Supporting Information for

A modified Hamiltonian in FEP calculations for reducing the computational cost of electrostatic interactions

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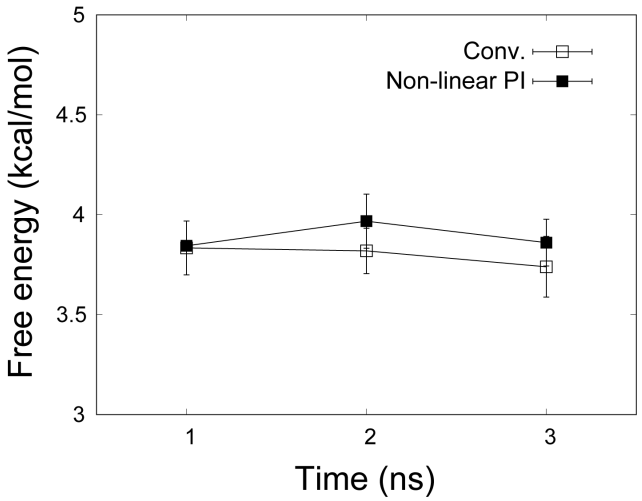

Figure S1. Time series of free energies for the mutation of the side-chain analog from Leu to Tyr in water.

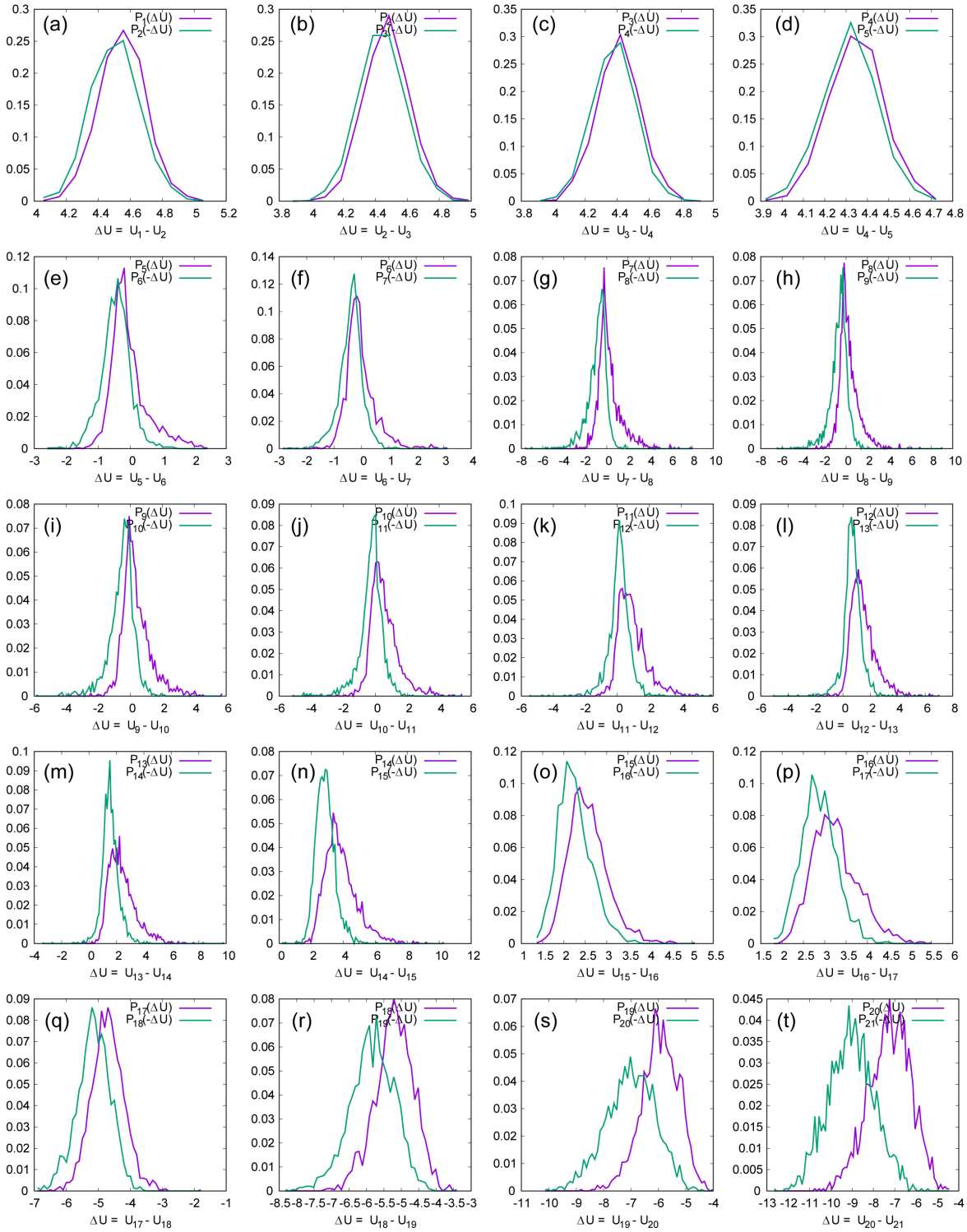

