Supporting Information

Accelerated Computation of Free Energy Profile at *Ab Initio* Quantum Mechanical/Molecular Mechanics Accuracy via a Semiempirical Reference Potential. 4. Adaptive QM/MM

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1 The restraints in the umbrella sampling simulations

The umbrella sampling was carried out with 84 windows, and the restraints are (restraint center in a unit of Å, k in $\frac{1}{2}k(\xi_m - \xi(\mathbf{r})^2)$ in a unit of $kcal/mol/\text{Å}^2$):

(1.500, 1800.00), (1.525, 1400.00), (1.550, 1000.00), (1.575, 800.00), (1.600, 600.00), (1.625, 400.00), (1.650, 200.00), (1.675, 250.00), (1.700, 300.00), (1.750, 600.00), (1.800, 600.00), (1.850, 800.00), (1.900, 800.00), (1.950, 800.00), (2.000, 1200.00), (2.025, 600.00), (2.050, 600.00), (2.075, 600.00), (2.100, 400.00), (2.150, 400.00), (2.200, 320.00), (2.250, 200.00), (2.300, 200.00), (2.350, 200.00), (2.400, 200.00), (2.450, 200.00), (2.500, 200.00), (2.550, 200.00), (2.600, 200.00), (2.650, 200.00), (2.700, 200.00), (2.750, 200.00), (2.800, 200.00), (2.825, 200.00), (2.850, 200.00), (2.875, 200.00), (2.900, 200.00), (2.950, 200.00), (3.000, 200.00), (3.050, 200.00), (3.100, 200.00), (3.150, 200.00), (3.200, 200.00), (3.250, 200.00), (3.300, 200.00), (3.350, 200.00), (3.400, 200.00), (3.450, 200.00), (3.500, 200.00), (3.550, 200.00), (3.600, 200.00), (3.650, 200.00), (3.700, 200.00), (3.750, 200.00), (3.800, 200.00), (3.850, 200.00), (3.900, 200.00), (3.950, 200.00), (4.000, 200.00), (4.025, 200.00), (4.050, 200.00), (4.075, 200.00), (4.100, 200.00), (4.150, 200.00), (4.200, 200.00), (4.250, 200.00), (4.300, 200.00), (4.350, 200.00), (4.400, 200.00), (4.450, 200.00), (4.475, 200.00), (4.500, 200.00), (4.525, 200.00), (4.550, 200.00), (4.575, 200.00), (4.600, 200.00), (4.650, 200.00), (4.700, 200.00), (4.750, 200.00), (4.800, 200.00), (4.850, 200.00), (4.900, 200.00), (4.950, 200.00), (5.000, 200.00)

2 Alternations of the total Mulliken charge of the two water molecules in the QM region at the PM6/MM level with two water molecules in the QM region

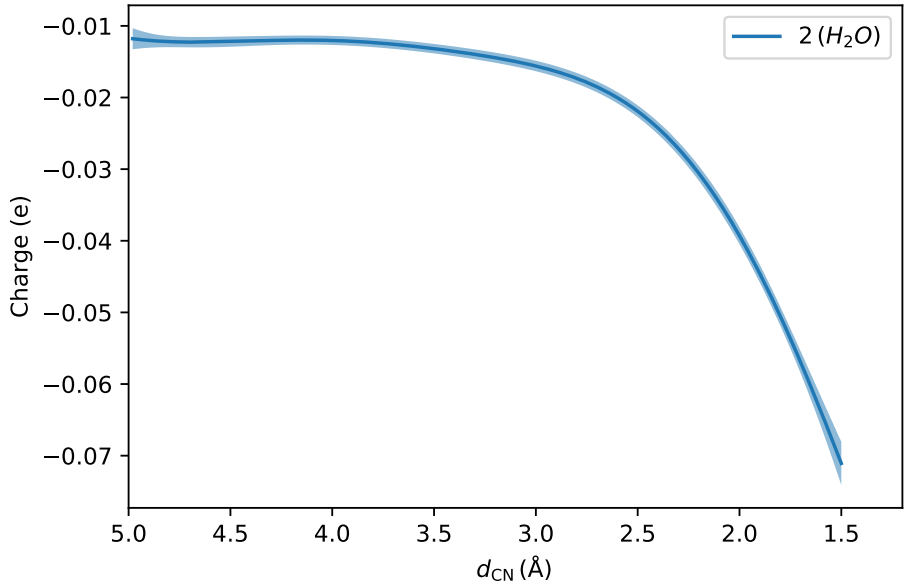

Figure S1: Alternations of the total Mulliken charge of the two water molecules in the QM region at the PM6/MM level with two water molecules in the QM region. The shaded areas are the 95% confidence intervals.

