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

Supplementary data

Assessing AMBER Force Fields for Protein Folding in Implicit Solvent

Qiang Shao*, Weiliang Zhu

Drug Discovery and Design Center, CAS Key Laboratory of Receptor Research, Shanghai Institute of Materia Medica, Chinese Academy of Sciences, 555 Zuchongzhi Road, Shanghai, 201203, China

*To whom correspondence should be addressed. Qiang Shao, Tel: +86 21 50806600-1304, E-mail: qshao@mail.shcnc.ac.cn.

System Name	Residue Number	Sequence
1E0Q	17	MQIFVKTLDGKTITLEV
Trpcage (TC10b)	20	DAYAQWLKDGGPSSGRPPPS
Villin (HP35)	35	LSDEDFKAVFGMTRSAFANLPLWKQQHLK KEKGLF
WW Domain (GTT)	35	GSKLPPGWEKRMSRDGRVYYFNHITGTTQF ERPSG

Table S1. Amino-acid sequence of peptides simulated in this work.

Peptide	Force Field	Temp. Range (K)[a]	Number of Temp. (*N*)[b]
1E0Q	FF99SBildn	270-430	80
	FF99SBnmr	270-430	80
	FF12SB	270-430	80
	FF14ipq	270-430	80
	FF14SB	270-430	80
	FF14SBonlysc	270-430	80
TC10b	FF99SBildn	270-430	100
	FF99SBnmr	270-430	100
	FF12SB	270-430	100
	FF14ipq	270-430	150
	FF14SB	270-430	100
	FF14SBonlysc	270-430	100
HP35	FF99SBildn	270-430	200
	FF99SBnmr	270-430	200
	FF12SB	270-430	200
	FF14ipq	270-430	200
	FF14SB	270-430	200
	FF14SBonlysc	270-430	200
GTT	FF99SBildn	270-430	200
	FF99SBnmr	270-430	200
	FF12SB	270-430	200
	FF14ipq	270-430	200
	FF14SB	270-430	200
	FF14SBonlysc	270-430	200

Table S2. Simulation parameters for ITS-MD simulations under study. [a]The temperature range $\{\beta_i\}$ integrated in ITS approach. [b]Number of temperature points in the desired range of ITS approach.

