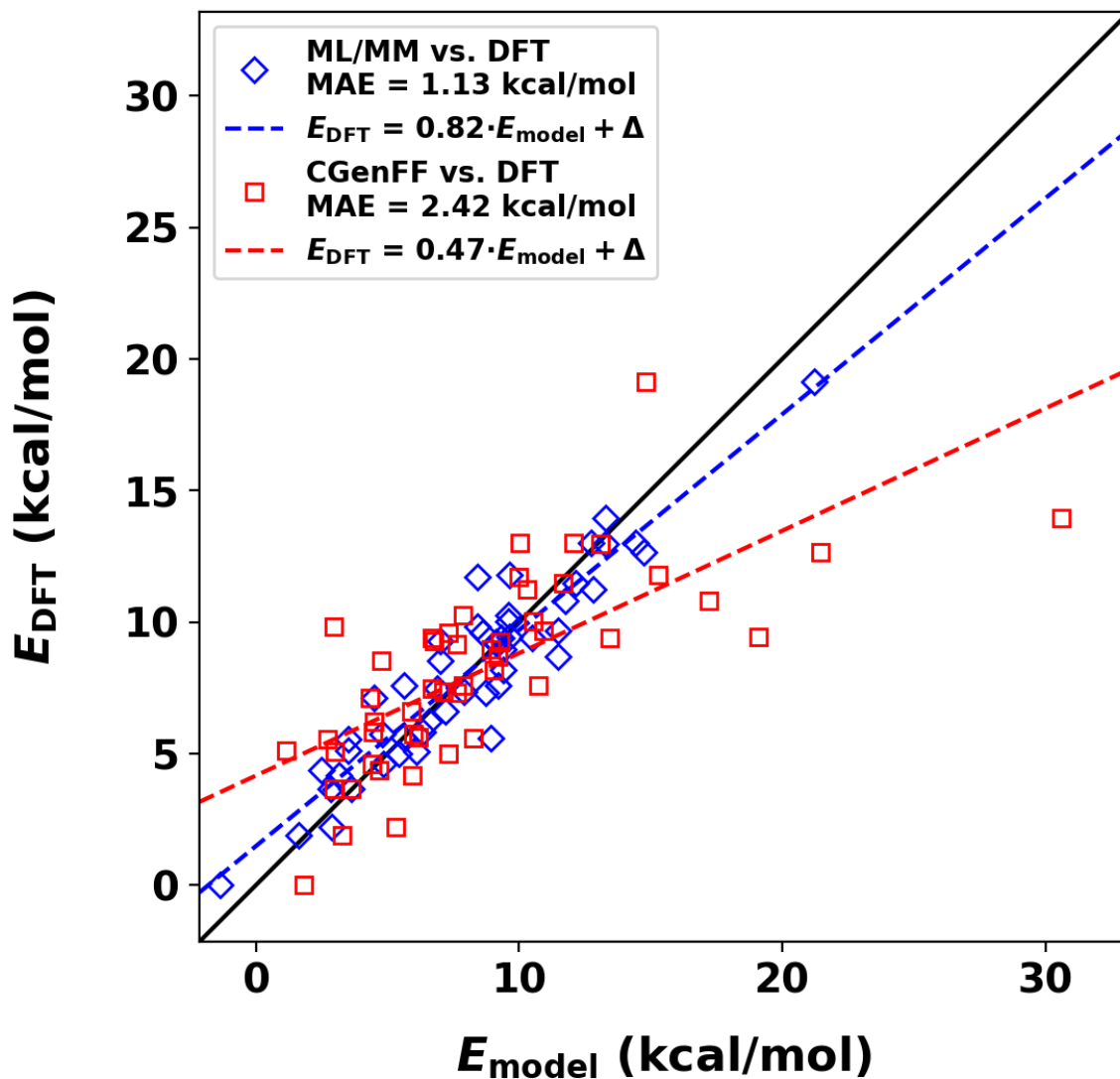


Figure S5: Correlation between DFT and model potential energies for FAD surrounded by the 4 closest water molecules (relative to the FAD center of mass) for 50 randomly chosen snapshots from 300 K simulations. The DFT energy of the energetically lowest structure is shifted to zero and the model energies are shifted to minimize the mean absolute error (MAE) with the DFT energies. The linear regression for ML/MM vs. DFT and CGenFF vs. DFT are the dashed blue and red lines, respectively. The slope of the linear fit is given in the legend. The solid black line is the ideal 1:1 correlation and the MAE reported is with respect to the black solid line.

