Supporting information for: Accelerated Computation of Free Energy Profile at ab Initio Quantum Mechanical/Molecular Mechanics Accuracy via a Semi-Empirical Reference Potential. II. Recalibrating Semi-Empirical Parameters with Force Matching

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Table S1: Recalibrated PM3 Parameters for identity S_N2 Reaction

parameters	H		C		Cl	
	PM3	PM3*-M	PM3	PM3*-M	PM3	PM3*-M
U_{ss} (eV)	−13.073 321	−12.970 052	−47.270 320	−49.059 914	−100.626 747	−105.390 135
U_{pp} (eV)			−36.266 918	−35.086 828	−53.614 396	−53.310 108
ζ_{ss} (au)	0.967 807	1.015 960	1.565 085	1.496 237	2.246 210	2.191 698
ζ_{pp} (au)			1.842 345	1.934 462	2.151 010	2.258 560
β_{ss} (eV)	−5.626 512	−5.763 640	−11.910 015	−11.321 773	−27.528 560	−26.192 495
β_{pp} (eV)			−9.802 755	−10.286 609	−11.593 922	−11.775 542
G_{ss} (eV)	14.794 208	14.113 737	11.200 708	11.495 051	16.013 601	16.814 281
G_{pp} (eV)			10.796 292	10.256 477	7.522 215	7.146 142
G_{sp} (eV)			10.265 027	10.126 762	8.048 115	7.925 465
G_{p2} (eV)			9.042 566	8.635 219	7.504 154	7.554 952
H_{sp} (eV)			2.290 980	3.370 560	3.481 153	3.482 882
a_1 (unitless)	1.128 750	1.185 149	0.050 107	0.048 206	−0.171 591	−0.163 011
b_1 ($1/Å^2$)	5.096 282	4.841 493	6.003 165	5.703 007	6.000 802	6.300 840
c_1 (Å)	1.537 465	1.601 794	1.642 214	1.724 325	1.087 502	1.033 128
a_2 (unitless)	−1.060 329	−1.007 350	0.050 733	0.052 891	−0.013 458	−0.012 785
b_2 ($1/Å^2$)	6.003 788	5.861 238	6.002 979	5.703 771	1.966 618	2.060 175
c_2 (Å)	1.570 189	1.641 263	0.892 488	0.937 112	2.292 891	2.178 246

Table S2: Recalibrated PM3 Parameters for Menshutkin Reaction

parameters	H		C		N		Cl	
	PM3	PM3*-M	PM3	PM3*-M	PM3	PM3*-M	PM3	PM3*-M
U_{ss} (eV)	−13.073 321	−13.426 947	−47.270 320	−47.117 078	−49.335 672	−50.838 345	−100.626 747	−105.657 056
U_{pp} (eV)			−36.266 918	−34.572 403	−47.509 736	−46.618 540	−53.614 396	−52.484 172
ζ_{ss} (au)	0.967 807	0.983 318	1.565 085	1.568 797	2.028 094	1.926 779	2.246 210	2.358 505
ζ_{pp} (au)			1.842 345	1.928 735	2.313 728	2.198 042	2.151 010	2.215 363
β_{ss} (eV)	−5.626 512	−5.544 784	−11.910 015	−12.505 516	−14.062 521	−14.723 054	−27.528 560	−26.152 167
β_{pp} (eV)			−9.802 755	−10.292 838	−20.043 848	−19.817 286	−11.593 922	−11.062 325
G_{ss} (eV)	14.794 208	15.533 885	11.200 708	10.640 673	11.904 787	12.344 280	16.013 601	16.778 293
G_{pp} (eV)			10.796 292	11.279 510	11.754 672	12.342 334	7.522 215	7.146 104
G_{sp} (eV)			10.265 027	9.947 610	7.348 565	7.002 125	8.048 115	7.737 159
G_{p2} (eV)			9.042 566	8.908 939	10.807 277	10.352 145	7.504 154	7.675 695
H_{sp} (eV)			2.290 980	2.397 114	1.136 713	1.191 151	3.481 153	3.493 780
a_1 (unitless)	1.128 750	1.162 157	0.050 107	0.051 170	1.501 674	1.532 350	−0.171 591	−0.163 011
b_1 ($1/Å^2$)	5.096 282	5.089 133	6.003 165	5.703 033	5.901 148	6.118 631	6.000 802	6.300 647
c_1 (Å)	1.537 465	1.614 273	1.642 214	1.724 319	1.710 740	1.690 710	1.087 502	1.033 127
a_2 (unitless)	−1.060 329	−1.049 336	0.050 733	0.051 080	−1.505 772	−1.519 344	−0.013 458	−0.012 785
b_2 ($1/Å^2$)	6.003 788	5.746 372	6.002 979	5.730 811	6.004 658	6.068 862	1.966 618	1.890 763
c_2 (Å)	1.570 189	1.636 463	0.892 488	0.934 418	1.716 149	1.699 353	2.292 891	2.407 533

