Electronic Supplementary Material (ESI) for Physical Chemistry Chemical Physics.

Supporting Information: BAR-based Multi-dimensional Nonequilibrium Pulling for Indirect Construction of QM/MM Free Energy Landscape

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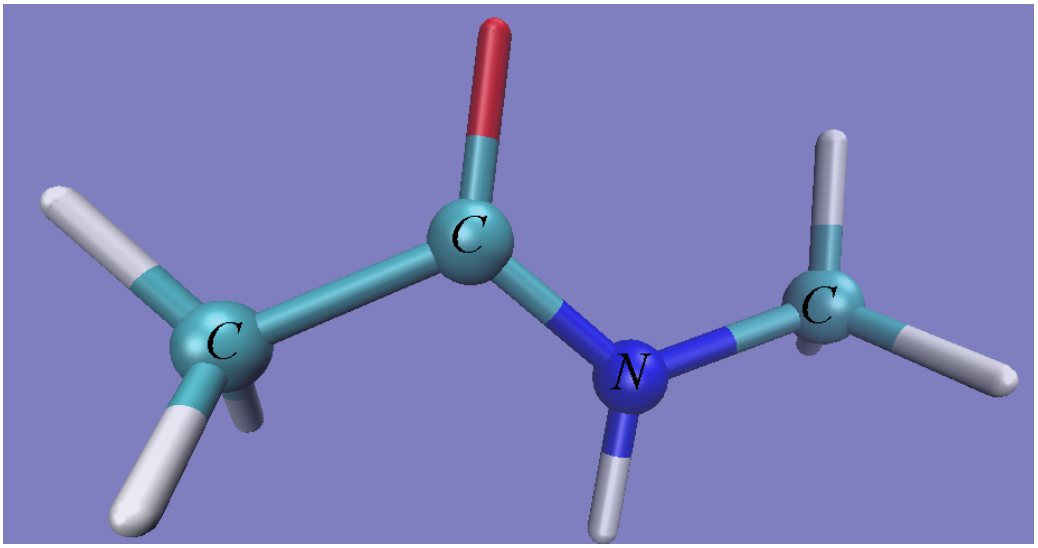
Fig. S1. Definitions of reaction coordinates.(Red O atom, cyan C, white H, green Cl, blue N atom.). a) the backbone dihedral in ACE-NME (C-C-N-C).



b) The end-to-end distance defined as the distance between carbon atom of the carboxyl group of N-terminus and that of the C-terminus is used to describe the stretching of deca-alanine.