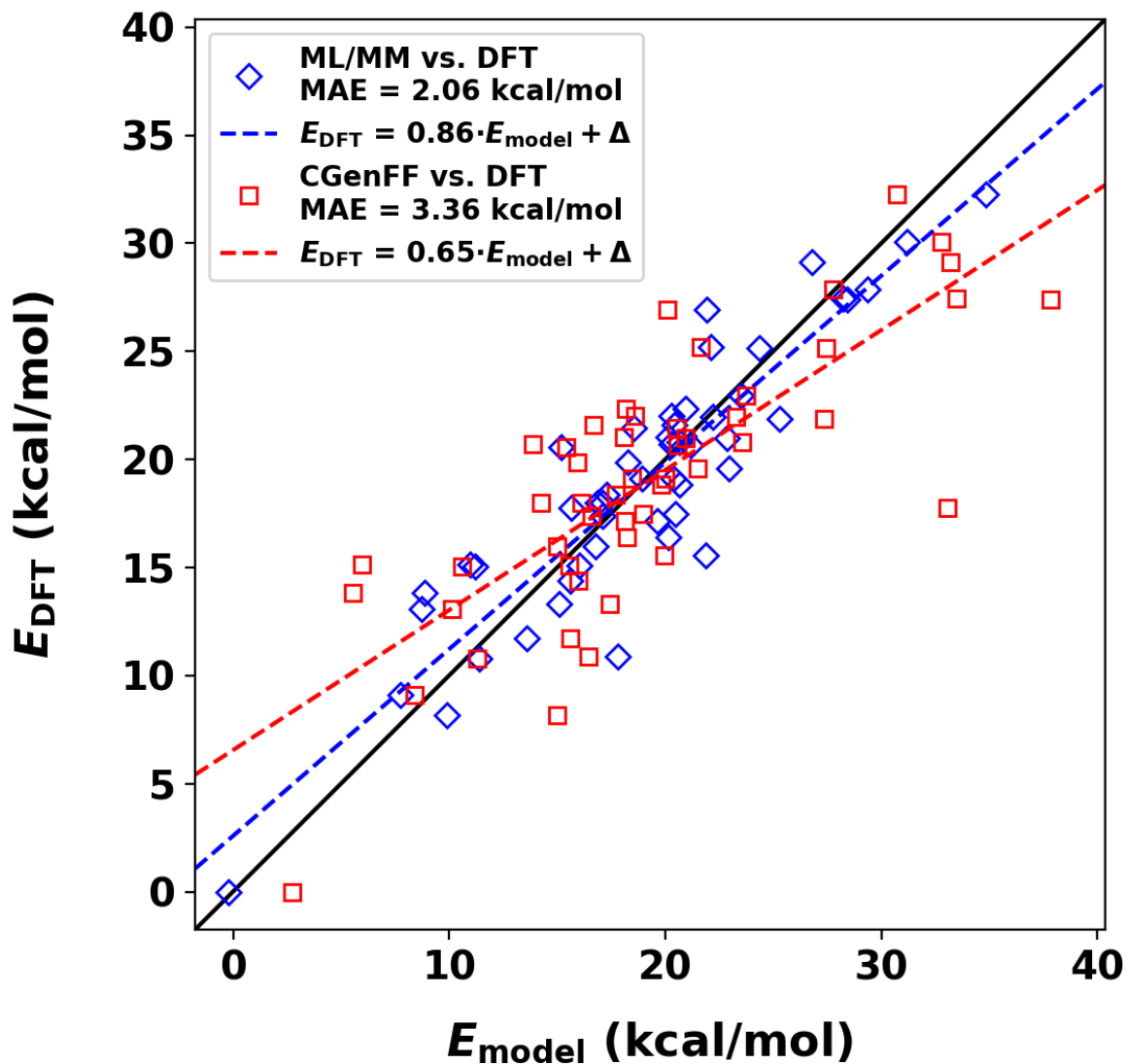


Figure S6: Correlation between DFT and model potential energies for FAD surrounded by the 8 closest water molecules (relative to the FAD center of mass) for 50 randomly chosen snapshots from 300 K simulations. The DFT energy of the energetically lowest structure is shifted to zero and the model energies are shifted to minimize the mean absolute error (MAE) with the DFT energies. The linear regression for ML/MM vs. DFT and CGenFF vs. DFT are the dashed blue and red lines, respectively. The slope of the linear fit is given in the legend. The solid black line is the ideal 1:1 correlation and the MAE reported is with respect to the black solid line.

