Supporting Information

Molecular Dynamics Simulations with Quantum Mechanics / Molecular Mechanics and Adaptive Neural Networks

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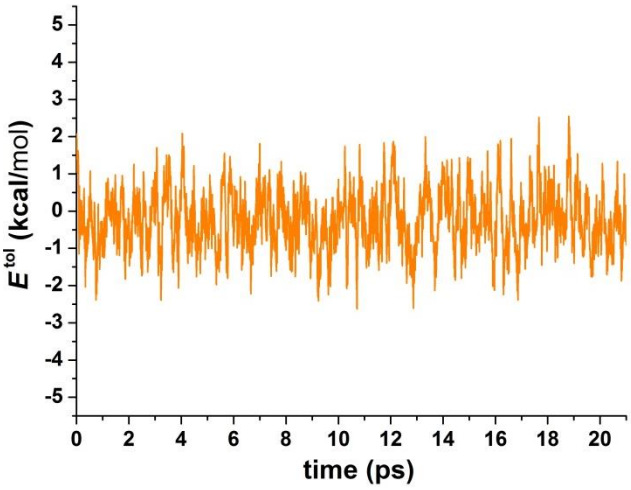
Table S1. Root mean squared errors (kcal/mol) of training and testing sets with Q^2 values (in parentheses) for S_N2 reaction using different QM models at the two levels. The same database in the initialization steps reported in the subsection *Free Energy Calculation on S_N2 Reaction in Water* in the section *RESULTS AND DISCUSSIONS* was used. All hyperparameters of NN were unchanged.

QM/MM Models		RMSE	
Low-Level	High-Level	Training Set	Testing Set
AM1/MM	CCSD(T)/aug-cc-pvtz/MM	1.10	1.09 (0.754)
DFTB2/MIO/MM	CCSD(T)/aug-cc-pvtz/MM	1.34	1.40 (0.488)
DFTB3/3OB/MM	CCSD(T)/aug-cc-pvtz/MM	1.34	1.44 (0.437)
HF/STO-3G/MM	CCSD(T)/aug-cc-pvtz/MM	1.38	1.46 (0.862)
B3LYP/6-31G(d)/MM	CCSD(T)/aug-cc-pvtz/MM	0.51	0.52 (0.840)

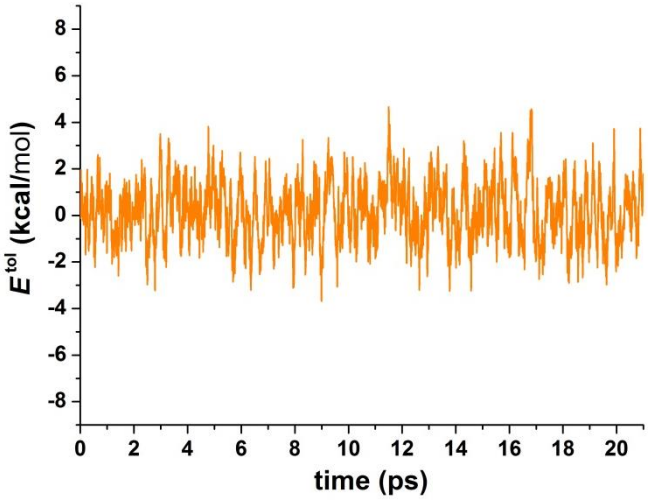
Table S2. Root mean squared errors (kcal/mol) of training and testing sets with Q^2 values for proton transfer reaction of glycine using different QM models at the two levels. The same database in the initialization steps reported in the subsection *Free Energy Calculation on Proton Transfer Reaction for Glycine in Water* in the section *RESULTS AND DISCUSSIONS* was used. All hyperparameters were unchanged.

QM/MM Models		RMSE	
Low-Level	High-Level	Training Set	Testing Set
DFTB2/MIO/MM	MP2/aug-cc-pvtz/MM	1.18	1.39 (0.975)
HF/STO-3G/MM	MP2/aug-cc-pvtz/MM	1.47	1.71 (0.995)
B3LYP/6-31G(d)/MM	MP2/aug-cc-pvtz/MM	0.53	0.59 (0.894)

Figure S1. Total energy as a function of simulation times for two representative trajectories during NVE simulations on the (a) S_N2 and (b) proton transfer reactions. The present model, DFTB2/MIO/MM with QM/MM-NN corrections, was applied to MD simulations. The value of R_c in the cutoff function for QM/MM-NN in Eq (9) was set as 6 Å, which is the same as that used in all simulations in this work. In order to remove the influence of other cutoff schemes in the conventional MM force field and QM/MM model, all nonbonded interactions were included under non-periodic conditions. The NVE simulations were performed for 20 ps with the time step as 1 fs.



(a)



(b)