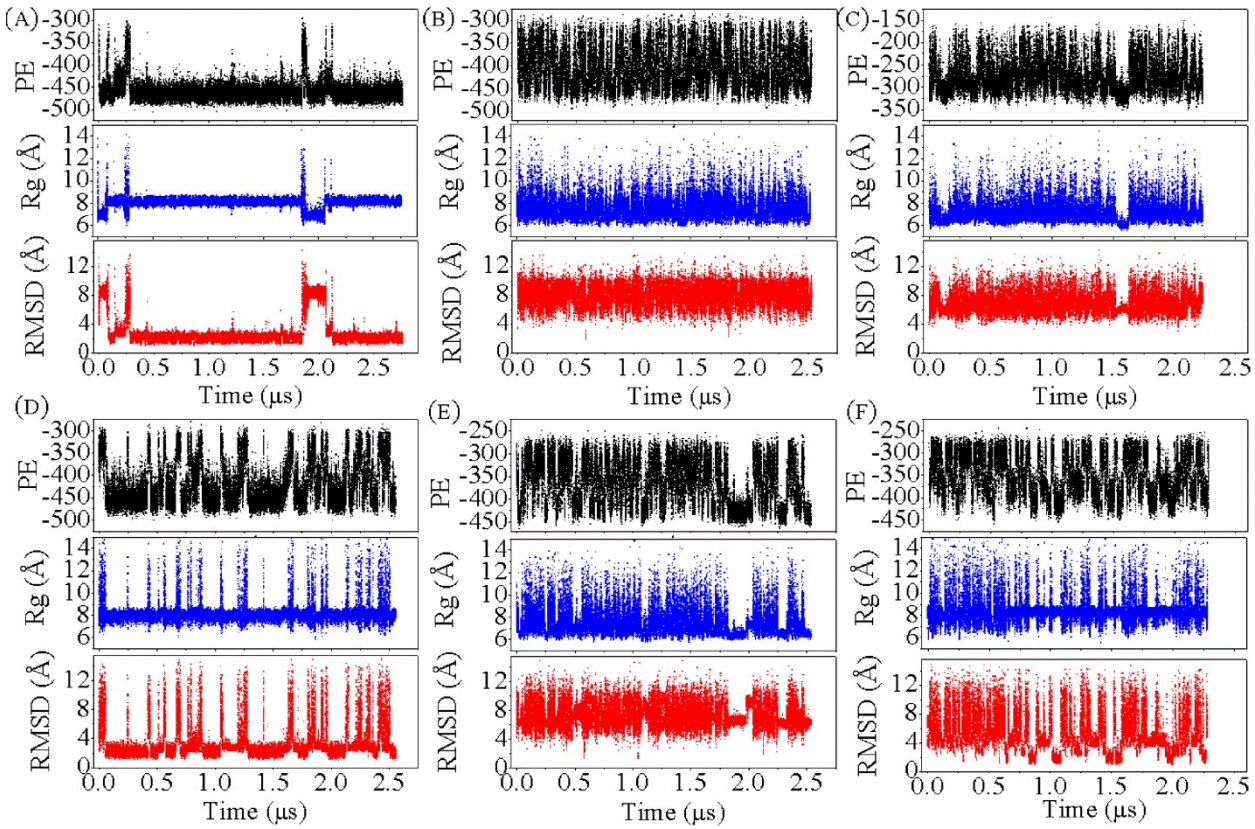

Figure S1. Time series of the potential energy (black line, unit: kcal/mol), the radius of gyration (Rg, blue line) and root-mean-square deviation (RMSD, red line) in individual trajectories of ITS-MD simulations of 1E0Q under the force fields of (A) FF99SBildn, (B) FF99SBnmr, (C) FF12SB, (D) FF14ipq, (E) FF14SB, and (F) FF14SBonlysc.