Figure S2. Distributions of energy differences between adjacent windows for conventional FEP in the three-step procedure. Purple and green lines represent the forward and backward energy differences, respectively.

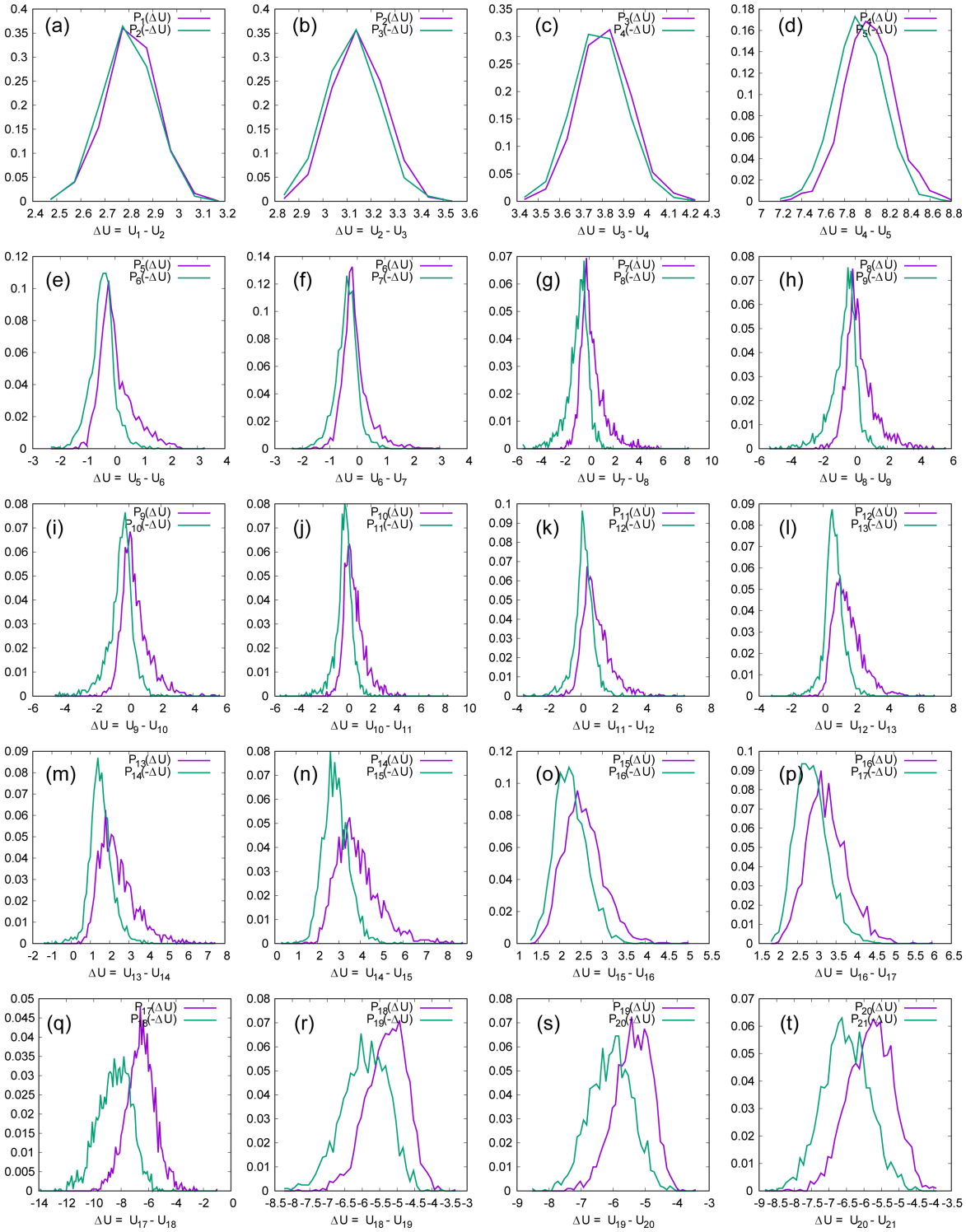

Figure S3. Distributions of energy differences between adjacent windows for the modified method in the three-step procedure. Purple and green lines represent the forward and backward energy differences, respectively.

