Supporting information for the article "Mechanism of Proteolysis in Matrix Metalloproteinase-2 Revealed by QM/MM Modeling"

Tatiana Vasilevskaya* Maria G. Khrenova †‡
Alexander V. Nemukhin †§ Walter Thiel*

May 26, 2015

Comparison of PBE0 and B3LYP functionals

We studied small model systems to compare the results obtained with different functionals with benchmark results presented in Ref. S1. We optimized the equilibrium geometries of Zn^{2+}-acetate and Zn^{2+}-acetic acid complexes at the PBE0/6-31G** and B3LYP/6-31G** levels of theory. Figure S1 summarizes the results. Both DFT functionals underestimate the charge on Zn^{2+}, but for B3LYP the error is larger. The distances between oxygen atoms and Zn^{2+} are longer than in the benchmark protocol in case of B3LYP but shorter in PBE0. This is likely the reason why the first intermediate (I1 in the main paper) is higher in energy at the B3LYP/6-31G** level of theory. We conclude that the B3LYP/6-31G** protocol underestimates the interactions between charged parts of the system (Zn^{2+} and $CH3COO^-$) and that the PBE0/6-31G** protocol is more reliable in this particular case.

*Max-Planck-Institut für Kohlenforschung, Mülheim an der Ruhr, Germany
†Chemistry Department, Lomonosov Moscow State University, Moscow, Russia
‡A.N. Bach Institute of Biochemistry, Russian Academy of Sciences, Moscow, Russia
§Emanuel Institute of Biochemical Physics, Russian Academy of Sciences, Moscow, Russia

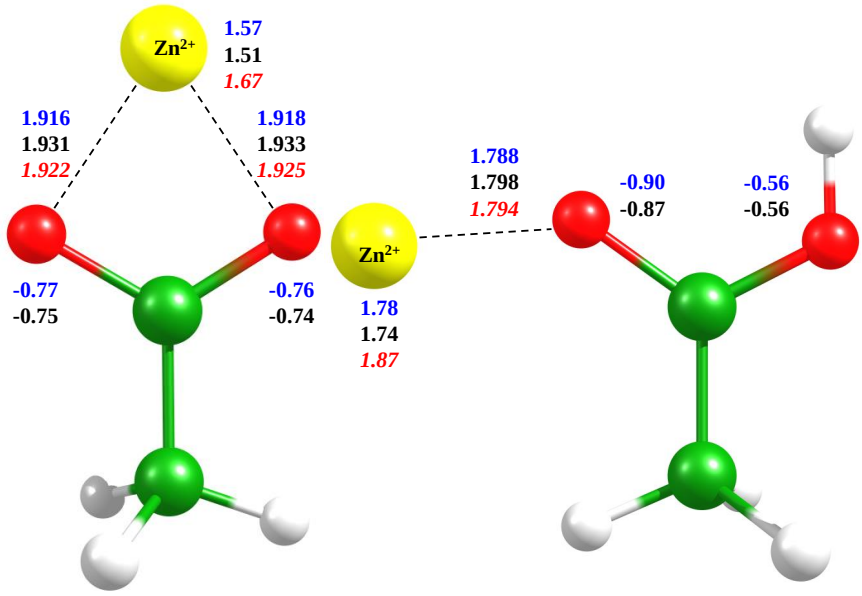

Figure S1: Equilibrium geometries of Zn^{2+}-acetate (left panel) and Zn^{2+}-acetic acid (right panel) complexes. Values calculated at PBE0/6-31G** and B3LYP/6-31G** are given in the blue upper line and black middle line, respectively. The red italic lower line lists benchmark results [1] obtained at the MP2/aug-cc-pVTZ level of theory. Values with 3 decimal digits are distances in Å; values with 2 decimal digits are natural charges.