Table S3: Recalibrated PM3 Parameters for Glycine Intramolecular Proton Transfer Reaction

parameters	H		C		N		O	
	PM3	PM3*-M	PM3	PM3*-M	PM3	PM3*-M	PM3	PM3*-M
U_{ss} (eV)	−13.073 321	−12.674 075	−47.270 320	−46.083 509	−49.335 672	−51.802 434	−86.993 002	−86.142 114
U_{pp} (eV)			−36.266 918	−34.968 507	−47.509 736	−49.236 109	−71.879 580	−74.960 007
ζ_{ss} (au)	0.967 807	0.975 870	1.565 085	1.643 321	2.028 094	1.926 690	3.796 544	3.764 822
ζ_{pp} (au)			1.842 345	1.881 360	2.313 728	2.198 120	2.389 402	2.348 195
β_{ss} (eV)	−5.626 512	−5.815 402	−11.910 015	−12.311 620	−14.062 521	−14.334 434	−45.202 651	−47.304 167
β_{pp} (eV)			−9.802 755	−10.292 698	−20.043 848	−21.044 231	−24.752 515	−24.279 161
G_{ss} (eV)	14.794 208	15.300 262	11.200 708	10.641 774	11.904 787	12.485 788	15.755 760	14.968 038
G_{pp} (eV)			10.796 292	11.317 896	11.754 672	12.342 130	13.654 016	14.328 987
G_{sp} (eV)			10.265 027	10.198 976	7.348 565	7.634 983	10.621 160	10.312 568
G_{p2} (eV)			9.042 566	8.925 504	10.807 277	10.757 669	12.406 095	13.026 097
H_{sp} (eV)			2.290 980	2.299 363	1.136 713	1.137 892	0.593 883	0.605 724
a_1 (unitless)	1.128 750	1.072 334	0.050 107	0.049 545	1.501 674	1.509 481	−1.131 128	−1.109 980
b_1 ($1/Å^2$)	5.096 282	5.351 091	6.003 165	6.107 455	5.901 148	5.751 272	6.002 477	6.024 874
c_1 (Å)	1.537 465	1.540 395	1.642 214	1.576 570	1.710 740	1.720 493	1.607 311	1.636 194
a_2 (unitless)	−1.060 329	−1.066 862	0.050 733	0.049 129	−1.505 772	−1.489 828	1.137 891	1.127 476
b_2 ($1/Å^2$)	6.003 788	5.703 609	6.002 979	5.844 730	6.004 658	5.963 964	5.950 512	5.924 373
c_2 (Å)	1.570 189	1.550 327	0.892 488	0.927 347	1.716 149	1.728 580	1.598 395	1.637 895

