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

Supporting Information

Effect of Monovalent Salt on the Energetics of Antimicrobial-Peptide: Micelle Dissociation

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Content

Table S1: Simulation setup details for umbrella sampling

	LL-14:SDS (NaCl = 0.0% w/v)	**LL-14:SDS (NaCl = 0.5% w/v)**	**LL-14:SDS (NaCl = 1.0% w/v)**
Total no of atoms	268833	268038	266918
No of Water molecules	88649	88292	87925
Na^+ ions	60	198	338
Cl^- ions	7	145	285
Molecular Dynamics parameters			
time step		0.002 ps	
boundary condition		Periodic boundary condition (pbc)	
Long range electrostatics		Particle Mesh Ewald (PME[1])	
Short-range neighbour list cut-off		1.4 nm	
Short-range electrostatic cut-off		1.4 nm	
Short-range van der Waals cut-off		1.4 nm	
Constraint algorithm (h-bonds)		lincs[2]	
Temperature control		velocity rescaling algorithm (V-rescale[3])	
Pressure control		Parrinello-Rahman[4]	

References

1 T. Darden, D. York and L. Pedersen, Particle mesh Ewald: An N·log(N) method for Ewald sums in large systems, *J Chem Phys*, 1993, **98**, 10089–10092.

2 B. Hess, H. Bekker, H. J. C. Berendsen and J. G. E. M. Fraaije, LINCS: A linear constraint solver for molecular simulations, *J Comput Chem*, , DOI:10.1002/(SICI)1096-987X(199709)18:12<1463::AID-JCC4>3.0.CO;2-H.

3 G. Bussi, D. Donadio and M. Parrinello, Canonical sampling through velocity rescaling, *J Chem Phys*, 2007, **126**, 014101.

4 M. Parrinello and A. Rahman, Strain fluctuations and elastic constants, *J Chem Phys*, 1982, **76**, 2662–2666.

Table S2: No restraint applied for SDS micelle during umbrella Sampling. Run-length (in ns) and estimated binding free energy from each independent replica are given. $\Delta G^{Averaged}$ is the average over multiple replicas. $\Delta\Delta G^{Averaged}$ = $\Delta G^{Averaged}$(0.5% or 1% NaCl) - $\Delta G^{Averaged}$(0% NaCl). Total Simulation length =(33745 ns *umbrella sampling* + 120.6 ns *equilibration* + 8 ns *SMD*) = 33873.6 ns ~33.87 µs. Error is in SEM given after ±.

	Replicas	Run-length of Umbrella Sampling	ΔG (kcal/mol)	$\Delta G^{Averaged}$ (kcal/mol)	$\Delta\Delta G^{Averaged}$ (kcal/mol)
LL-14:SDS (NaCl = 0.0%)	**Trial 1**	43 windows × 50 ns = 2150 ns	-33.85 ± 0.97	-33.53 ± 0.86	0.0
	Trial 2	43 windows × 55 ns = 2365 ns	-34.15 ± 1.16		
	Trial 3 (Highest Sampling)	**43 windows × 250 ns = 10750 ns**	**-33.19 ± 0.75**		
LL-14:SDS (NaCl = 0.5%)	**Trial 1**	43 windows × 50 ns = 2150 ns	-25.58 ± 0.86	-25.61 ± 0.93	-7.92
	Trial 2	43 windows × 55 ns = 2365 ns	-25.79 ± 1.12		
LL-14:SDS (NaCl = 1.0%)	**Trial 1**	43 windows × 50 ns = 2150 ns	-21.54 ± 0.98	-21.58 ± 1.02	-11.95
	Trial 2	43 windows × 55 ns = 2365 ns	-21.80 ± 1.16		

Alternate Approach* In each window, "d_{COM}" and SDS micelle were harmonically restrained, employing a force constant of 1000 kJ mol^{-1} nm^{-2} relative to the starting coordinate. Snapshots selected from fast pulling simulations, pulling rate = 0.01 nm ps^{-1}). In trial 4, umbrella sampling was performed by choosing the snapshots from a slow pull (pulling rate = 0.005 nm ps^{-1}) simulation. The SDS micelle was modelled as an immobile reference (restrained) during the umbrella sampling simulations.