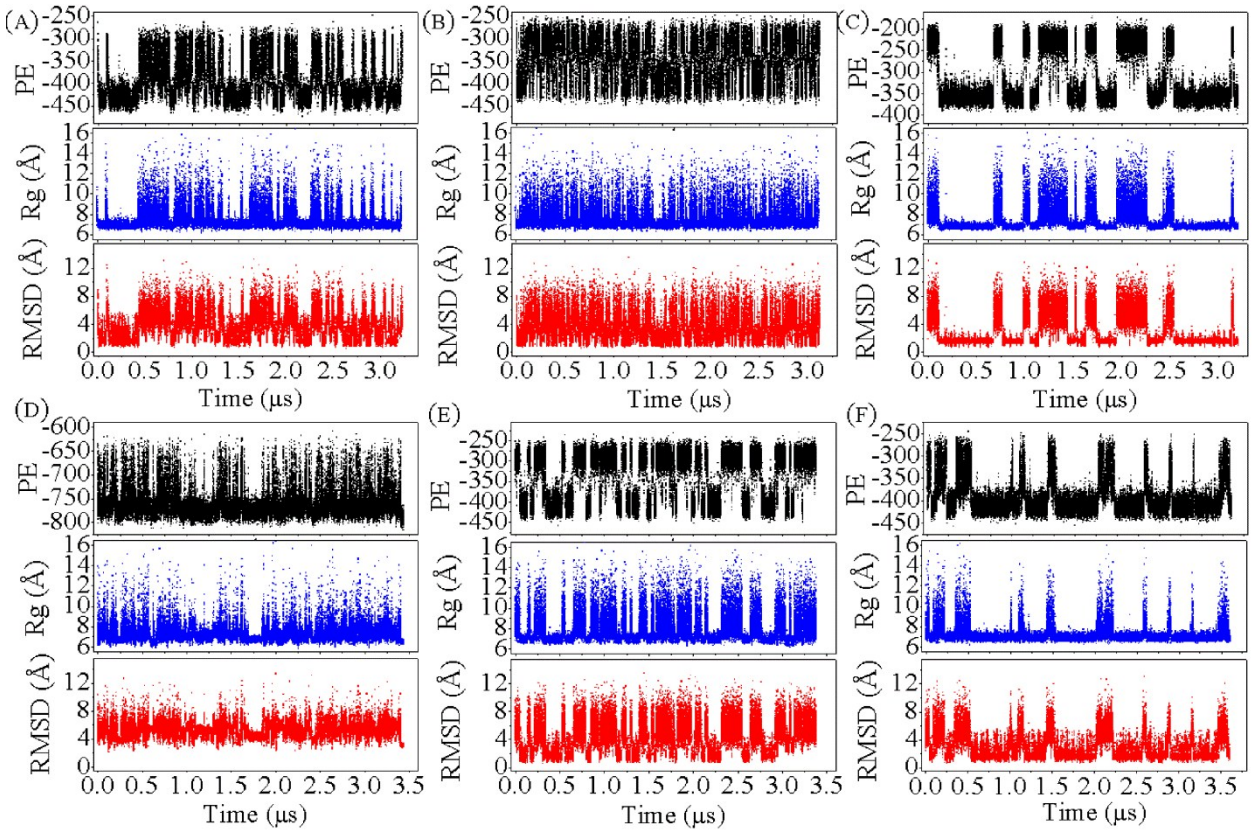

Figure S2. Time series of the potential energy (black line, unit: kcal/mol), the radius of gyration (Rg, blue line), and root-mean-square deviation (RMSD, red line) in individual trajectories of ITS-MD simulations of Trpcage (TC10b) under the force fields of (A) FF99SBildn, (B) FF99SBnmr, (C) FF12SB, (D) FF14ipq, (E) FF14SB, and (F) FF14SBonlysc.