Table S4: Recalibrated PM3 Parameters for Chorismate Mutase Reaction

parameters	H		C		O	
	PM3	PM3*-M	PM3	PM3*-M	PM3	PM3*-M
U_{ss} (eV)	−13.073 321	−13.726 100	−47.270 320	−44.906 804	−86.993 002	−91.159 430
U_{pp} (eV)			−36.266 918	−35.767 445	−71.879 580	−73.725 303
ζ_{ss} (au)	0.967 807	0.950 991	1.565 085	1.643 339	3.796 544	3.837 914
ζ_{pp} (au)			1.842 345	1.800 254	2.389 402	2.269 932
β_{ss} (eV)	−5.626 512	−5.723 666	−11.910 015	−12.232 924	−45.202 651	−45.095 535
β_{pp} (eV)			−9.802 755	−9.312 675	−24.752 515	−24.501 735
G_{ss} (eV)	14.794 208	14.596 995	11.200 708	10.646 209	15.755 760	15.108 124
G_{pp} (eV)			10.796 292	10.435 611	13.654 016	14.336 625
G_{sp} (eV)			10.265 027	9.751 776	10.621 160	11.052 484
G_{p2} (eV)			9.042 566	9.494 557	12.406 095	12.079 680
H_{sp} (eV)			2.290 980	2.402 069	0.593 883	0.601 646
a_1 (unitless)	1.128 750	1.106 093	0.050 107	0.052 610	−1.131 128	−1.103 303
b_1 ($1/Å^2$)	5.096 282	5.350 960	6.003 165	6.303 323	6.002 477	6.278 579
c_1 (Å)	1.537 465	1.545 676	1.642 214	1.622 373	1.607 311	1.575 164
a_2 (unitless)	−1.060 329	−1.026 373	0.050 733	0.048 211	1.137 891	1.168 329
b_2 ($1/Å^2$)	6.003 788	5.703 599	6.002 979	6.145 504	5.950 512	6.098 653
c_2 (Å)	1.570 189	1.574 917	0.892 488	0.847 864	1.598 395	1.564 796

Table S5: Free Energy Barriers (in kcal/mol) for $CH_3Cl + Cl^- \longrightarrow Cl^- + CH_3Cl$ (S_N2), Menshutkin Reaction (MEN) Calculated Indirectly from PM3*-M

reaction	B3LYP[a]	B3LYP[b]	M06-2X[b]	ωB97X-D[b]	ωB97X-V[b]	Exp.
S_N2	21.8 ± 0.3	22.9 ± 0.3	26.8 ± 0.3	27.5 ± 0.3	27.9 ± 0.3	26.5
MEN	15.7 ± 0.3	18.5 ± 0.5	21.6 ± 0.4	21.3 ± 0.5	22.4 ± 0.4	> 23

[a] Basis set: 6-31G*; [b] Basis set: def2-TZVPPD.

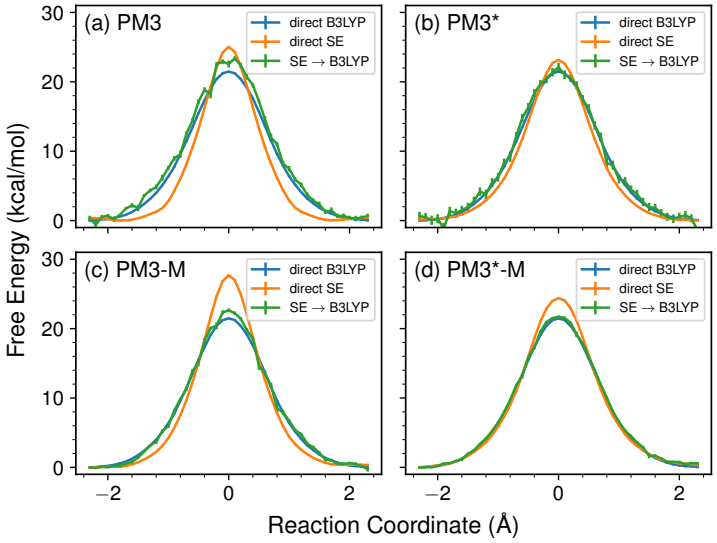

Figure S1: Direct and indirect FE profiles (without Gaussian Process Regression) for identity S_N2 reaction estimated by using (a) the standard PM3 parameters and the standard QM-MM electrostatics, (b) the recalibrated PM3 parameters and the standard QM-MM electrostatics, (c) the standard PM3 parameters and the modified QM-MM electrostatics, and (d) the recalibrated PM3 parameters and the modified QM-MM electrostatics. This figure is the same as Fig. 2 in the main text.