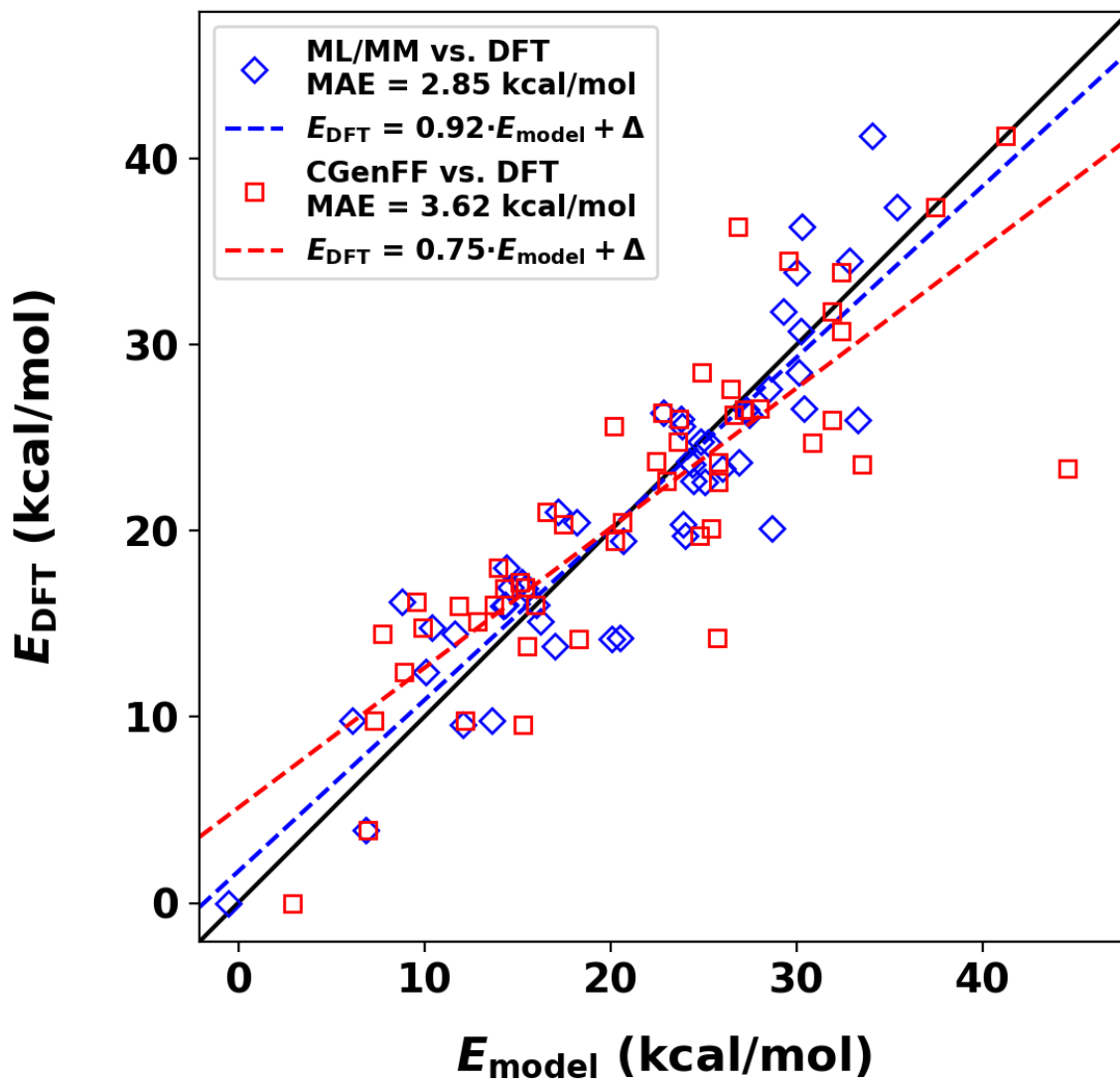


Figure S7: Correlation between DFT and model potential energies for FAD surrounded by the 12 closest water molecules (relative to the FAD center of mass) for 50 randomly chosen snapshots from 300 K simulations. The DFT energy of the energetically lowest structure is shifted to zero and the model energies are shifted to minimize the mean absolute error (MAE) with the DFT energies. The linear regression for ML/MM vs. DFT and CGenFF vs. DFT are the dashed blue and red lines, respectively. The slope of the linear fit is given in the legend. The solid black line is the ideal 1:1 correlation and the MAE reported is with respect to the black solid line.