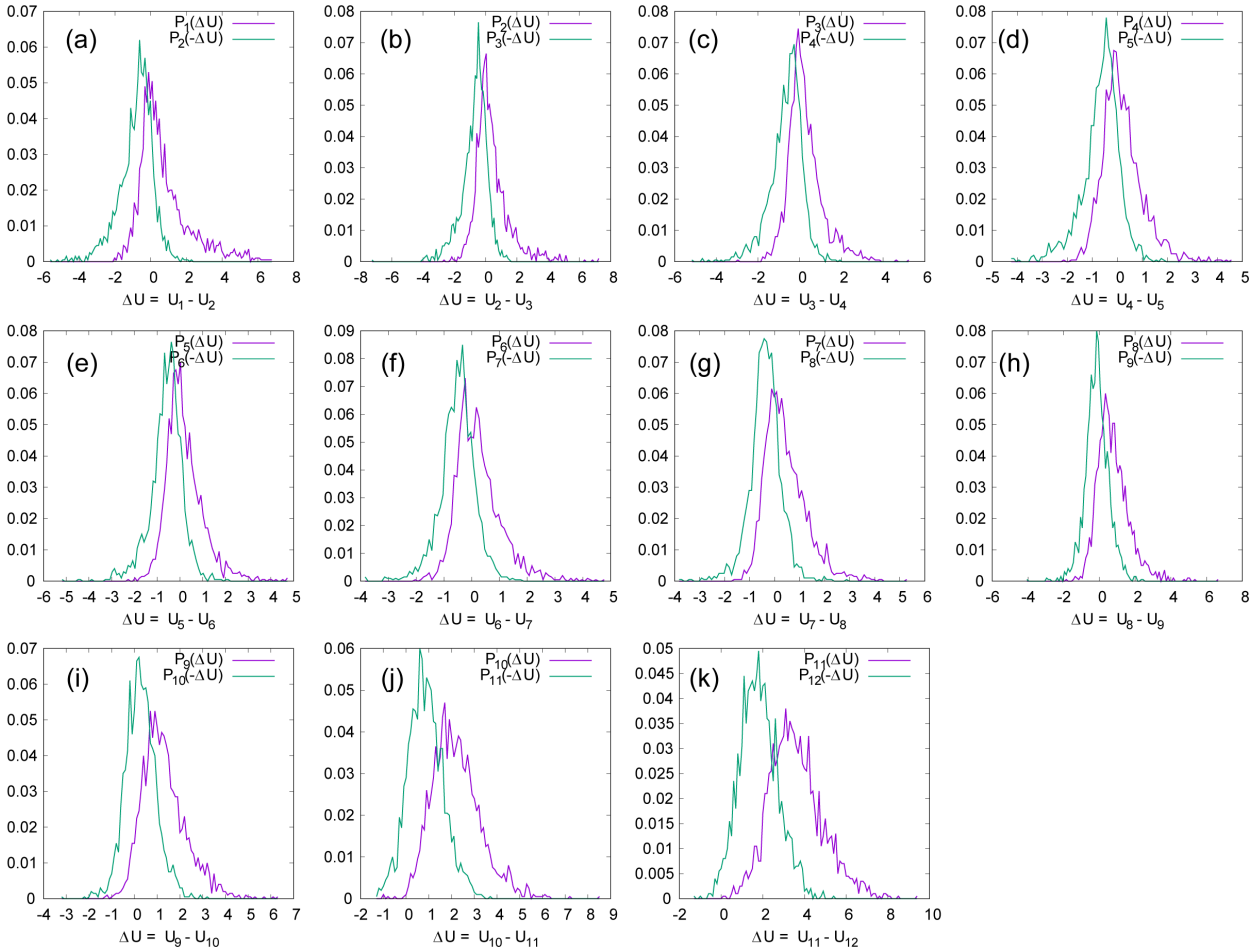

Figure S4. Distributions of energy differences between adjacent windows for conventional FEP in the one-step procedure. Purple and green lines represent the forward and backward energy differences, respectively.