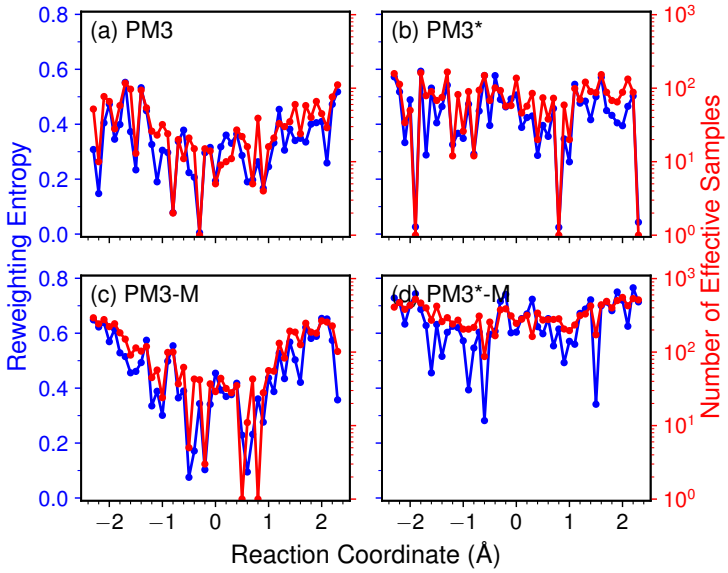

Figure S2: Reweighting entropies and numbers of effective samples for weighted TP for identity S_N2 reaction calculated from (a) the standard PM3 parameters and the standard QM-MM electrostatics, (b) the recalibrated PM3 parameters and the standard QM-MM electrostatics, (c) the standard PM3 parameters and the modified QM-MM electrostatics, and (d) the recalibrated PM3 parameters and the modified QM-MM electrostatics. For each bin, the number of effective samples excludes those frames contributing to the last 0.05 kcal/mol of free energy correction of that bin.

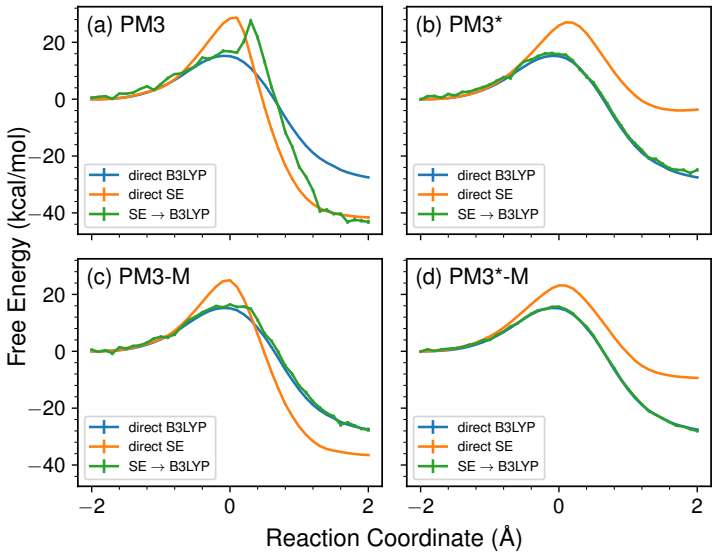

Figure S3: Direct and indirect FE profiles (without Gaussian Process Regression) for Menshutkin reaction estimated by using (a) the standard PM3 parameters and the standard QM-MM electrostatics, (b) the recalibrated PM3 parameters and the standard QM-MM electrostatics, (c) the standard PM3 parameters and the modified QM-MM electrostatics, and (d) the recalibrated PM3 parameters and the modified QM-MM electrostatics.