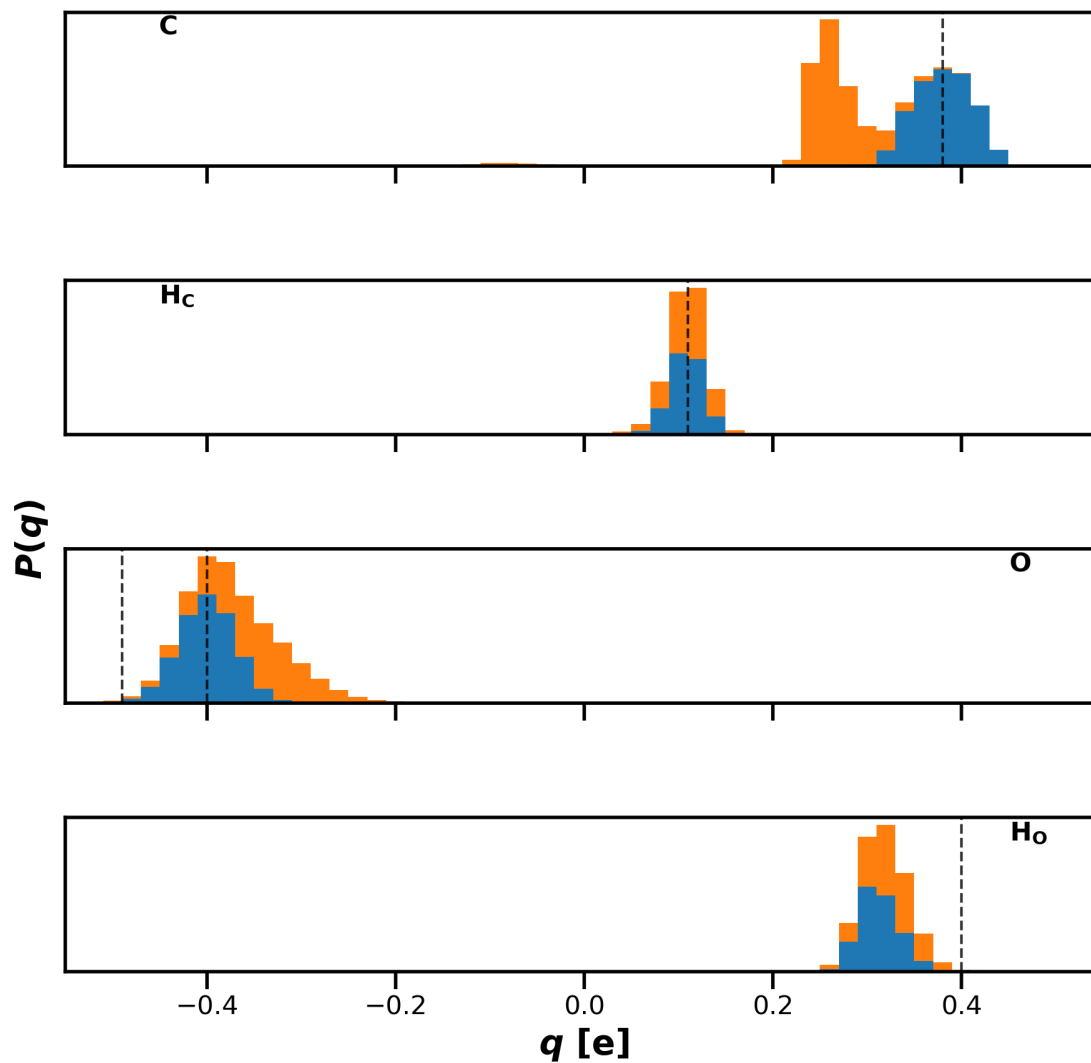


Figure S8: Predicted atomic charge probability distributions  $P(q)$  from the trained PhysNet model for FAD. The distributions are shown for the carbon atoms C, carbon-bonded hydrogen atoms  $H_c$ , oxygen atoms O and oxygen-bonded hydrogen atoms  $H_o$ . Blue:  $P(q)$  for 10000 conformations of cyclic-FAD from gas phase MD simulations; orange:  $P(q)$  for 10000 conformations of non-cyclic FAD. The vertical black dashed lines mark the atomic charges for the corresponding atom types from the CGenFF force field.<sup>1</sup>