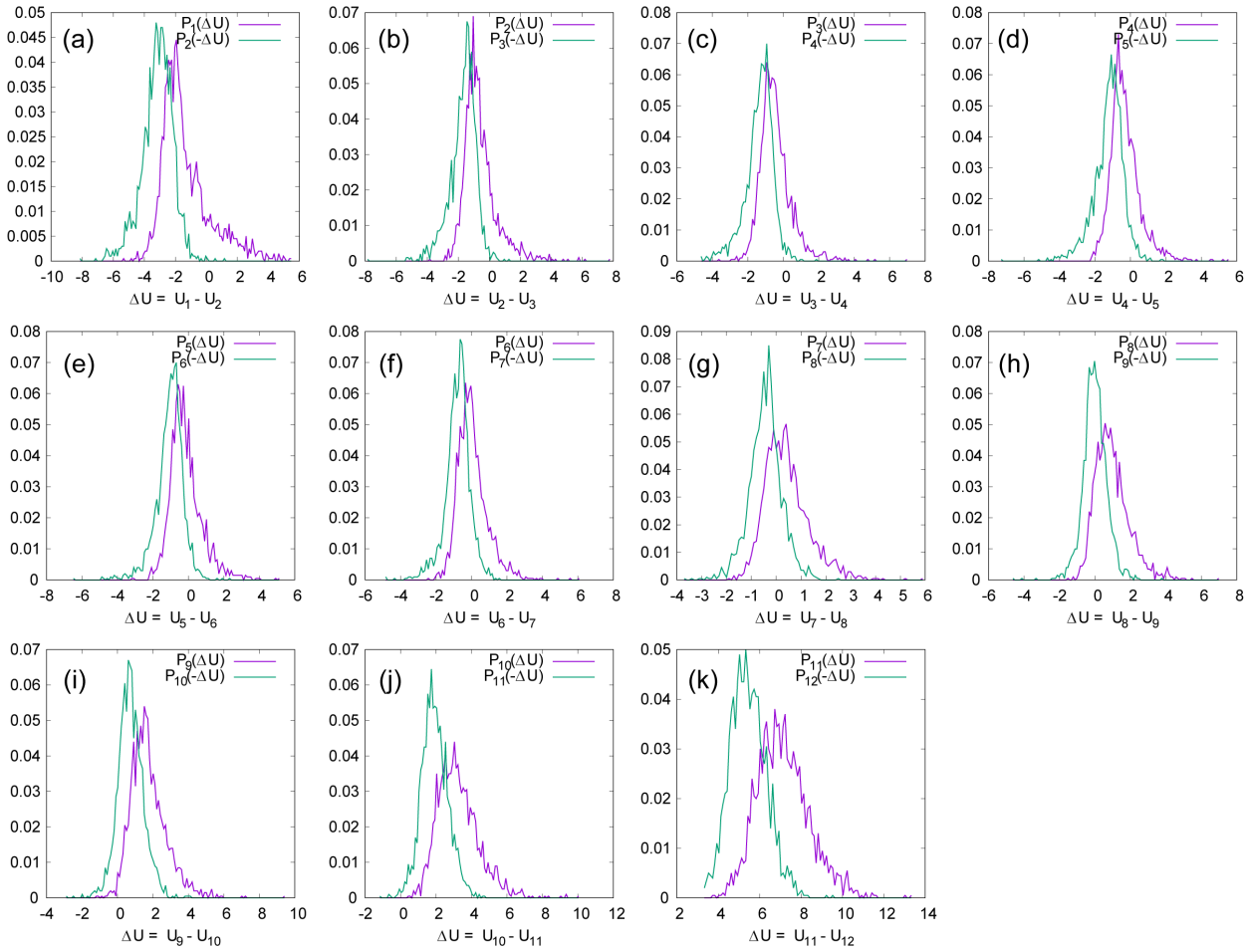

Figure S5. Distributions of energy differences between adjacent windows for the modified method in the one-step procedure. Purple and green lines represent the forward and backward energy differences, respectively.