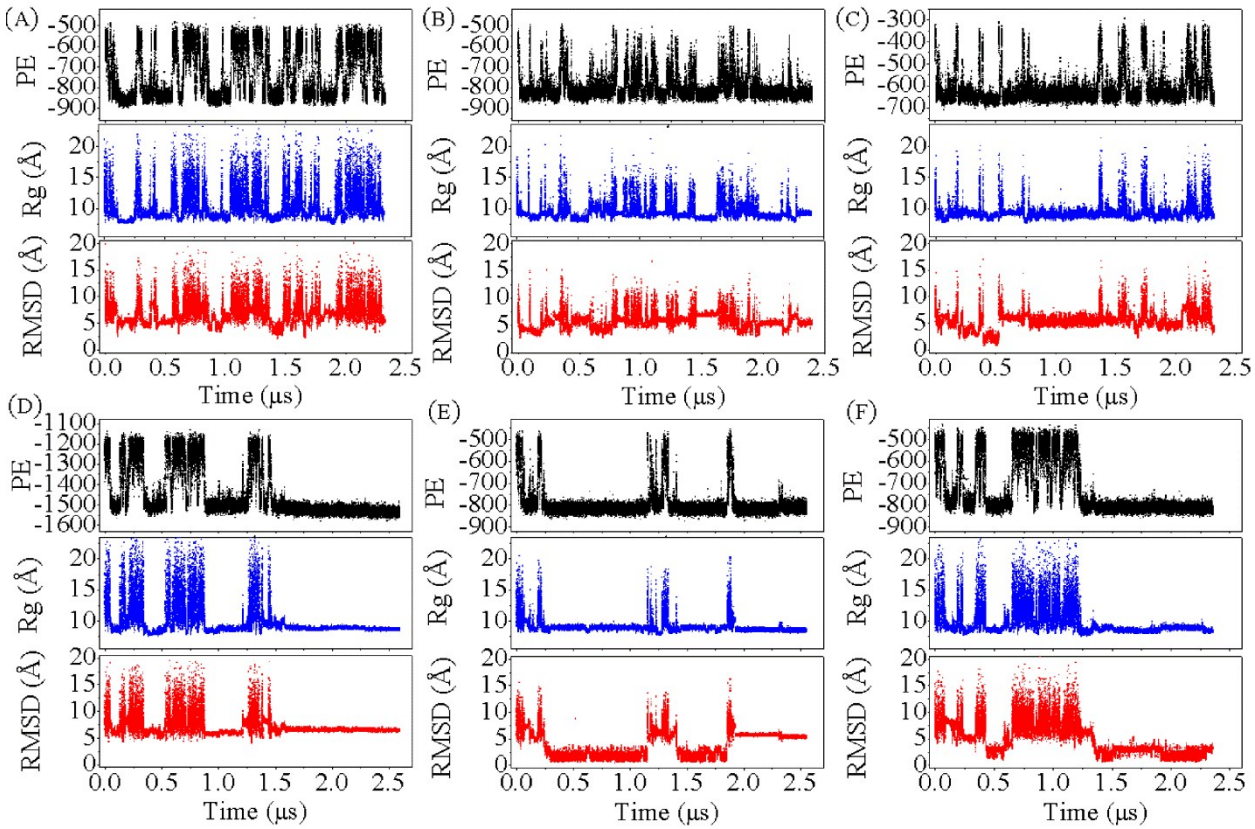

Figure S3. Time series of the potential energy (black line, unit: kcal/mol), the radius of gyration (Rg, blue line), and root-mean-square deviation (RMSD, red line) in individual trajectories of ITS-MD simulations of Villin HP35 under the force fields of (A) FF99SBildn, (B) FF99SBnmr, (C) FF12SB, (D) FF14ipq, (E) FF14SB, and (F) FF14SBonlysc.

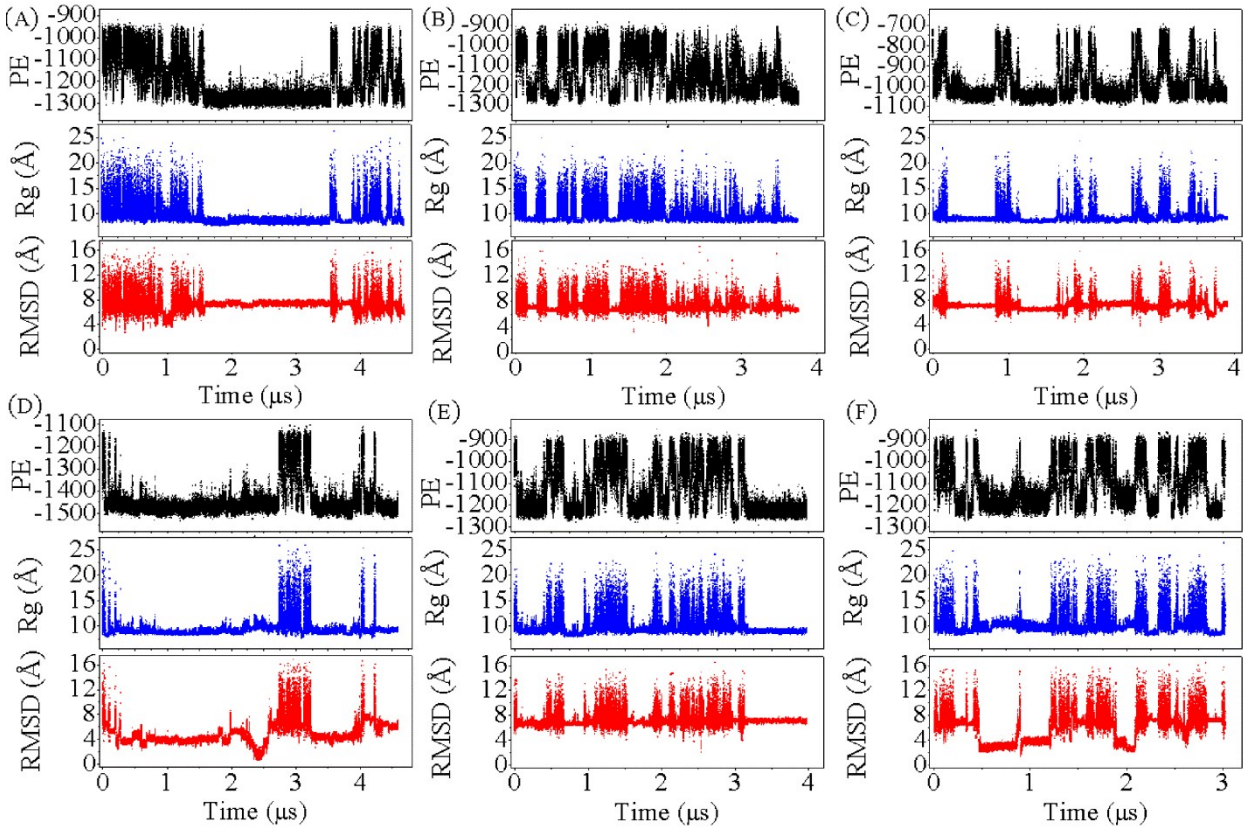

Figure S4. Time series of the potential energy (black line, unit: kcal/mol), the radius of gyration (Rg, blue line), and root-mean-square deviation (RMSD, red line) in individual trajectories of ITS-MD simulations of GTT under the force fields of (A) FF99SBildn, (B) FF99SBnmr, (C) FF12SB, (D) FF14ipq, (E) FF14SB, and (F) FF14SBonlysc.