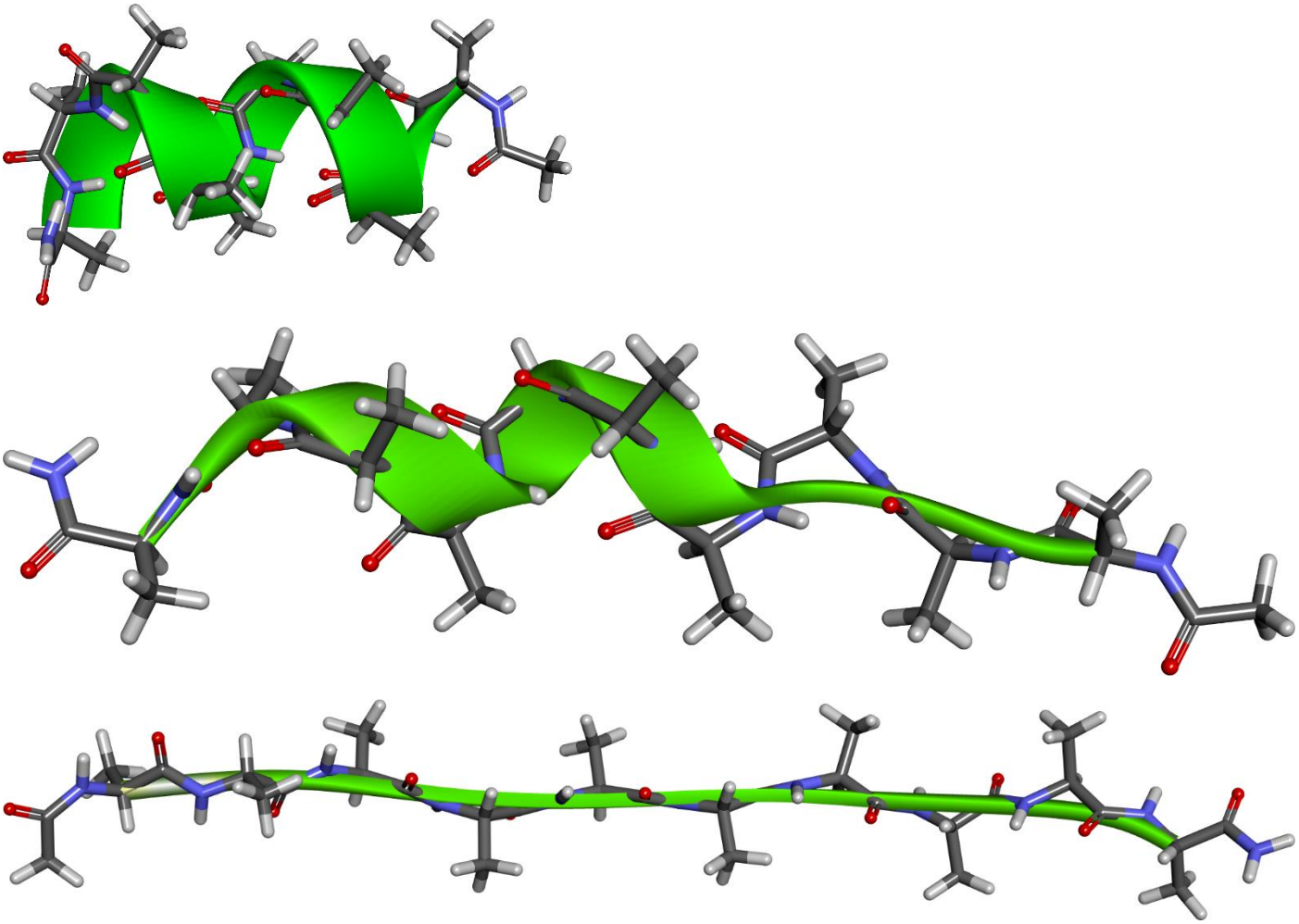


Fig. S2. Comparison between dimensionless SD profiles and overlap profiles in a-b) ACE-NME and c-d) deca-alanine. a and c give the direct free energy simulations while b and d give those in MM<->QM correction.