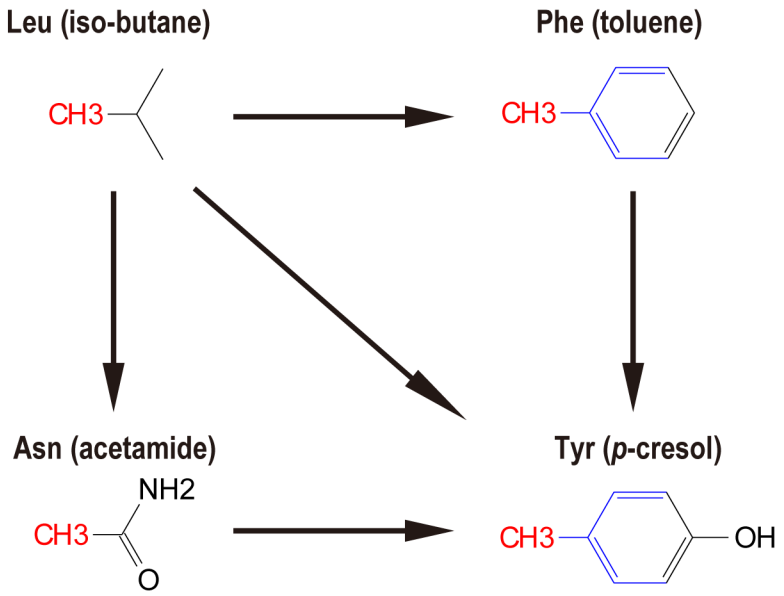

Figure S6. Chemical structures of amino acid side chain analogs and their mutations. The names in parentheses represent the chemical compounds corresponding to the amino acid side chain analog. The CH3 group, shown in red is the common part during the mutations of Leu to Phe, Leu to Tyr, Leu to Asn, and Asn to Tyr. Blue-colored atoms are also included in the common part during the mutation of Phe to Tyr.

