Supplementary Material: "Evaluating the Performance of the FF99SB Force Field Based on Scalar Coupling Data"

Lauren Wickstrom,* Asim Okur[†#] and Carlos Simmerling*[†]

*Biochemistry and Structural Biology Program; [†]Department of Chemistry, Stony Brook University, Stony Brook, NY 11794; [#]current address Laboratory of Computational Biology, NHLBI, NIH, Bethesda, Maryland 20892

Simulation Details

We simulated Ala_3 and Ala_5 with a free N- and protonated C-terminus. These sequences and termini correspond to conditions used in the experimental studies(1). All simulations were performed in Amber version 9(2) and used the FF99SB(3) force field. SHAKE(4) was used to constrain bonds to hydrogen. The time step was 2 fs. Temperatures were maintained using weak Berendsen coupling(5). Explicit water simulations were performed in a truncated octahedron box with the TIP3P(6) and TIP4P-Ew(7) water models. Simulations were run in the NVT ensemble and particle mesh Ewald(8) was used to calculate long-range electrostatic interactions.

ALA_3

For both water models, an extended structure of Ala_3 was solvated with approximately 500 water molecules (498 for TIP4P and 525 for TIP3P). The structures were equilibrated at 300 K for 50 ps with harmonic restraints on solute atoms, followed by minimization with gradually reduced positional restraints and three 5 ps MD simulations with gradually reduced restraints at constant pressure (1 atm) and temperature (300 K) to generate starting structures.

To improve sampling, we used replica exchange molecular dynamics(9, 10) as implemented in Amber 9. The target exchange acceptance ratio for all simulations was approximately 20 % between temperatures ranging from 260 – 580 K. Exchanges between neighboring temperatures was attempted every 1 ps. In order to evaluate convergence, an additional simulation was run using a structure which started from an α-helical conformation in the 2nd residue. The simulations were run for 50,000 exchange attempts. The first 5 ns of each simulation was discarded.

ALA_5

For both water models, an extended structure of Ala_5 was solvated with 891 water molecules. The structures were equilibrated at 300 K for 50 ps with harmonic restraints on solute atoms, followed by minimization with gradually reduced positional restraints and three 5 ps MD simulations with gradually reduced restraints at constant pressure (1 atm) and temperature (300 K) to generate starting structures. REMD simulations were run using a target acceptance ratio of approximately 20 % between the temperatures 293 to 415 K. Exchanges between neighboring temperatures were attempted every 1 ps. In order to evaluate convergence, we ran an additional simulation starting from an α-helical conformation of Ala5. Both simulations were run for 50,000 exchange attempts. The first 5 ns of each simulation was discarded.

Analysis Details

Karplus Parameter Details

The equation used for the calculation of the J coupling constants was:

$$J(\theta) = A\cos^2(\theta + \Delta) + B\cos(\theta + \Delta) + C \qquad \textbf{(1)}$$

where A, B, C and Δ are listed in Tables S1 through S3 except in the case of $J_{HNC\alpha}$ which uses the following equation:

$$\begin{aligned} J_{HNC\alpha}(\varphi_i,\psi_{i-1}) &= -0.23\cos\varphi_i - 0.20\cos\psi_{i-1} \\ &+ 0.07\sin\varphi_i + 0.08\sin\psi_{i-1} + 0.07\cos\varphi_i\cos\psi_{i-1} \\ &+ 0.12\cos\varphi_i\sin\psi_{i-1} - 0.08\sin\varphi_i\cos\psi_{i-1} \\ &- 0.14\sin\varphi_i\sin\psi_{i-1} + 0.54 \end{aligned} \qquad \textbf{(2)}$$

These calculations were done comparably to the work by Graf et. al and Best et al.(1, 11)

Phi and psi dihedrals for the central residue of the Ala peptides were calculated using the ptraj module in Amber 10(2) .

Error Analysis

The agreement between the experimental and calculated constants was evaluated using the following relation, following the procedure previously reported (11):

$$\chi^2 = \mathrm{N}^{-1} \sum_{j=1}^{N} (\langle J_j \rangle_{sim} - J_{j,\exp})^2 / \sigma_j^2 \qquad \textbf{(3)}$$

where $\langle J_j \rangle_{sim}$ is the average coupling constant j obtained from the simulation while $J_{j,\exp}$ is the experimental coupling constant for J. The average was calculated using the scalar coupling constants $^3J_{HNH\alpha}$, $^3J_{HNC'}$, $^3J_{H\alpha C'}$, $^3J_{CC'}$, $^3J_{HNC\beta}$, $^1J_{NC\alpha}$, $^2J_{NC\alpha}$, and $^3J_{HNC\alpha}$ where N is the total number of J values. The systematic error σ_j was included to account for possible substituent effects neglected in the Karplus equation for each coupling constant (Table S4). The estimates in Table S4 of this document were used for this work. We note that these are identical to those used by Best et. al. in reference (11) but that they do not match the values provided in Table S4 of that publication (G. Hummer, pers. comm.).