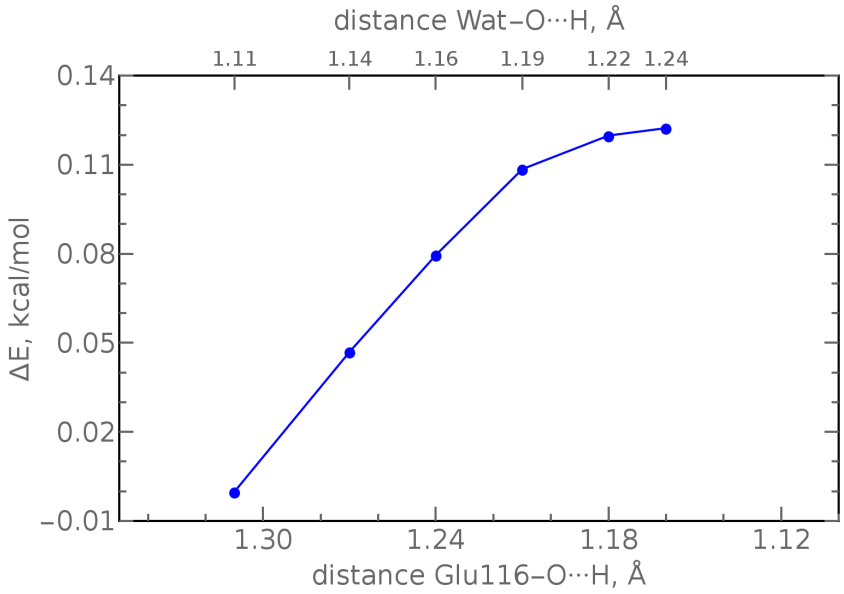

Figure S2: Potential energy surface for proton transfer between Glu116 and the adjacent water molecule in the Michaelis complex. The energy of the Michaelis complex is set to zero.

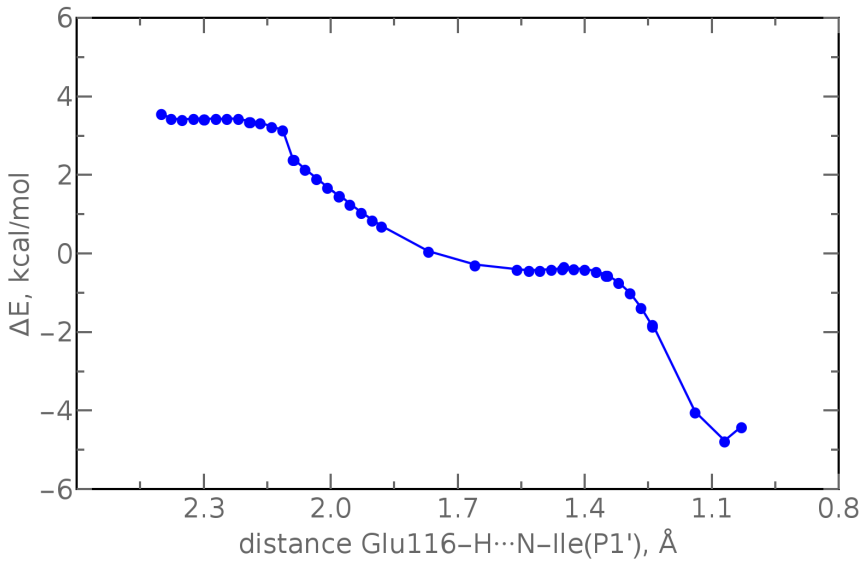

Figure S3: Potential energy surface for the second and third steps of the catalytic reaction.

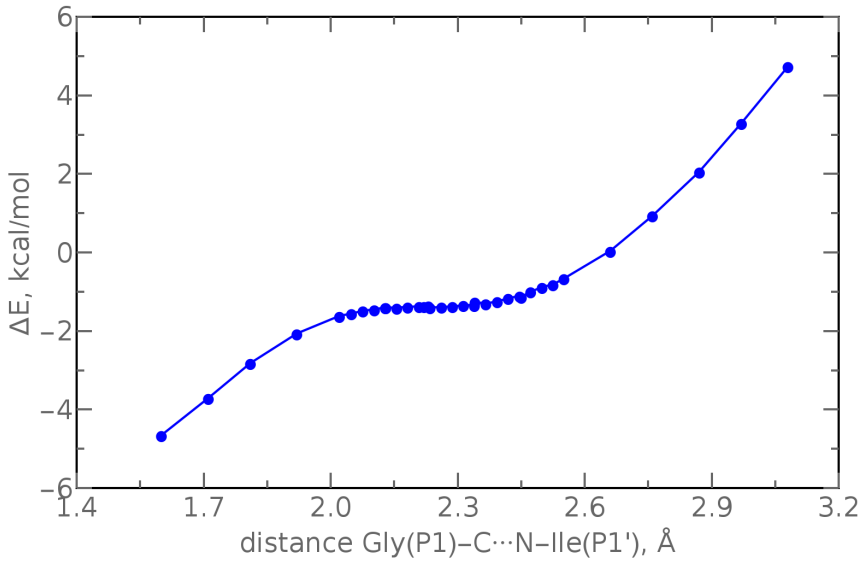

Figure S4: Potential energy surface for the fourth step of the catalytic reaction.