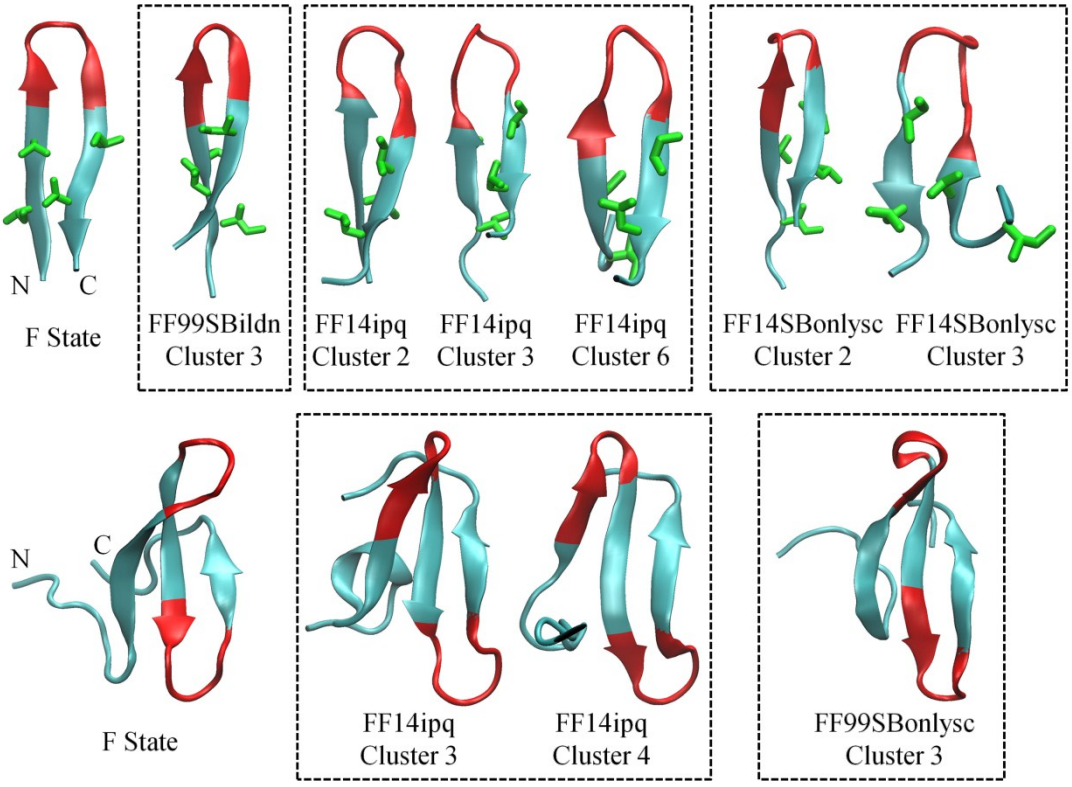

Figure S5. Comparison of the misfolded β-hairpin structures under different force fields to the experimental native structures (F state) for (top) 1E0Q and (bottom) GTT. The turn regions are marked with red color. The cross-strand hydrophobic side-chains of 1E0Q are shown with green colored licorice representation.