Alternate Approach*	Replicas	Run-length of Umbrella Sampling	ΔG (kcal/mol)	$\Delta G^{Averaged}$ (kcal/mol)	$\Delta\Delta G^{Averaged}$ (kcal/mol)
LL-14:SDS (NaCl = 0.0%)	**Trial 1**	43 windows × 10 ns = 430 ns	-61.95 ± 0.95	-61.09 ± 0.85	0.0
	Trial 2	43 windows × 50 ns = 2150 ns	-60.09 ± 0.88		
	Trial 3	43 windows × 10 ns = 430 ns	-61.03 ± 0.97		
	Trial 4 *(Slow Pull SMD)*	44 windows × 10 ns = 440 ns	-61.29 ± 0.93		
LL-14:SDS (NaCl = 0.5%)	**Trial 1**	43 windows × 10 ns = 430 ns	-46.14 ± 0.52	-46.04 ± 0.45	-15.04
	Trial 2	43 windows × 50 ns = 2150 ns	-45.94 ± 0.44		

LL-14:SDS (NaCl = 1.0%)	**Trial 1**	43 windows × 10 ns = 430 ns	-42.58 ± 0.49	-42.34 ± 0.32	-18.77
	Trial 2	43 windows × 50 ns = 2150 ns	-42.09 ± 0.31		

The absolute value of estimated free energies (ΔG) was strongly dependent on the adopted approach (Restrained or unrestrained SDS micelle). However, the salt-induced systematic change in the binding affinity, disfavouring LL-14 binding to SDS micelle, was a robust feature independent of the adopted approach.

Table S3: LL-14:DPC micelle binding free energy estimated from umbrella sampling (Approach 2: No restraint on the DPC micelle, Snapshot selected from COM pull rate = 0.01 nm/ps). SEM given after ±.

Approach 2	Replicas	Run-length of Umbrella Sampling	ΔG (kcal/mol)
LL-14:DPC (NaCl = 0.0%)	**Trial 1**	42 windows × 20 ns = 840 ns	-11.58 ± 0.98