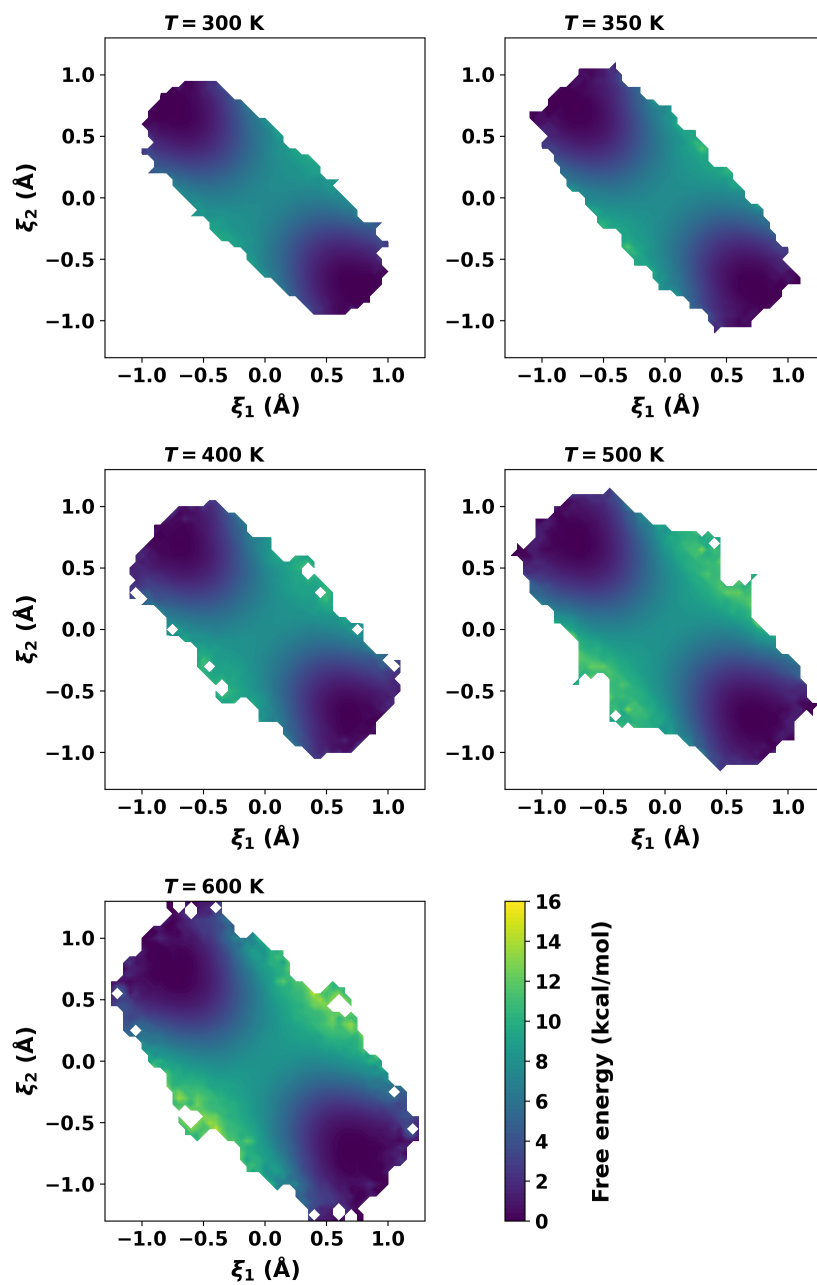


Figure S9: 2-dimensional free energy surfaces  $G(\xi_1, \xi_2)$  for DPT in FAD in solution with fluctuating charges for different temperatures.