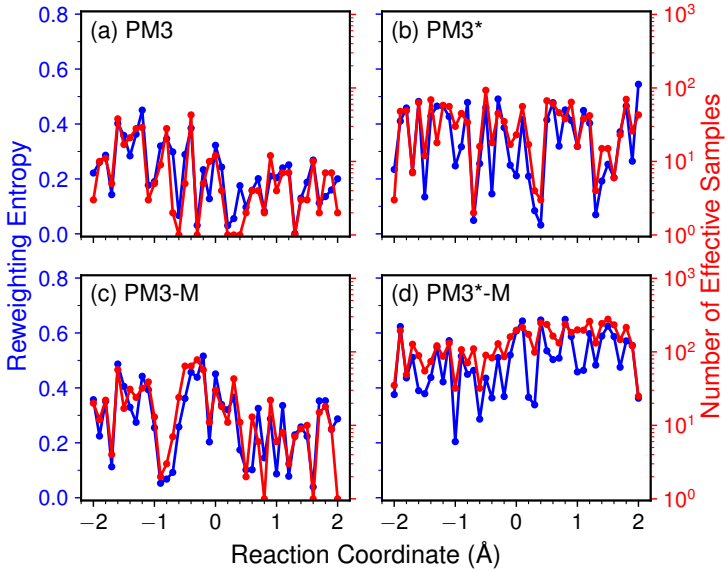

Figure S4: Reweighting entropies and numbers of effective samples for weighted TP for Menshutkin reaction calculated from (a) the standard PM3 parameters and the standard QM-MM electrostatics, (b) the recalibrated PM3 parameters and the standard QM-MM electrostatics, (c) the standard PM3 parameters and the modified QM-MM electrostatics, and (d) the recalibrated PM3 parameters and the modified QM-MM electrostatics. For each bin, the number of effective samples excludes those frames contributing to the last 0.05 kcal/mol of free energy correction of that bin.

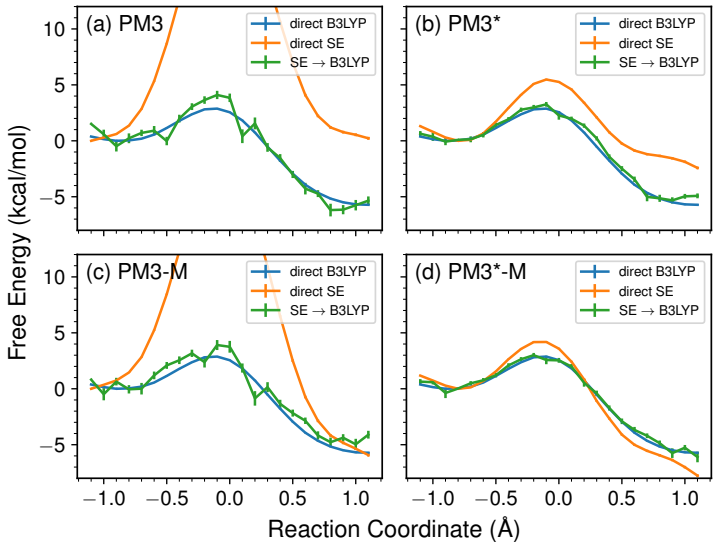

Figure S5: Direct and indirect FE profiles (without Gaussian Process Regression) for glycine intramolecular proton transfer reaction estimated by using (a) the standard PM3 parameters and the standard QM-MM electrostatics, (b) the recalibrated PM3 parameters and the standard QM-MM electrostatics, (c) the standard PM3 parameters and the modified QM-MM electrostatics, and (d) the recalibrated PM3 parameters and the modified QM-MM electrostatics.