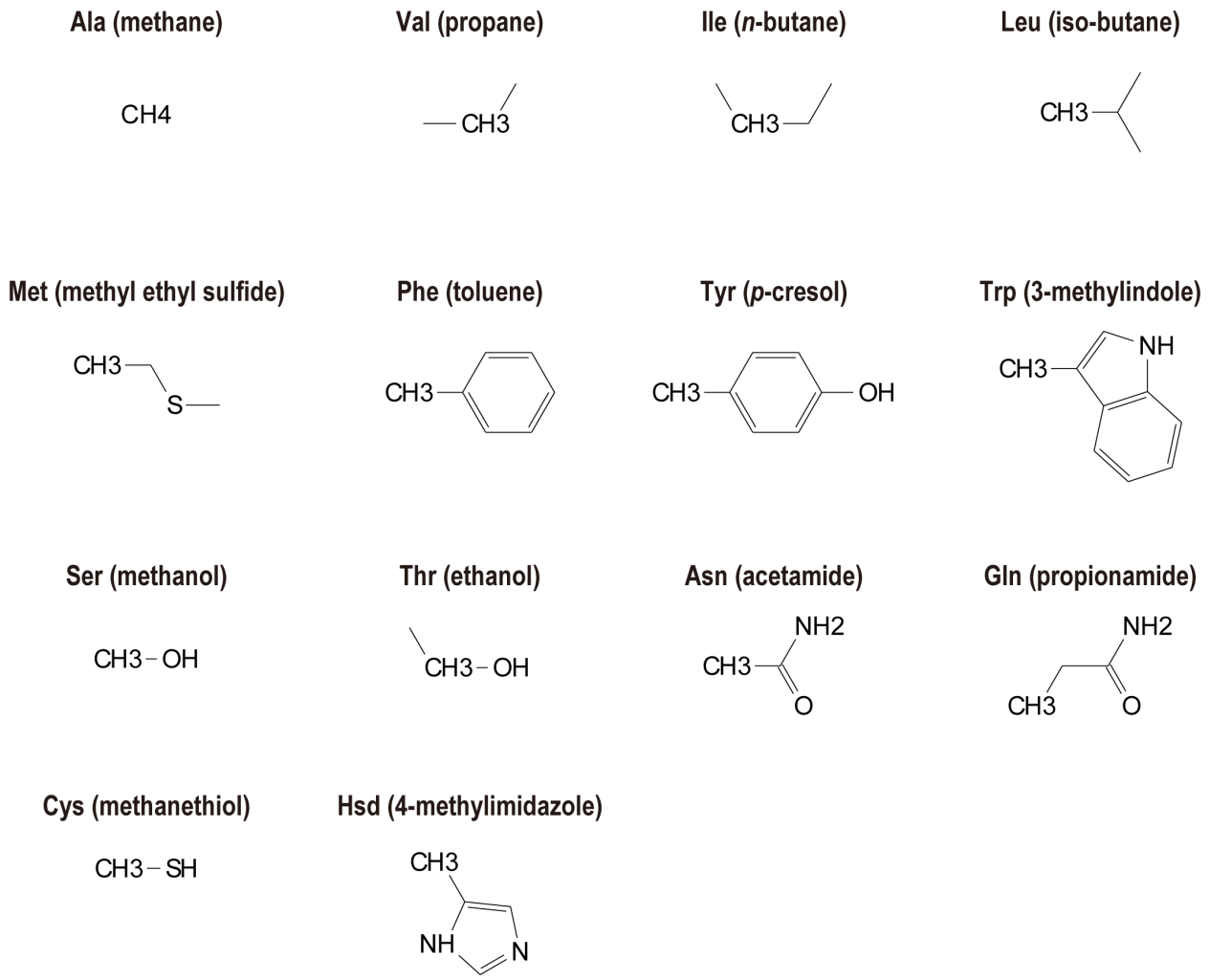

Figure S7. Chemical structures of amino acid side chain analogs. The names in parentheses represent the chemical compounds corresponding to the amino acid side chain analog. The force field parameters of CH3 are modified as described in Ref.[1].

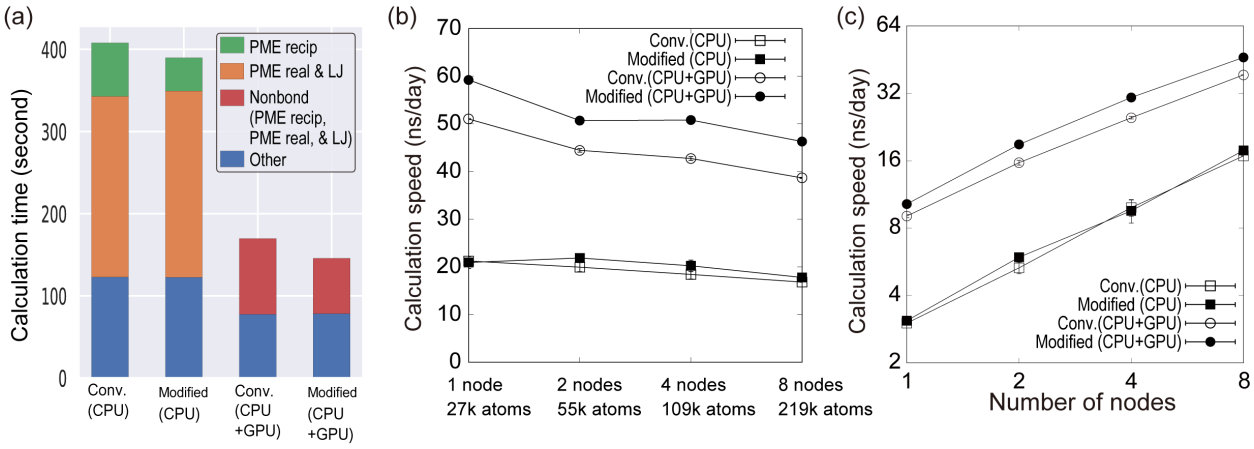

Figure S8. Computer times of FEP using the r-RESPA integrator with a 2.5-fs time step. (a) Calculation times for 100-ps FEP simulations. Times for PME reciprocal-space and real-space calculations are colored green and orange, respectively, while times for other calculations are colored blue. For the CPU+GPU hybrid computation, calculation times for nonbonded interactions are colored red. (b) Performance of FEP simulations in fixing the number of atoms per processor. (c) Performance of FEP simulations for the large system (219k atoms).

Table S1. Relative solvation free energies of amino acid side-chain analogs.