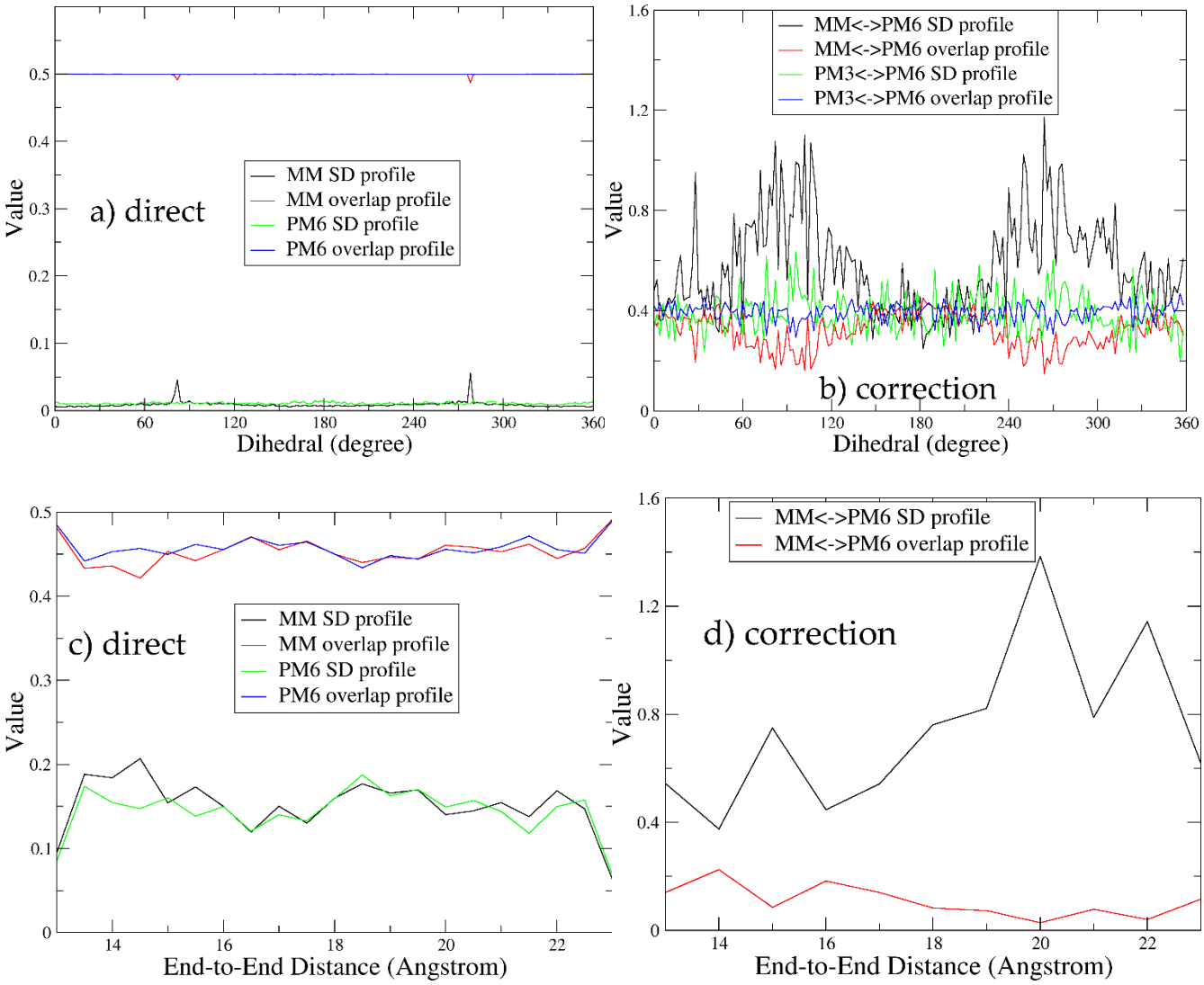


Fig. S3. The analytical result of $O_{ij} = \sigma_{ij} = \sqrt[3]{\frac{1}{2n}\left(1+\sqrt{1+\frac{32}{27n}}\right)} + \sqrt[3]{\frac{1}{2n}\left(1-\sqrt{1+\frac{32}{27n}}\right)}$.