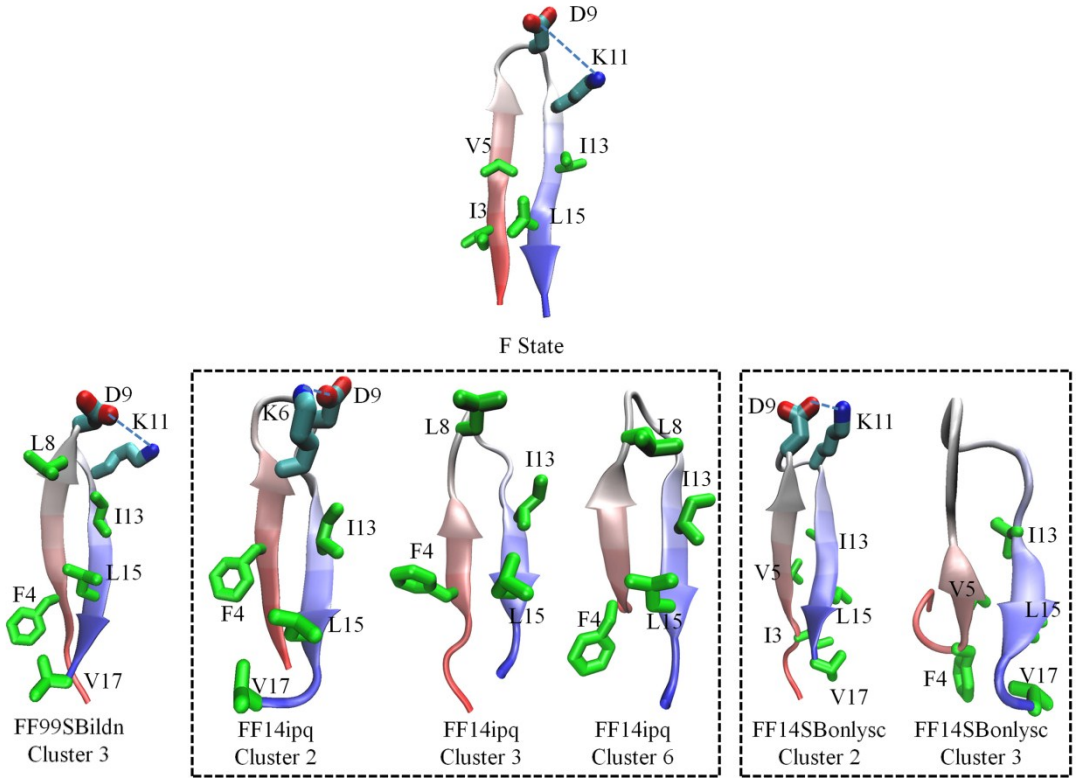

Figure S6. Detailed salt-bridges (connected by cyan dash lines) and cross-strand hydrophobic side-chain contacts formed in the native structure (F state) and misfolded structures of 1E0Q in simulations of various force fields.