	Three-step procedure		One-step procedure		
	Conventional FEP (kcal/mol)	Modified FEP (kcal/mol)	Conventional FEP (kcal/mol)	Modified FEP (kcal/mol)	Experiment[2] (kcal/mol)
Leu to Phe	-2.58 ± 0.05	-2.61 ± 0.07	-2.58 ± 0.03	-2.56 ± 0.08	-3.04
Leu to Asn	-10.49 ± 0.07	-10.54 ± 0.05	-10.46 ± 0.02	-10.41 ± 0.03	-11.96
Leu to Tyr	-7.11 ± 0.04	-7.01 ± 0.03	-7.09 ± 0.05	-7.02 ± 0.05	-8.39
Phe to Tyr	-4.50 ± 0.04	-4.50 ± 0.07	-4.51 ± 0.03	-4.48 ± 0.04	-5.35
Asn to Tyr	3.47 ± 0.07	3.41 ± 0.07	3.39 ± 0.12	3.44 ± 0.07	3.57

Table S2. Absolute solvation free energies of amino acid side-chain analogs.

	Conventional FEP (kcal/mol)	Modified FEP (kcal/mol)	Experiment[2] (kcal/mol)
Ala	2.48 ± 0.02	2.47 ± 0.03	1.94
Asn	-7.56 ± 0.02	-7.52 ± 0.03	-9.68
Cys	-0.06 ± 0.05	-0.02 ± 0.04	-1.24
Gln	-7.09 ± 0.02	-7.16 ± 0.09	-9.38
Hsd	-9.72 ± 0.07	-9.68 ± 0.04	-10.27
Ile	2.71 ± 0.06	2.82 ± 0.15	2.15
Leu	2.92 ± 0.07	2.86 ± 0.09	2.28
Met	1.20 ± 0.09	1.07 ± 0.07	-1.48
Phe	0.27 ± 0.04	0.37 ± 0.06	-0.76
Ser	-4.67 ± 0.11	-4.71 ± 0.07	-5.06
Thr	-4.63 ± 0.08	-4.52 ± 0.04	-4.88
Trp	-4.61 ± 0.10	-4.73 ± 0.05	-5.88
Tyr	-4.18 ± 0.17	-4.16 ± 0.11	-6.11
Val	2.61 ± 0.04	2.55 ± 0.02	1.99

Table S3. Free-energy changes in binding affinities of Barnase-Barstar complex upon Y29A mutation.

	$\Delta G_{\mathrm{mut}}^{\mathrm{complex}}$ (kcal/mol)	$\Delta G_{\mathrm{mut}}^{\mathrm{monomer}}$ (kcal/mol)	$\Delta\Delta G$ (kcal/mol)
Conventional FEP	10.07 ± 0.29	8.72 ± 0.12	1.34 ± 0.32
Modified FEP	10.60 ± 0.41	8.93 ± 0.15	1.67 ± 0.44
Experiment[3]			3.4

Table S4. Performance of FEP simulations when fixing the number of atoms per processor (Velocity Verlet integrator with 2.0-fs time step).

Number of nodes	Number of atoms	Conventional FEP (CPU) (ns/day)	Modified FEP (CPU) (ns/day)	Conventional FEP (CPU+GPU) (ns/day)	Modified FEP (CPU+GPU) (ns/day)
1	27k atoms	14.6 ± 0.0	16.1 ± 0.0	31.4 ± 0.6	40.0 ± 1.0
2	55k atoms	14.3 ± 0.0	14.9 ± 0.8	29.3 ± 0.4	36.8 ± 0.2
4	109k atoms	12.4 ± 0.6	14.5 ± 0.8	27.1 ± 0.4	35.5 ± 0.4
8	219k atoms	11.2 ± 0.0	12.5 ± 0.0	22.9 ± 0.0	30.9 ± 0.1

Table S5. Performance of FEP simulations for the large system (219k atoms) (Velocity Verlet integrator with 2.0-fs time step).

Number of nodes	Conventional FEP (CPU) (ns/day)	Modified FEP (CPU) (ns/day)	Conventional FEP (CPU+GPU) (ns/day)	Modified FEP (CPU+GPU) (ns/day)
1	2.1 ± 0.0	2.2 ± 0.0	5.3 ± 0.2	6.4 ± 0.3
2	4.0 ± 0.0	4.0 ± 0.3	9.1 ± 0.3	11.8 ± 0.3
4	6.7 ± 0.4	6.9 ± 0.5	14.7 ± 0.4	19.3 ± 0.3
8	11.2 ± 0.0	12.5 ± 0.0	22.9 ± 0.0	30.9 ± 0.1

Table S6. Performance of FEP simulations when fixing the number of atoms per processor (r-RESPA integrator with 2.5-fs time step).