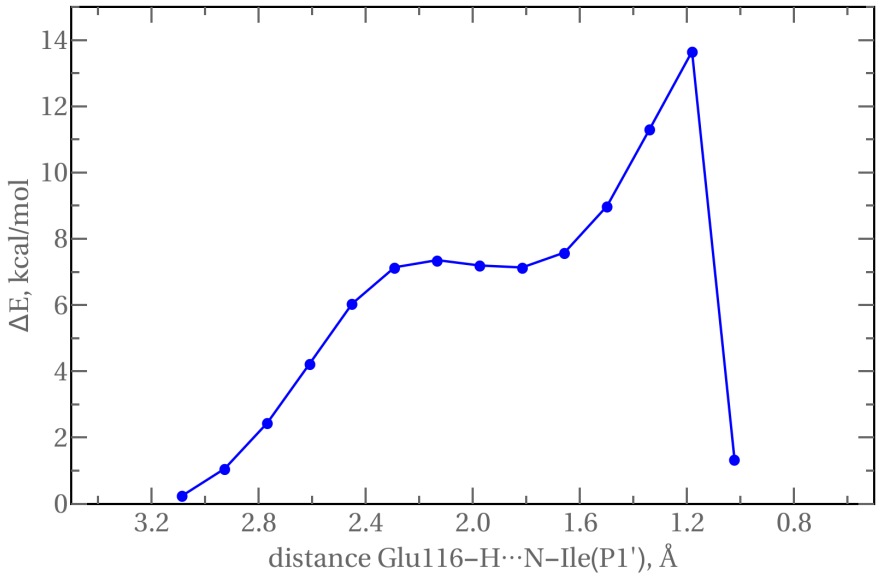

Figure S5: Potential energy surface for proton transfer between Glu116 and the amino group of Ile(P1) starting from the I4 structure. The energy of the I4 intermediate is set to zero.

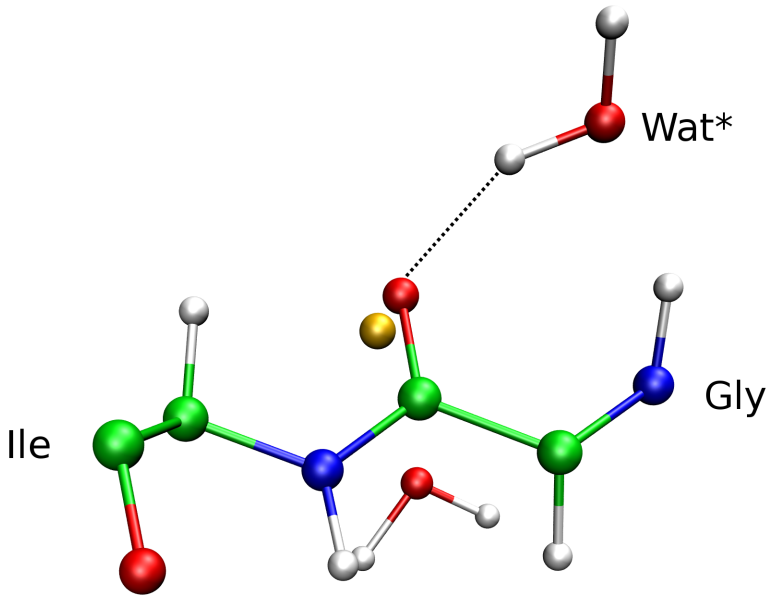

Figure S6: H-bond between the auxiliary water molecule Wat* and the carbonyl oxygen atom of the substrate.

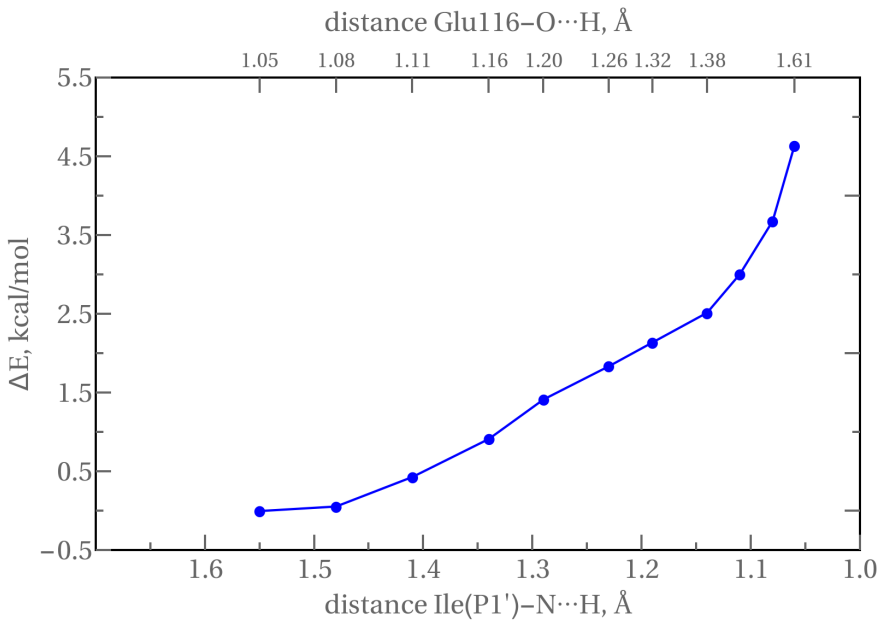

Figure S7: Potential energy surface for proton transfer between Glu116 and the amino group of Ile. The reaction coordinate is the difference between the N-H and O-H distances. The energy of the I5 intermediate is set to zero.