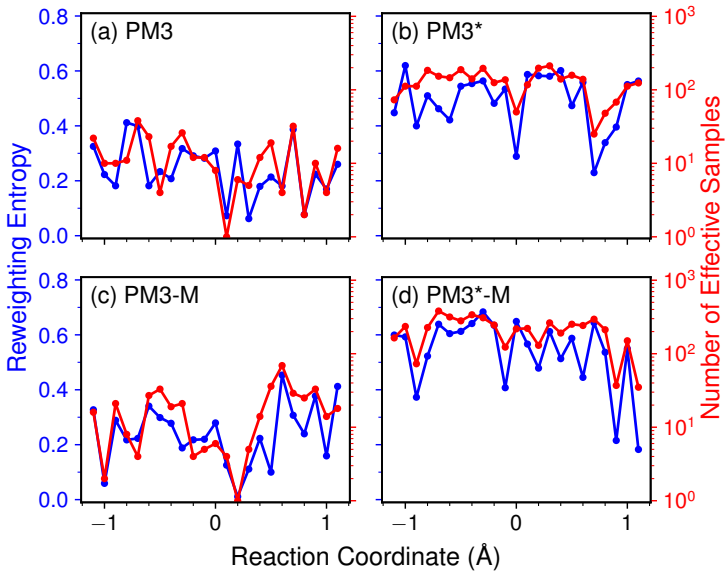

Figure S6: Reweighting entropies and numbers of effective samples for weighted TP for glycine intramolecular proton transfer reaction calculated from (a) the standard PM3 parameters and the standard QM-MM electrostatics, (b) the recalibrated PM3 parameters and the standard QM-MM electrostatics, (c) the standard PM3 parameters and the modified QM-MM electrostatics, and (d) the recalibrated PM3 parameters and the modified QM-MM electrostatics. For each bin, the number of effective samples excludes those frames contributing to the last 0.05 kcal/mol of free energy correction of that bin.

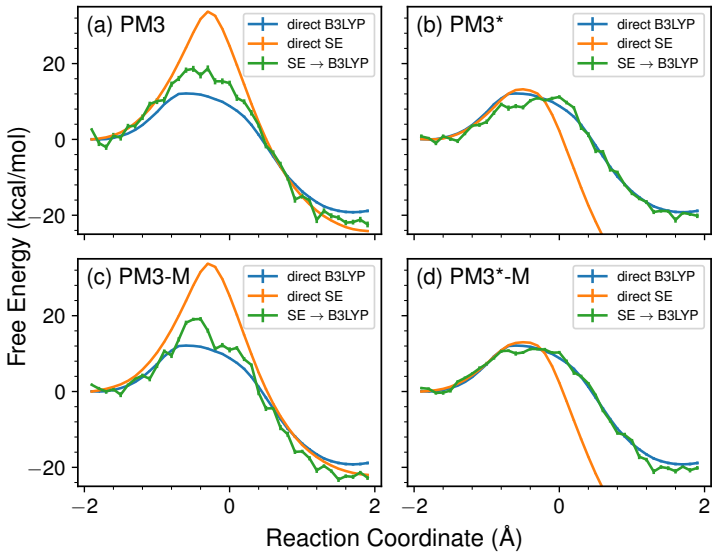

Figure S7: Direct and indirect FE profiles (without Gaussian Process Regression) for chorismate mutase reaction estimated by using (a) the standard PM3 parameters and the standard QM-MM electrostatics, (b) the recalibrated PM3 parameters and the standard QM-MM electrostatics, (c) the standard PM3 parameters and the modified QM-MM electrostatics, and (d) the recalibrated PM3 parameters and the modified QM-MM electrostatics. This figure is the same as Fig. 6 in the main text.