Populations of secondary structure for the central residue of Ala_5

Populations of secondary structure were calculated using the basin definitions in the previous work(11). Secondary structure basin populations for central residues were calculated based on phi/psi dihedral angle pairs. The definitions of the four principle regions were as follows: right handed helix (α_R), (φ,ψ) ~ (-160 to -20, -120 to +50); extended β-strand conformation, (-180 to -110, +50 to +240; or +160 to +180, +110 to +180); and polyproline II, (-90 to -20, +50 to +240). The number of structures in individual regions were summed up and divided up by the total number of structures and multiplied by 100 to get the percentages in each basin. Error bars were constructed from the independent runs. Dictionary of secondary structural prediction (DSSP)(12) analysis was performed by the ptraj module of Amber 10(2).

Table S1: Original ("Orig") parameters used in the Karplus equation (1) from Graf et. al (1) .

Coupling	Torsion	A (Hz)	B (Hz)	C (Hz)	Δ(°)
$^{3}J_{HNH\alpha}$	φ_i	7.09	-1.42	1.55	-60
$^{3}J_{HNC'}$	φ_i	4.29	-1.01	0.00	180
$^{3}J_{H\alpha C'}$	φ_i	3.72	-2.18	1.28	120
$^{3}J_{CC'}$	φ_i	1.36	-0.93	0.60	0
$^{3}J_{HNC\beta}$	φ_i	3.06	-0.74	0.13	60
$^{1}J_{NC\alpha}$	ψ_i	1.70	-0.98	9.51	0
$^{2}J_{NC\alpha}$	ψ_{i-1}	-0.66	-1.52	7.85	0

Table S2: "DFT1" parameters used in the Karplus equation (13). Parameters for unlisted J coupling constants used parameters in S1.

Coupling	Torsion	A (Hz)	B (Hz)	C (Hz)	Δ(°)
$^{3}J_{HNH\alpha}$	φ_i	9.44	-1.53	-0.07	-60
$^{3}J_{HNC'}$	φ_i	5.58	-1.06	-0.30	180
$^{3}J_{H\alpha C'}$	φ_i	4.38	-1.87	0.56	120
$^{3}J_{CC'}$	φ_i	2.39	-1.25	0.26	0
$^{3}J_{HNC\beta}$	φ_i	5.15	0.01	-0.32	60

Table S3: "DFT2" parameters used in the Karplus equation (13). Parameters for unlisted J coupling constants used parameters in S1.

Coupling	Torsion	A (Hz)	B (Hz)	C (Hz)	Δ(°)
$^3J_{HNH\alpha}$	φ_i	9.14	-2.28	-0.29	-64.51
$^3J_{HNC'}$	φ_i	5.34	-1.46	-0.29	172.49
$^3J_{H\alpha C'}$	φ_i	4.77	-1.85	0.49	118.61
$^3J_{CC'}$	φ_i	2.71	-0.91	0.21	-2.56
$^3J_{HNC\beta}$	φ_i	4.58	-0.36	-0.31	58.18

Table S4: Estimates of errors σ_j for each scalar coupling reported in Best et al(11)

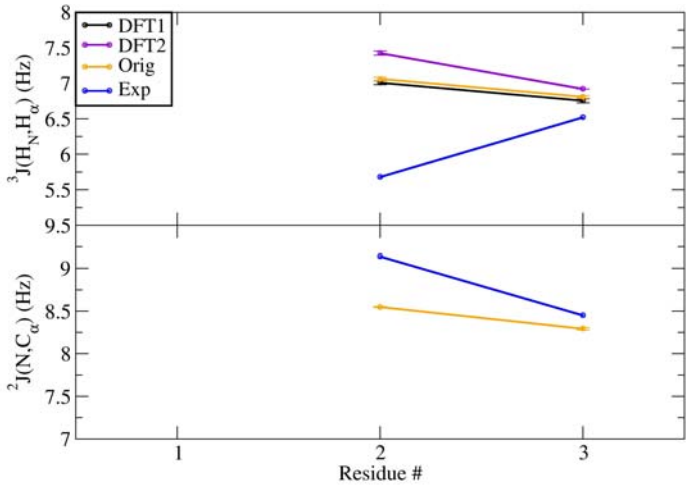
Coupling	σ_j
$^3J_{HNH\alpha}$	0.91
$^3J_{HNC'}$	0.59
$^3J_{H\alpha C'}$	0.38
$^3J_{CC'}$	0.22
$^3J_{HNC\beta}$	0.39
$^1J_{NC\alpha}$	0.59
$^2J_{NC\alpha}$	0.50
$^3J_{HNC\alpha}$	0.10

Table S5: Populations of α, β and PP_{II} basins on the Ramachandran map for the central residue of Ala_5. Error bars were calculated from the average difference of each basin population for two independent simulations.