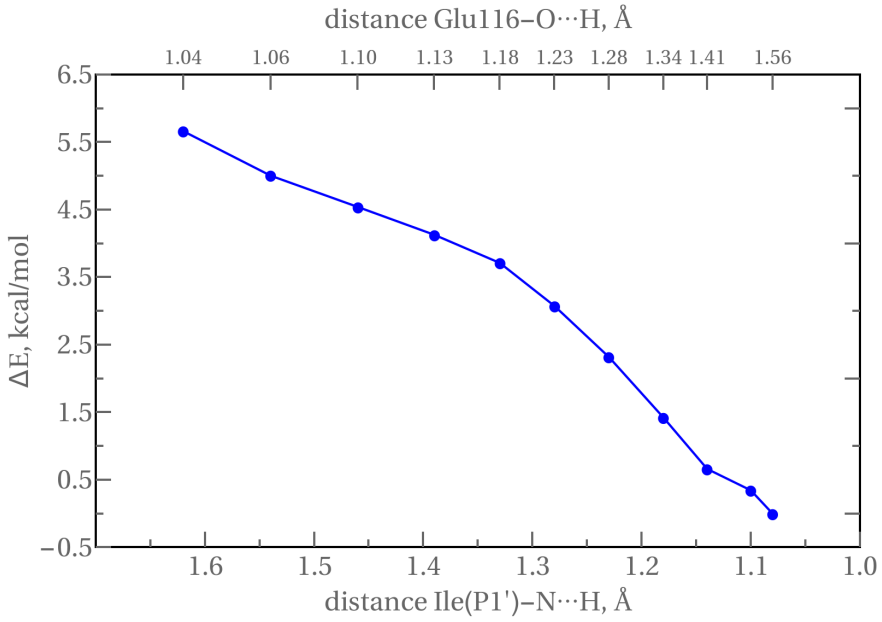

Figure S8: Potential energy surface for proton transfer between Glu116 and the amino group of Ile. The reaction coordinate is the difference between the N-H and O-H distances. The energy of the P structure is set to zero.

Estimation of the C-product release PMF

To estimate the PMF of the C-product release four different pulling simulations were performed and Jarzynski's equality was used[S2]. The resulting PMF (Fig. S9) was calculated applying the second order cumulant expansion formula

$$F(c(t)) - F(c(0)) = < W(t) > - \frac{1}{2T}[< W(t)^2 > - < W(t) >^2].$$

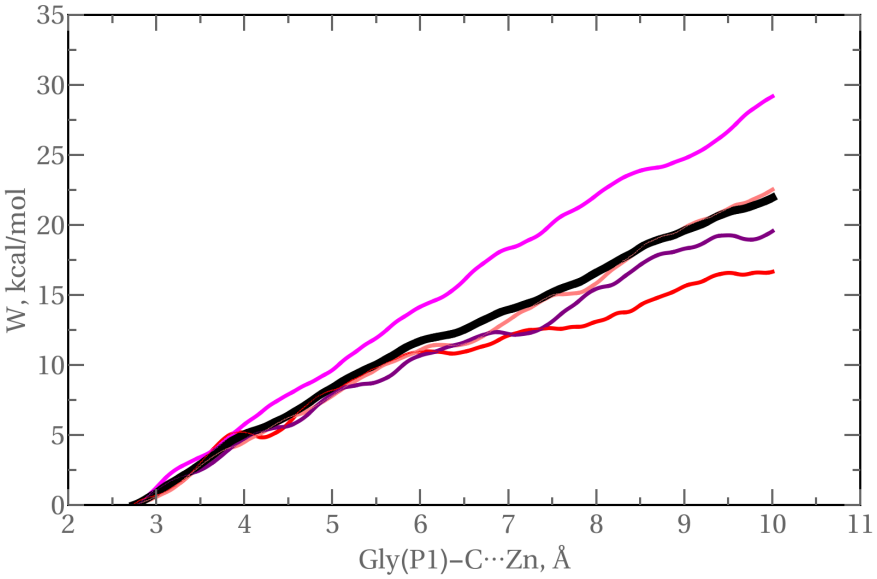

Figure S9: Work done on the system during the C-product release process for 4 pulling trajectories (magenta, pink, purple, red curves) and the estimated PMF (bold black curve).

References

S1. Rayón, V. M.; Valdés, H.; Díaz, N.; Suárez, D. *J. Chem. Comput.* **2008**, *4*, 243-256.

S2. Park, S.; Khalili-Araghi, F.; Tajkhorshid, E.; Schulten, K. *J. Chem. Phys.* **2003**, *119*, 3559-3566.