Theoretical study of the mechanism of the hydride transfer between Ferredoxin $NADP^+$ reductase and $NADP^+$. The role of Tyr303.

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Abbreviations:

NADP, Nicotinamide Adenine Dinucleotide Phosphate; FAD, Flavin Adenine Dinucleotide; FNR_{ox}, oxidized Ferredoxin-$NADP^+$ Reductase; FNR_{red}, reduced Ferredoxin-$NADP^+$ Reductase; MD, Molecular Dynamics; QM/MM, Quantum Mechanics/Molecular Mechanics; WHAM, Weighted Histogram Analysis Method; *An*FNR, Anabaena FNR; ApoFNR, FNR Apoenzyme; ET, Electron Transfer; AMP, Adenosine monophosphate; WT, Wild-Type; HT, Hydride Transfer; AM1, Austin Model 1; B3LYP, Becke, three-parameter, Lee-Yang-Parr exchange-correlation functional; 1-D, one-Dimensional; GHO, Generalized Hybrid Orbital; GDC, Grimme Dispersion Correction; B3LYP –D, B3LYP with the GDC; PMF, Potential of Mean Force; PBC, Periodic Boundary Conditions ; NPT, isothermal-isobaric ensemble

Reference 25b: Brooks, B. R.; Brooks, C. L., III.; 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.; Karplus, M. *J Compu Chem* **2009,** *30*, 1545-1614.

Figure S1. AM1/MM potential energy profile as a function of the reaction coordinate with Tyr303 residue not included in the QM region.

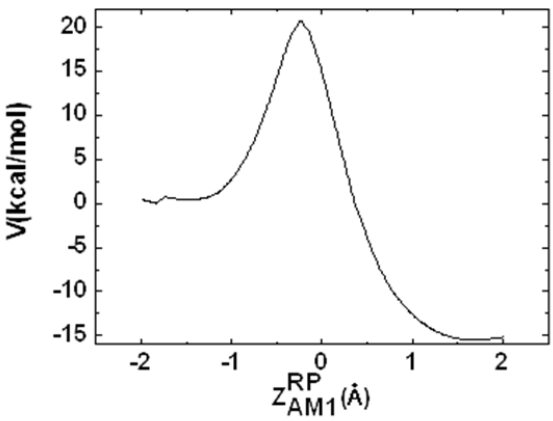

Figure S2. Grimme dispersion correction contribution along the coordinate in the B3LYP/MM potential energy profile.

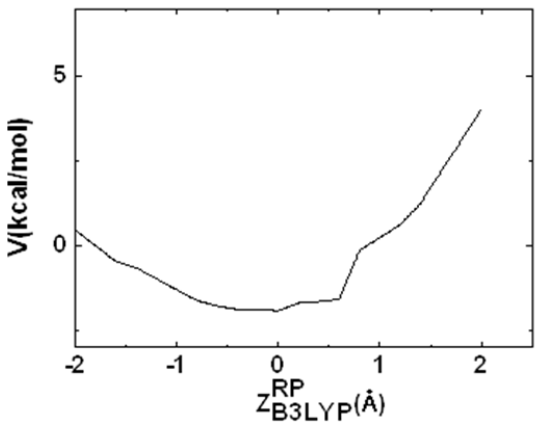

Figure S3. AM1/CHARMM22 classical mechanical PMF with Tyr303 residue not included in the QM region.

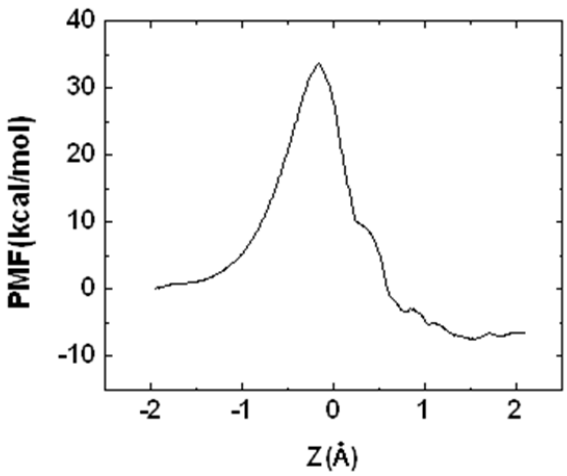

Figure S4. AM1/CHARMM22 classical mechanical PMF obtained from the string simulations including the OH-HH distance as one of the collective coordinates.

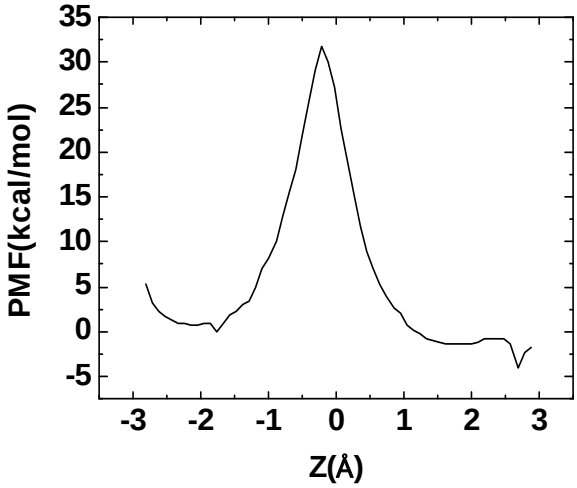

Figure S5. Cis and trans conformation of the amide group in the nicotinamide ring along the 45 images used in the string method.