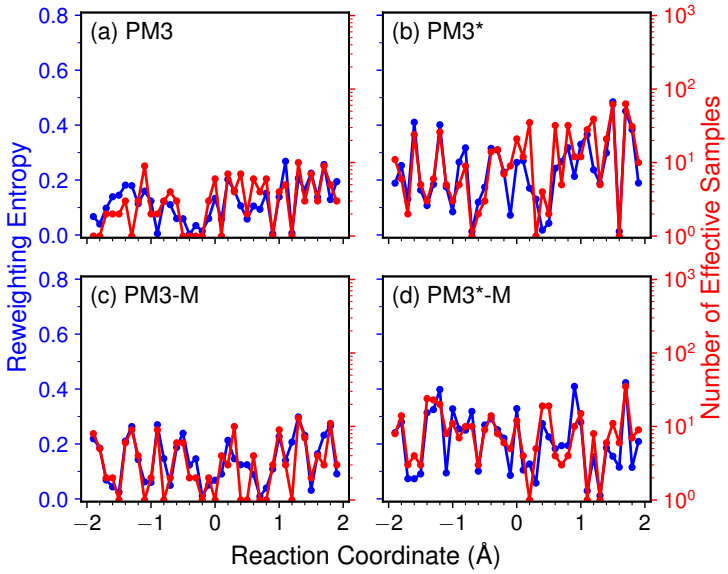

Figure S8: Reweighting entropies and numbers of effective samples for weighted TP for chorismate mutase reaction calculated from (a) the standard PM3 parameters and the standard QM-MM electrostatics, (b) the recalibrated PM3 parameters and the standard QM-MM electrostatics, (c) the standard PM3 parameters and the modified QM-MM electrostatics, and (d) the recalibrated PM3 parameters and the modified QM-MM electrostatics. For each bin, the number of effective samples excludes those frames contributing to the last 0.05 kcal/mol of free energy correction of that bin.

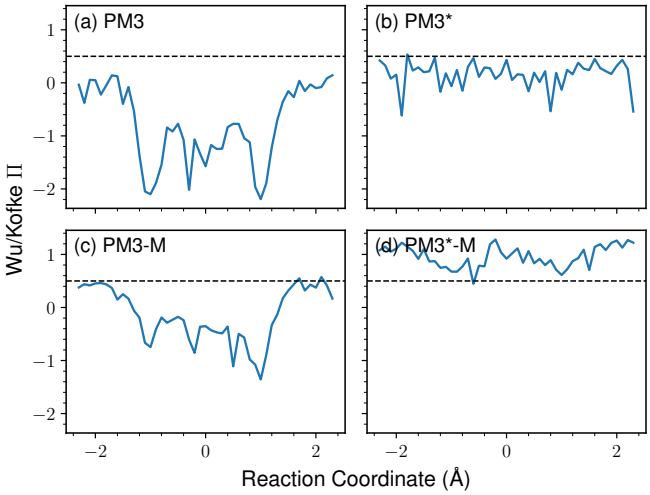

Figure S9: Wu and Kofke bias metrics (Π) for identity S_N2 reaction estimated by using (a) the standard PM3 parameters and the standard QM-MM electrostatics, (b) the recalibrated PM3 parameters and the standard QM-MM electrostatics, (c) the standard PM3 parameters and the modified QM-MM electrostatics, and (d) the recalibrated PM3 parameters and the modified QM-MM electrostatics.