Number of nodes	Number of atoms	Conventional FEP (CPU) (ns/day)	Modified FEP (CPU) (ns/day)	Conventional FEP (CPU+GPU) (ns/day)	Modified FEP (CPU+GPU) (ns/day)
1	27k atoms	21.2 ± 0.0	20.9 ± 1.2	51.0 ± 0.1	59.2 ± 0.0
2	55k atoms	19.9 ± 0.9	21.9 ± 0.0	44.5 ± 0.4	50.7 ± 0.1
4	109k atoms	18.4 ± 1.0	20.2 ± 1.2	42.7 ± 0.4	50.8 ± 0.6
8	219k atoms	16.8 ± 0.0	17.8 ± 0.0	38.7 ± 0.1	46.3 ± 0.1

Table S7. Performance of FEP simulations for the large system (219k atoms) (r-RESPA integrator with 2.5-fs time step).

Number of nodes	Conventional FEP (CPU) (ns/day)	Modified FEP (CPU) (ns/day)	Conventional FEP (CPU+GPU) (ns/day)	Modified FEP (CPU+GPU) (ns/day)
1	3.0 ± 0.0	3.1 ± 0.0	9.1 ± 0.3	10.2 ± 0.3
2	5.3 ± 0.4	5.9 ± 0.0	15.7 ± 0.4	18.9 ± 0.4
4	9.9 ± 0.7	9.6 ± 0.8	24.9 ±0.4	30.6 ± 0.2
8	16.8 ± 0.0	17.8 ± 0.0	38.7 ± 0.1	46.3 ± 0.1

COMPUTATIONAL METHODS

Lambda values for FEP simulations

For absolute solvation free energies of amino-acid side-chain analogs, the following 27 windows were used with different coupling parameters: λ_{elec}^{A} (1.0, 0.8, 0.6, 0.4, 0.2, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0), λ_{LJ}^{A} (1, 1, 1, 1, 1, 1, 0.95, 0.9, 0.85, 0.8, 0.75, 0.7, 0.65, 0.6, 0.55, 0.5, 0.45, 0.4, 0.35, 0.3, 0.25, 0.2, 0.15, 0.1, 0.05, 0.025, 0), and all values of λ_{elec}^{B} and λ_{LJ}^{B} were set to zero.

For relative solvation free energies of amino-acid side-chain analogs, the following 21 windows were used for the three-step procedure: λ_{elec}^{A} (1, 0.75, 0.5, 0.25, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0), λ_{elec}^{B} (0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0.25, 0.5, 0.75, 1), λ_{LJ}^{A} (1, 1, 1, 1, 1, 0.95, 0.9, 0.8, 0.7, 0.6, 0.5, 0.4, 0.3, 0.2, 0.1, 0.05, 0, 0, 0, 0, 0), and λ_{LJ}^{B} (0, 0, 0, 0, 0, 0.05, 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 0.95, 1, 1, 1, 1, 1). For the one-step procedure, the 12 windows were used: λ_{elec}^{A} and λ_{LJ}^{A} (1, 0.909, 0.818, 0.727, 0.636, 0.545, 0.455, 0.364, 0.273, 0.182, 0.091, and 0), and λ_{elec}^{B} and λ_{LJ}^{B} (0, 0.091, 0.182, 0.273, 0.364, 0.455, 0.545, 0.636, 0.727, 0.818, 0.909, and 1).

For the relative binding free energy changes in the barnase-barstar complex, the following 31 windows were used: λ_{elec}^{A} (1, 0.8, 0.6, 0.4, 0.2, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0), λ_{elec}^{B} (0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0.2, 0.4, 0.6, 0.8, 1), λ_{LJ}^{A} (1, 1, 1, 1, 1, 1, 0.95, 0.9, 0.85, 0.8, 0.75, 0.7, 0.65, 0.6, 0.55, 0.5, 0.45, 0.4, 0.35, 0.3, 0.25, 0.2, 0.15, 0.1, 0.05, 0, 0, 0, 0, 0, 0), and λ_{LJ}^{B} (0, 0, 0, 0, 0, 0, 0.05, 0.1, 0.15, 0.2, 0.25, 0.3, 0.35, 0.4, 0.45, 0.5, 0.55, 0.6, 0.65, 0.7, 0.75, 0.8, 0.85, 0.9, 0.95, 1, 1, 1, 1, 1, 1).

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