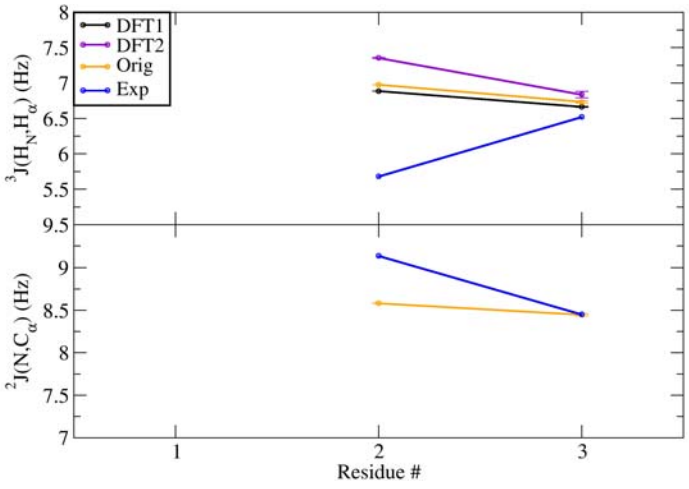
Peptide	**Water model**	**α**	**B**	**PP_{II}**
ALA_5	TIP3P	19.6 +/- 1.4	34.2 +/- 0.4	41.0 +/- 0.8
	TIP4P-Ew	15.1 +/- 4.6	36.6 +/- 2.7	45.1 +/- 2.0

Figure S1. Average $^{3}J_{HNH\alpha}$, , and $^{2}J_{NC\alpha}$ coupling constants of each residue for the simulations of Ala_3 and Ala_5 in TIP3P (A/C) and TIP4P-Ew (B) solvent model at 300 K. Ala_5 simulations in TIP4P-Ew are included in the main text. DFT1, DFT2 and Original (Orig) correspond to the Karplus parameter set used in the calculation. The experimental values are also included on each graph(1). Error bars were calculated from the average difference of the two independent simulations.

A.



B.



C.

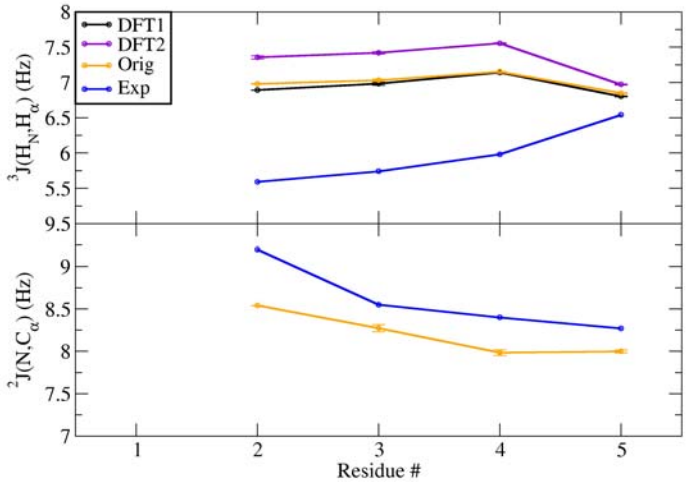
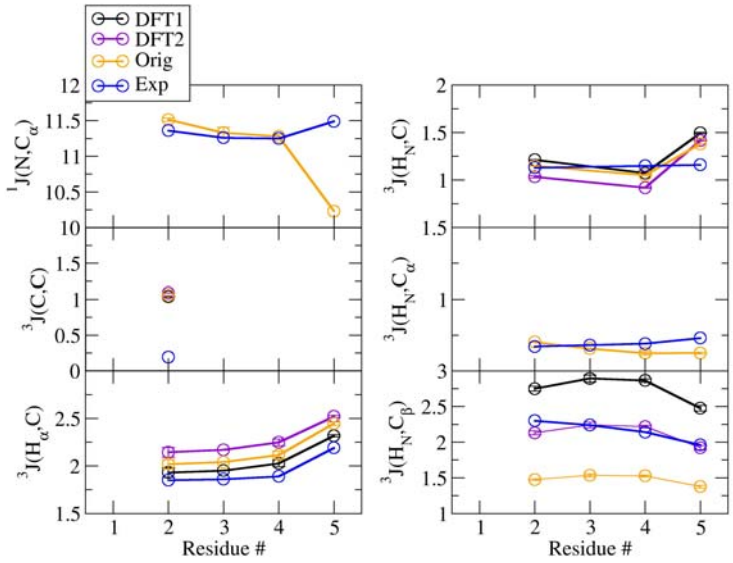


Figure S2. Average $^1J_{NC\alpha}$,$^3J_{CC}$,$^3J_{H\alpha,C}$ $^3J_{HNC}$, $^3J_{HNC\alpha}$, and $^3J_{HNC\beta}$ coupling constants of each residue for the simulations of Ala_5 in TIP4P-Ew solvent model at 300 K. DFT1, DFT2 and Original (Orig) correspond to the Karplus parameter set used in the calculation. The experimental values are also included on each graph(1). Error bars were calculated from the average difference of the two independent simulations.



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