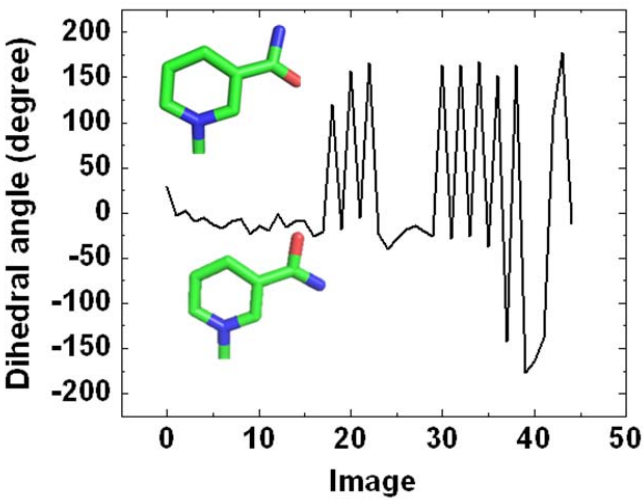

Figure S6. AM1/CHARM22 classical mechanical PMF with the amide group of nicotinamide in the trans conformation, obtained from the string simulations including the dihedral angle of the amide group of the nicotinamide ring as one of the collective coordinates

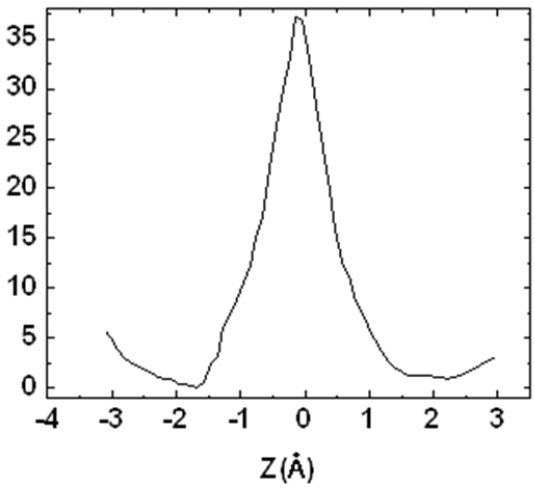

Figure S7. Evolution of the N_5-O(Tyr303) and C_4N-O(Tyr303) distances along the reaction coordinate z when the sampling of configurations is done directly along z and when it is performed along the string.

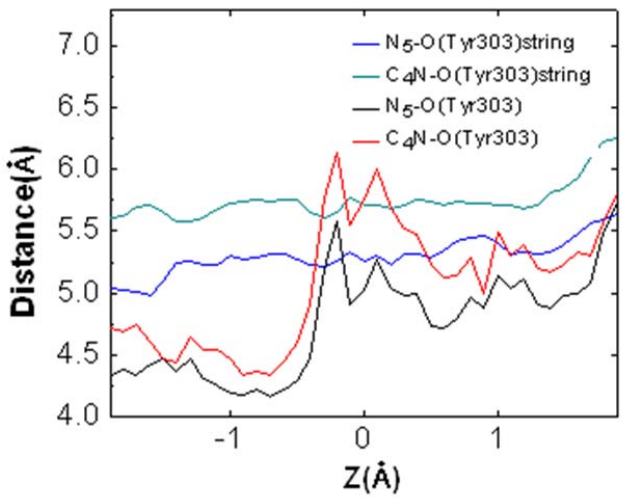

Figure S8. Evolution of the angles between each pair of rings along the reaction coordinate z

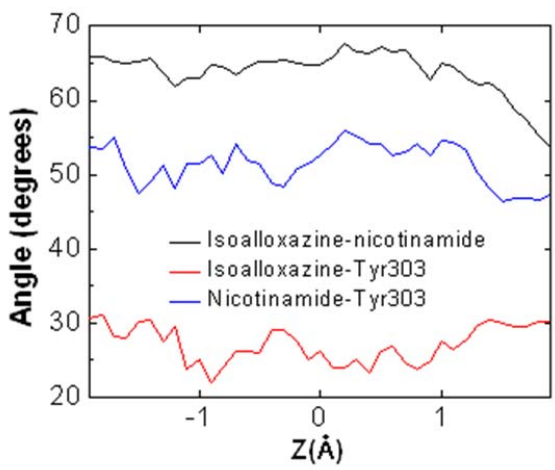

Table S1. Values of the important geometric parameters at the reactant, transition state, and product structures of the AM1/MM and B3LYP-D/MM potential energy profiles (Figures 3 and 4, respectively). Distances in Å and angles in degree.

	AM1			B3LYP-D/MM		
Distances/Angles	R	TS	P	R	TS	P
N_5-C_4N	3.4	2.7	3.7	2.8	2.6	3.1
N_{10}-N_1N	5.8	5.5	6	5.8	5.6	5.8
N_5-O(Tyr303)	5.7	5.5	5.7	5	5.1	5.2
C_4N-O(Tyr)	6.1	6	6.4	5.7	5.6	5.8
N_5-H-C_4N	165.5	172.8	132.1	79.4	164.6	147.9