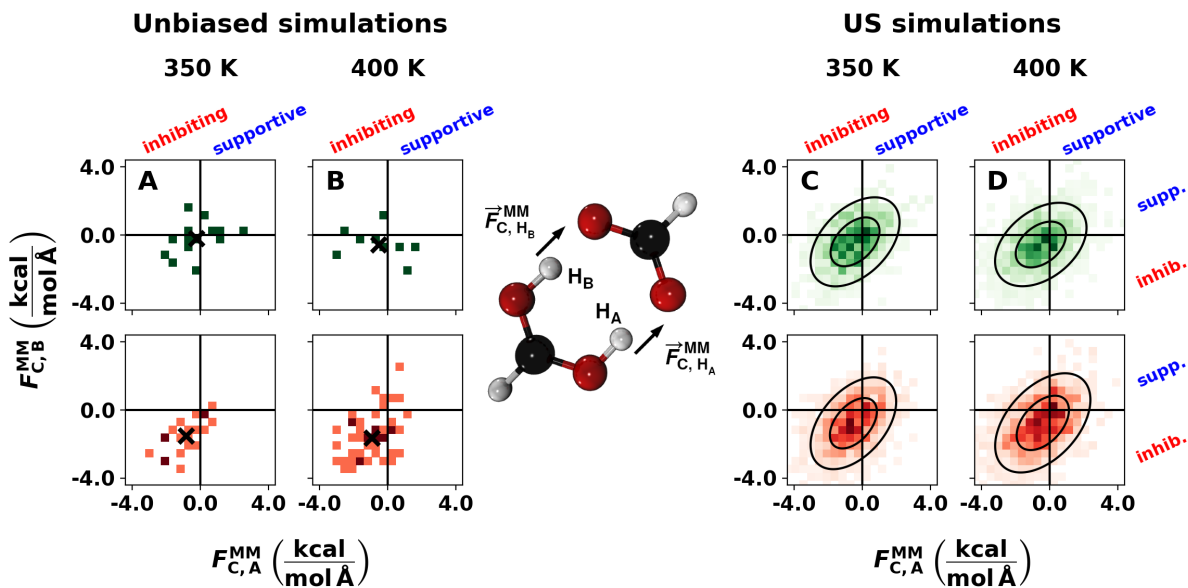


Figure S10: Correlation between the magnitude and direction of the electrostatic component of the solvent force  $F_C^{\text{MM}}$  at the position of the transferring hydrogen atom during the second PT for successful (green) and attempted (red) DPT. For definitions see Analysis section. Results from unbiased (A and B) and US simulations (C and D) are shown separately from simulations at (A and C) 350 K and (B and D) 400 K. The forces on the hydrogen atom  $H_A$  involved in the first PT are given on the horizontal axis. In the vertical axis the forces on the hydrogen atom  $H_B$  are shown performing either the second PT or no PT for successful or attempted DPT, respectively. By definition, the force vector always points towards  $O_{\text{acc}}$  in the H-bond after the first PT. An electrostatic force on the hydrogen atom towards  $O_{\text{acc}}$  in the respective H-bond is labelled as “supportive”, and “inhibiting” otherwise.

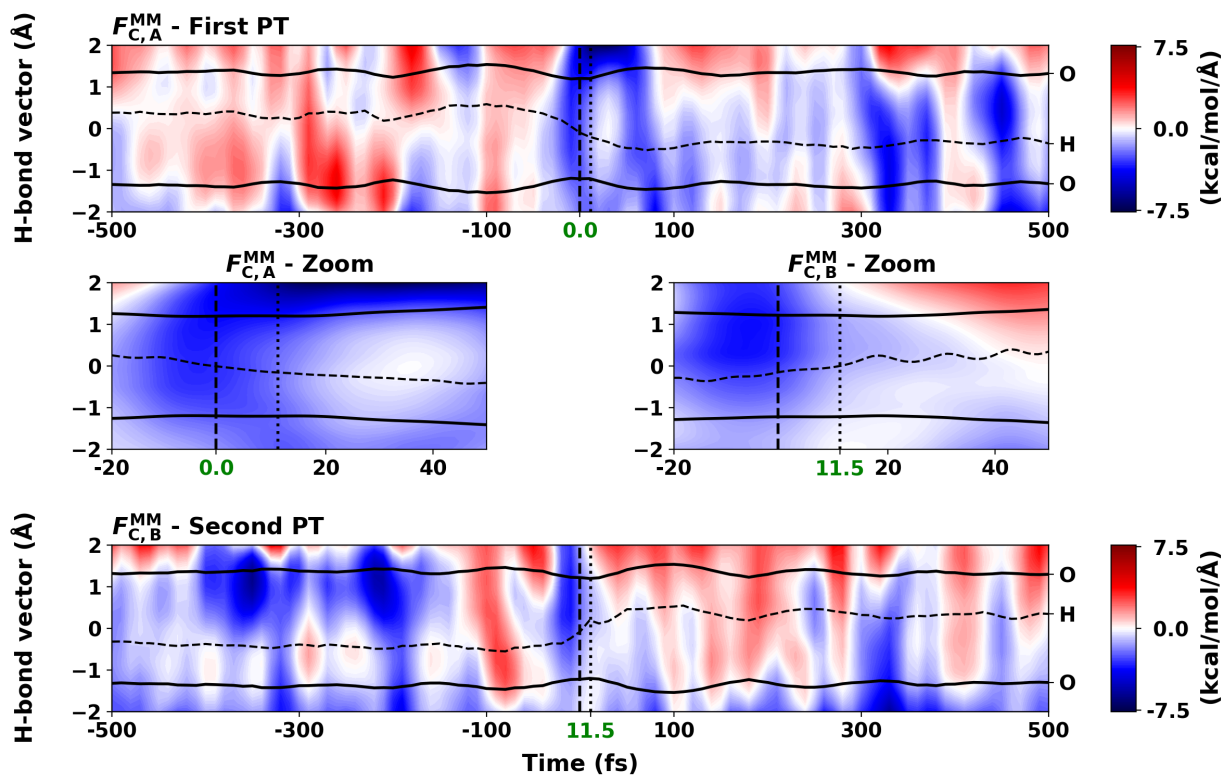


Figure S11: Time sequence covering 1 ps of reporting the solvent-generated Coulomb force  $F_C^{MM}$  on the hydrogen atoms in both H-bonds before and after the first (top panel) and second PT (bottom panel) for a successful DPT at 350 K. The black solid and dashed lines follow the position of the O and H atoms in the respective H-bond. The two center panels provide the  $F_C^{MM}$  sequence in both H-bonds across a 70 fs window around the DPT. The red colormap denotes a Coulomb force on the respective H atom parallel and the blue colormap antiparallel along the H-bond vector defined between both oxygen atoms. The horizontal solid and dashed lines follow the position of the O and H atoms in the respective H-bond. The vertical dashed line at 0 fs is the time point of the first PT in the H<sub>A</sub>-bond and dotted line of the second PT in the H<sub>B</sub>-bond.