3 Comparison of the free energy profiles with three water molecules in the QM region from restrained simulation and the adaptive simulation

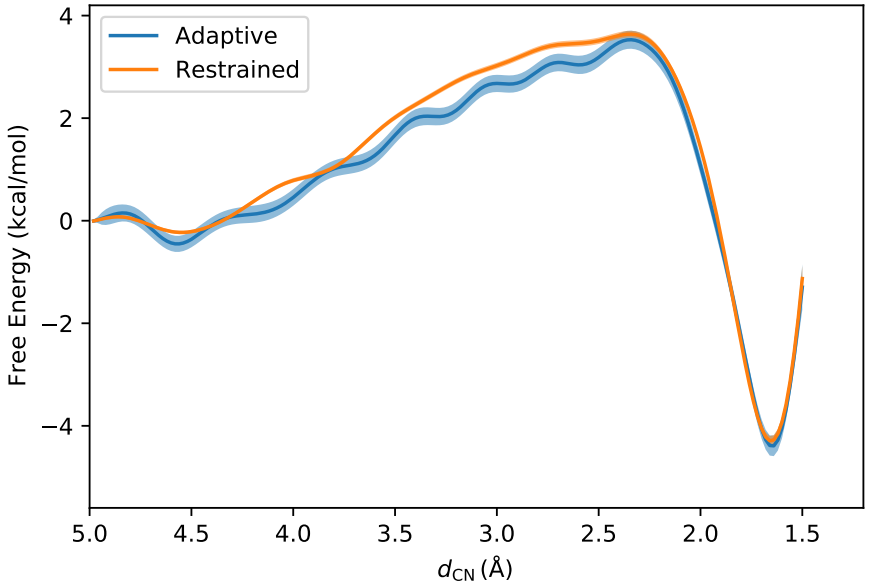

Figure S2: Free energy profiles at the PM6/MM level with three water molecules in the QM region from restrained QM/MM simulation (orange) and the adaptive QM/MM simulation (blue). The shaded areas are the 95% confidence intervals.

4 Alternative partition scheme with two water molecules in the QM region

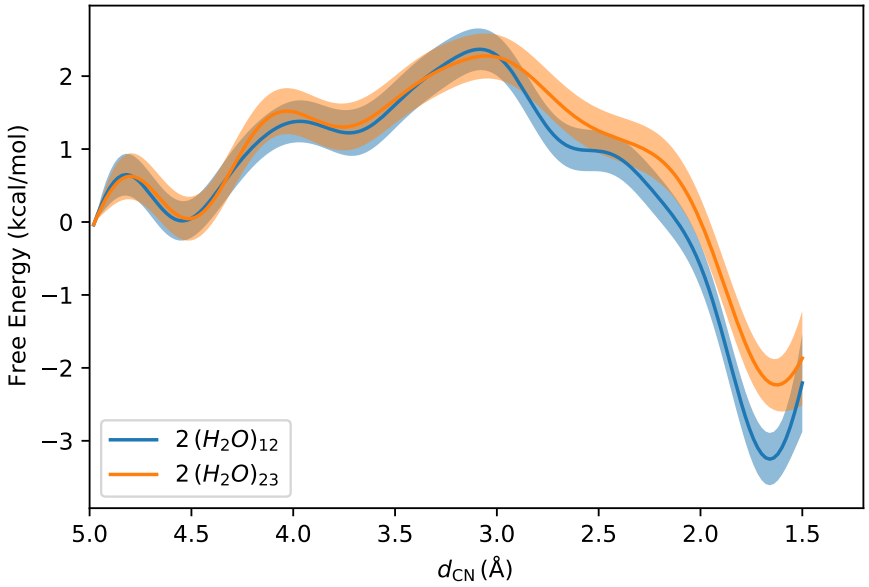

Figure S3: Free energy profiles at the DFT/MM levels with the nearest two water molecules included in the QM region (blue), and with the 2nd and the 3rd nearest water molecules in the QM region (orange). The shaded areas are the 95% confidence intervals.