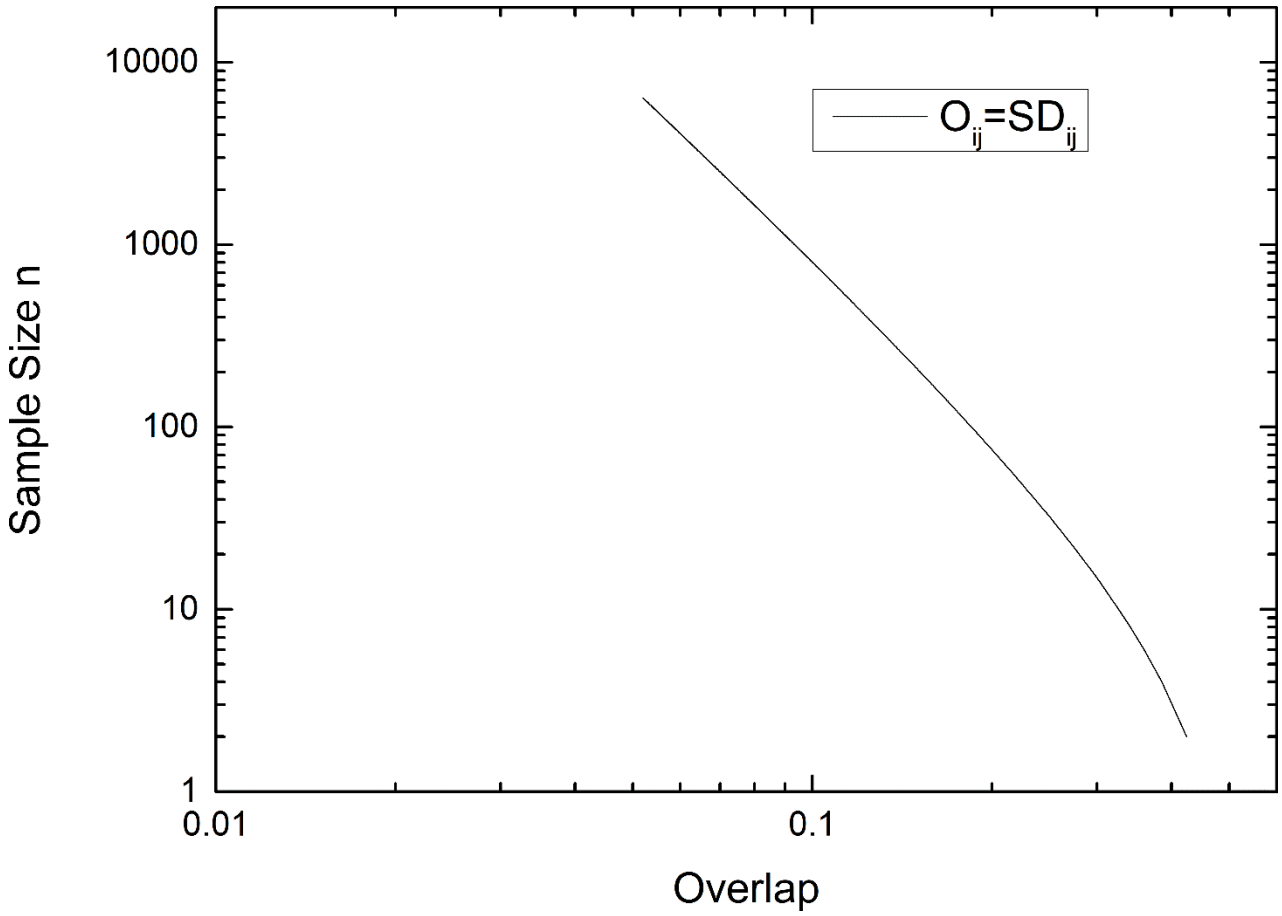


Table S1. Efficiency comparison of direct and indirect QM/MM simulation for the dihedral case. Total simulation time in direct scheme is given by $N_{\text{segments}} * N_{\text{traj}} * (\phi_{\text{NEW}} + \phi_{\text{eq}})$, while the total simulation time in the indirect scheme is the sum of $N_{\text{segments,MM}} * N_{\text{traj.MM}} * (\phi_{\text{NEW,MM}} + \phi_{\text{eq,MM}})$ at MM level and $N_{\text{traj,MM->QM}} * (\phi_{\text{NEW,MM->QM}} + \phi_{\text{eq,MM}}) + N_{\text{traj,QM->MM}} * (\phi_{\text{NEW,QM->MM}} + \phi_{\text{eq,QM}})$ in MM<->QM correction. N_{segments} is the number of segments and N_{traj} is the number of realizations per segment. The simulation time at QM level is scaled by the ratio of computational cost under QM Hamiltonian and that under MM Hamiltonian in Table 1 to be the effective simulation time at MM level, enabling direct comparison between computational costs. The computational cost of MM->PM3 differs from PM3->MM, as the initial configuration sampling procedures proceed under different Hamiltonians.

Terms / Hamiltonian	ϕ_{eq} for each initial configuration (ps)	ϕ_{NEW} in each segment (ps)	Number of segments	Number of realizations per segment	Total simulation time (ps) scaled to MM Hamiltonian	Relative efficiency
direct MM	0.05	0.5x2=1	180	25	4725.00	2.62
MM->PM3	same with MM	0.05	same with MM	3	97.79	-
PM3->MM	same with PM6	0.05	same with MM	3	141.58	-
indirect PM3	-	-	-	-	4964.37	2.50
direct PM3	0.05	0.5x2=1	180	25	12388.09	1.00