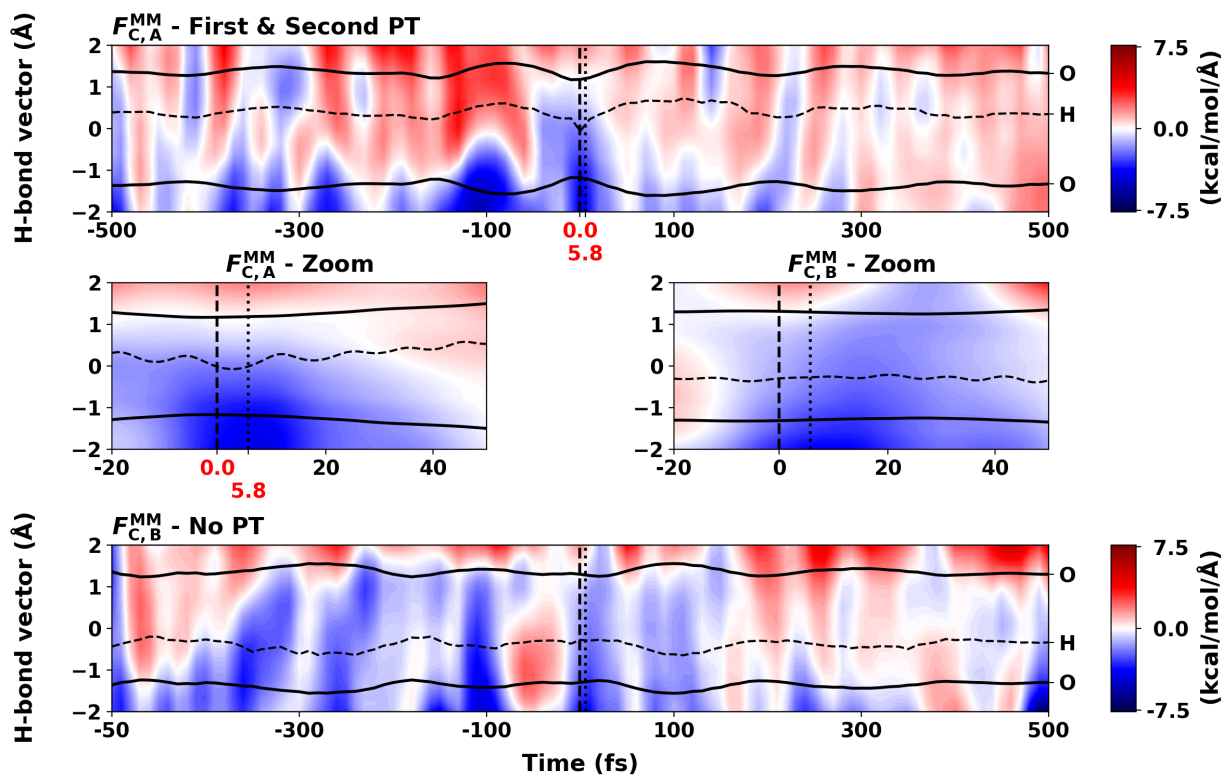


Figure S12: Time sequence covering 1 ps of reporting the solvent-generated Coulomb force  $F_C^{MM}$  on the hydrogen atoms in both H-bonds before and after the first (top panel) and second PT (bottom panel) for an attempted DPT event at 350 K. The black solid and dashed lines follow the position of the O and H atoms in the respective H-bond. The two center panels provide the  $F_C^{MM}$  sequence in both H-bonds across a 70 fs window around the DPT. The red colormap denotes a Coulomb force on the respective H atom parallel and the blue colormap antiparallel along the H-bond vector defined between both oxygen atoms. The horizontal passing solid and dashed line shows the position of the O and H atoms in the respective H-bond. The vertical dashed line at 0 fs is the time point of the first PT in the H<sub>A</sub>-bond and dotted line of the second PT in the H<sub>B</sub>-bond.