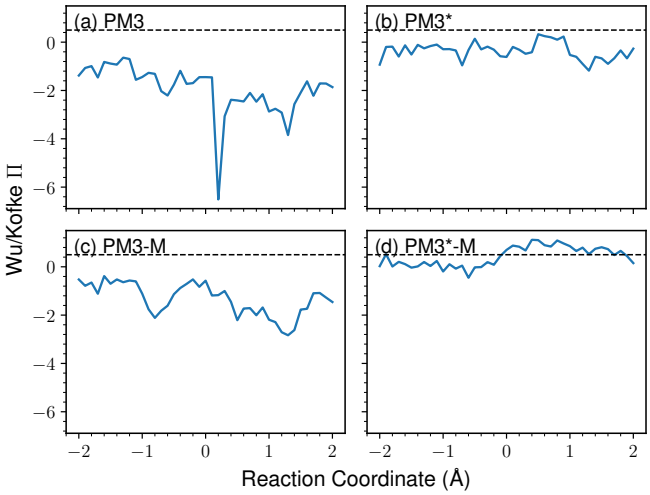

Figure S10: Wu and Kofke bias metrics (Π) for Menshutkin reaction estimated by using (a) the standard PM3 parameters and the standard QM-MM electrostatics, (b) the recalibrated PM3 parameters and the standard QM-MM electrostatics, (c) the standard PM3 parameters and the modified QM-MM electrostatics, and (d) the recalibrated PM3 parameters and the modified QM-MM electrostatics.

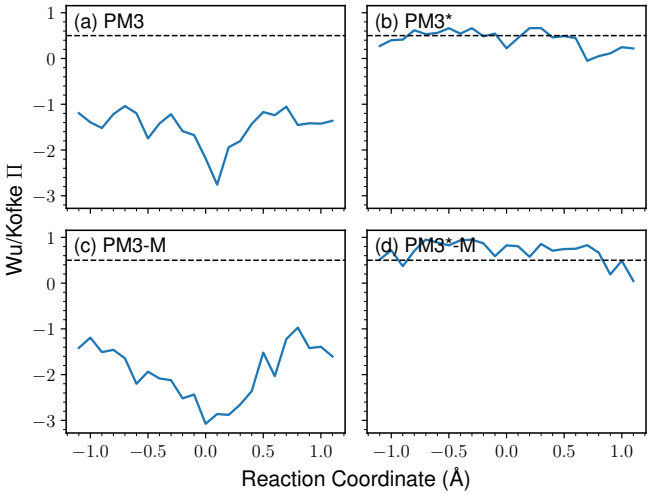

Figure S11: Wu and Kofke bias metrics (Π) for glycine intramolecular proton transfer reaction estimated by using (a) the standard PM3 parameters and the standard QM-MM electrostatics, (b) the recalibrated PM3 parameters and the standard QM-MM electrostatics, (c) the standard PM3 parameters and the modified QM-MM electrostatics, and (d) the recalibrated PM3 parameters and the modified QM-MM electrostatics.

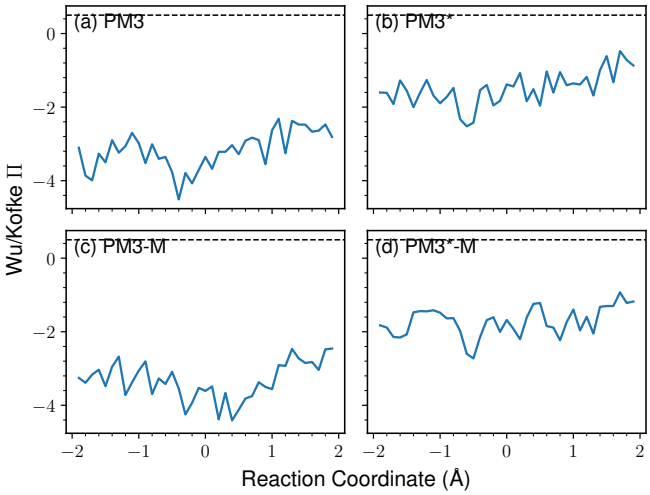

Figure S12: Wu and Kofke bias metrics (Π) for chorismate mutase reaction estimated by using (a) the standard PM3 parameters and the standard QM-MM electrostatics, (b) the recalibrated PM3 parameters and the standard QM-MM electrostatics, (c) the standard PM3 parameters and the modified QM-MM electrostatics, and (d) the recalibrated PM3 parameters and the modified QM-MM electrostatics.