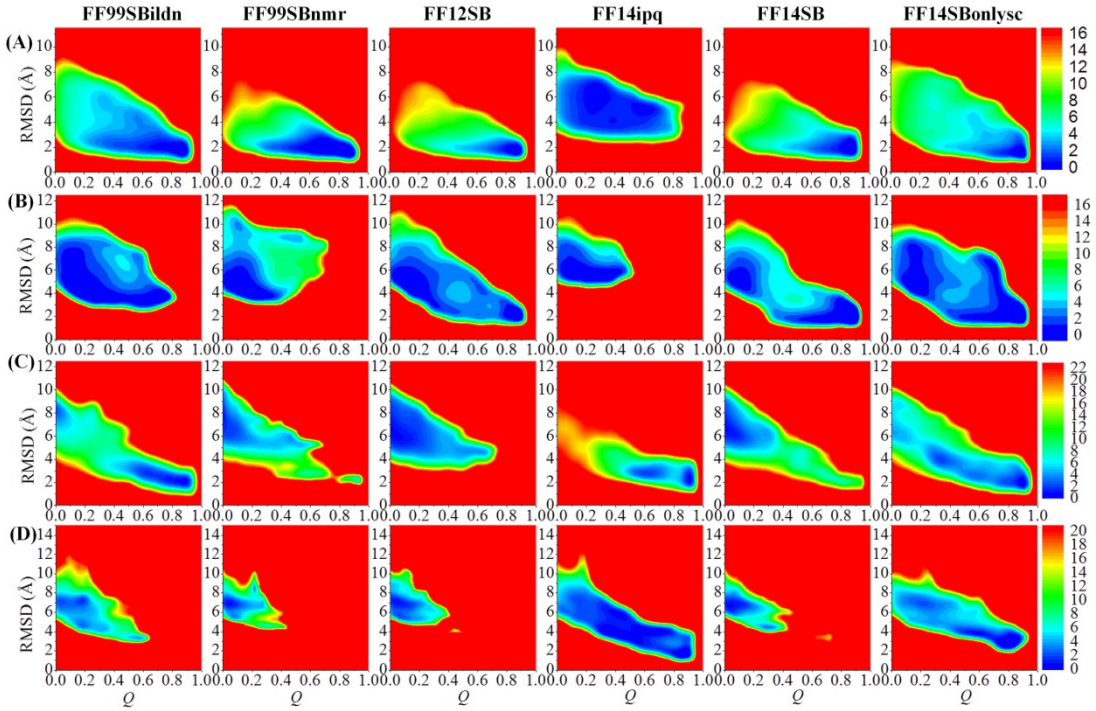

Figure S7. Two-dimensional free-energy profiles as the function of backbone RMSD and the fraction of native contacts (Q) for (A) TC10b, (B) HP35, (C) 1E0Q, and (D) GTT at 300 K simulated by different force fields. The contours in the profiles are spaced at intervals of 0.5 k_BT.

Hydrogen Bonding	FF99SBildn	FF14ipq	FF14SBonlysc	Expt.
Met1O-Val17N	5.63	3.58	6.88	4.0±0.4
Leu15O-Ile3N	5.12	3.42	6.58	3.4±0.2
Ile3O-Leu15N	4.24	3.70	6.18	3.13±0.08
Ile13O-Val5N	3.85	3.37	5.97	3.7±0.4
Val5O-Ile13N	4.06	3.74	5.90	3.8±0.3
Lys11O-Thr7N	4.05	3.42	5.66	3.6±0.2

Table S3. Average N···O distances (in unit of Å) of native hydrogen bonding of 1E0Q measured by simulations and experiment.

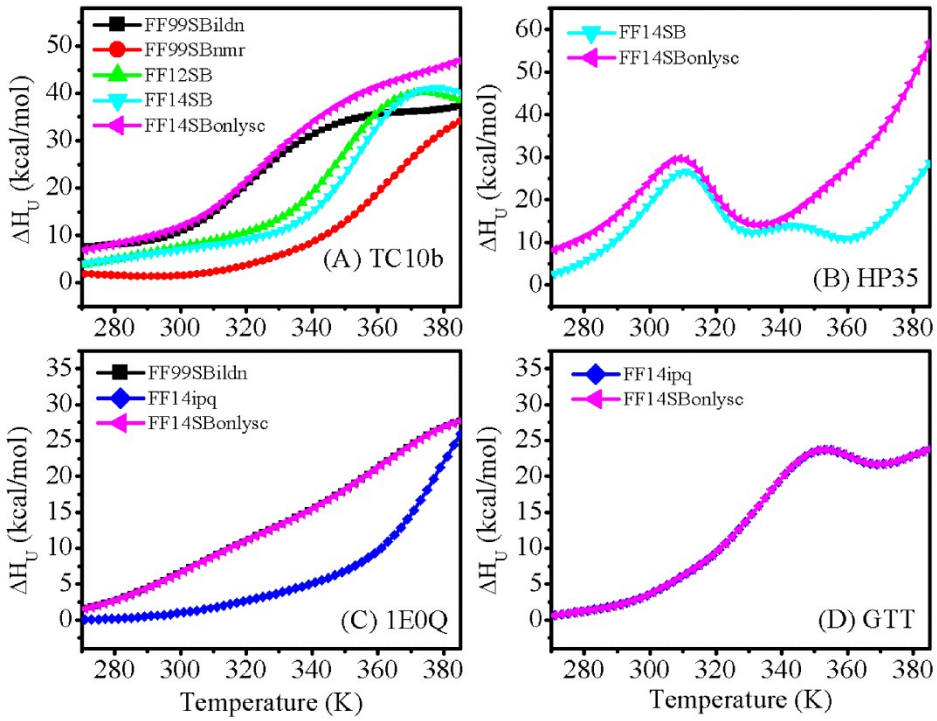

Figure S8. The unfolding enthalpy (ΔH_U) as a function of temperature for (A) TC10b, (B) HP35, (C) 1E0Q, and (D) GTT. The data is calculated for the force fields that could show reasonable weights for the native states on one-dimensional free-energy profiles (Figure 5).