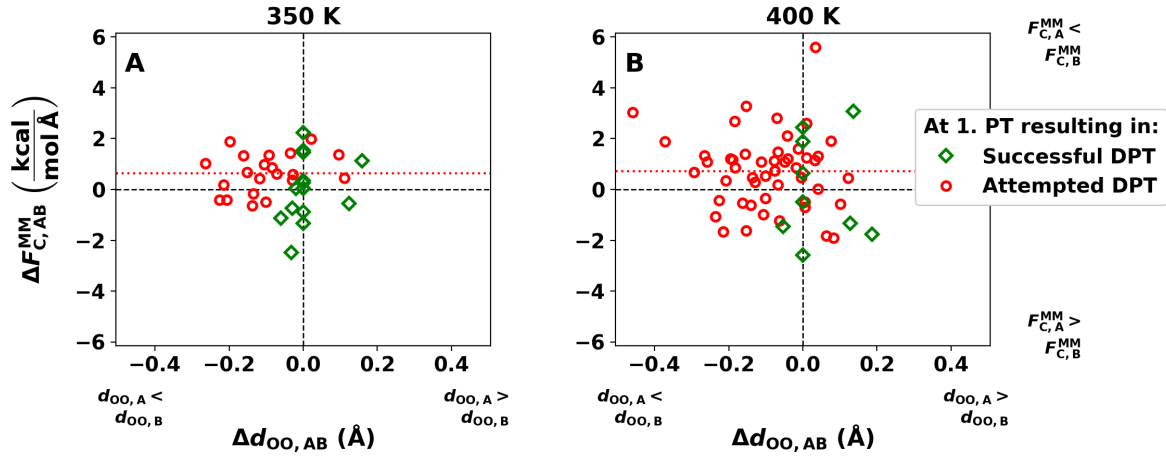


Figure S13: Correlation between difference in O–O separation  $\Delta d_{OO,AB} = d_{OO,A} - d_{OO,B}$  and difference in solvent-generated Coulomb force  $\Delta F_{C,AB}^{MM} = F_{C,A}^{MM} - F_{C,B}^{MM}$  of both H-bonds for the first PT at 350 K and 400 K of unbiased simulations, respectively. The average force difference for attempted DPT is indicated as the dashed red line. Manifestly, the average  $\Delta d_{OO,AB} < 0$  for attempted DPT whereas  $\Delta d_{OO,AB} \sim 0$ , i.e. the structure is symmetric, for successful DPT.

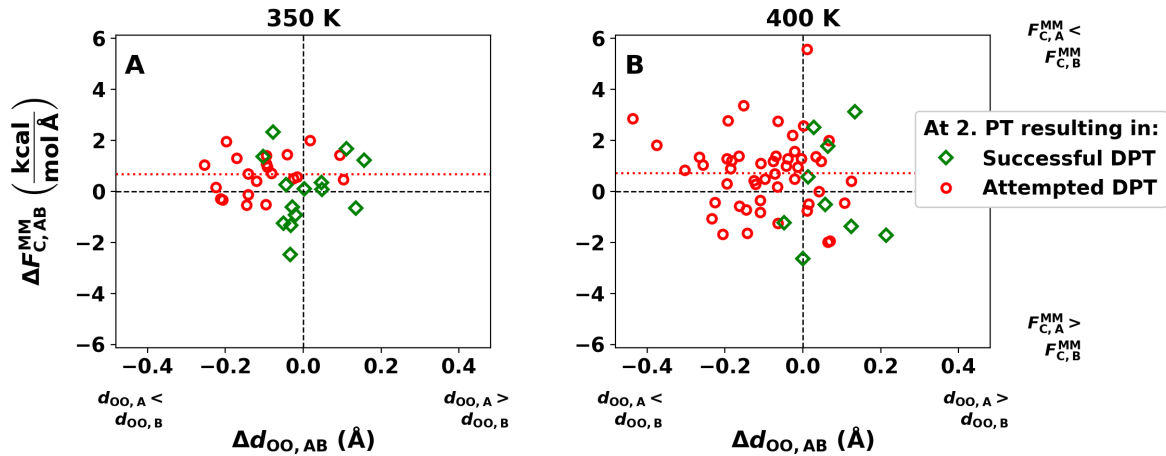


Figure S14: Correlation between difference in O–O separation  $\Delta d_{OO,AB} = d_{OO,A} - d_{OO,B}$  and difference in solvent-generated Coulomb force  $\Delta F_{C,AB}^{MM} = F_{C,A}^{MM} - F_{C,B}^{MM}$  of both H-bonds for the second PT at 350 K and 400 K of unbiased simulations, respectively. The average force difference for attempted DPT is indicated as the dashed red line. Manifestly, the average  $\Delta d_{OO,AB} < 0$  for attempted DPT whereas  $\Delta d_{OO,AB} \sim 0$ , i.e. the structure is symmetric, for successful DPT. Note the slight displacements in position and forces compared with Figure S13 as the first and second PT are separated by a few femtoseconds.

## References

- (1) Vanommeslaeghe, K.; Hatcher, E.; Acharya, C.; Kundu, S.; Zhong, S.; Shim, J.; Darian, E.; Guvench, O.; Lopes, P.; Vorobyov, I. et al. CHARMM General Force Field: A Force Field for Drug-like Molecules Compatible with the CHARMM All-Atom Additive Biological Force Fields. *J. Comput. Phys.* **2010**, *31*, 671–690.