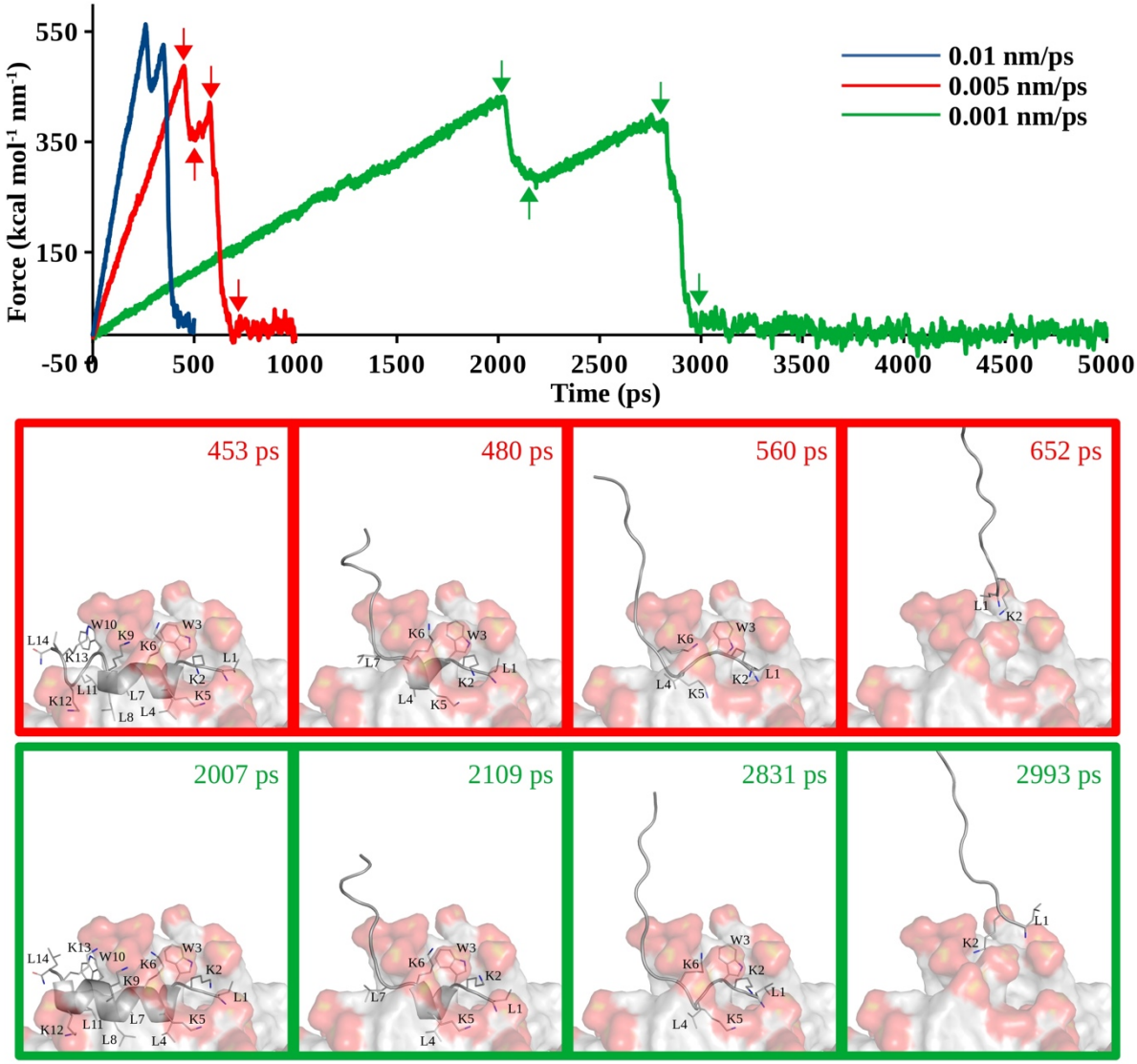

Fig. S1 Force versus time plots from various SMD simulations (pull rates = 0.01nm/ps, 0.005 nm/ps, and 0.001 nm/ps). The shape of the force profile was independent of the pull rates. Structures from various time-points shown in the boxes (**red** : 0.005 nm/ps pull-rate, **green** : 0.001 nm/ps pull-rate).

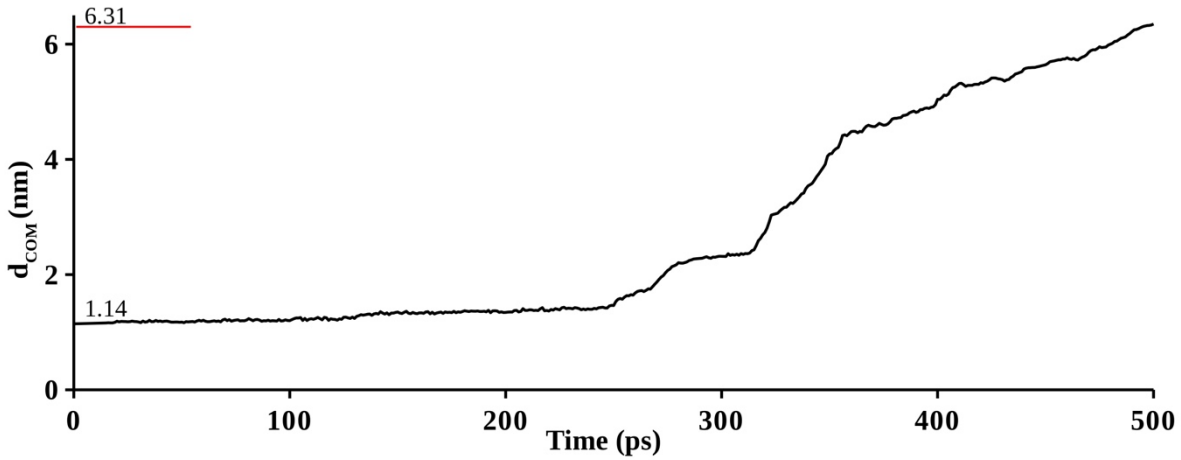

Fig. S2 Center-of-mass pulling simulation (d_{COM} vs. time plot, pulling rate = 0.01 nm/ps). d_{COM} = Distance between the center-of-mass of the LL-14 and SDS micelle. "d_{COM}" range (Minimum = 1.14 nm, Maximum = 6.31nm).

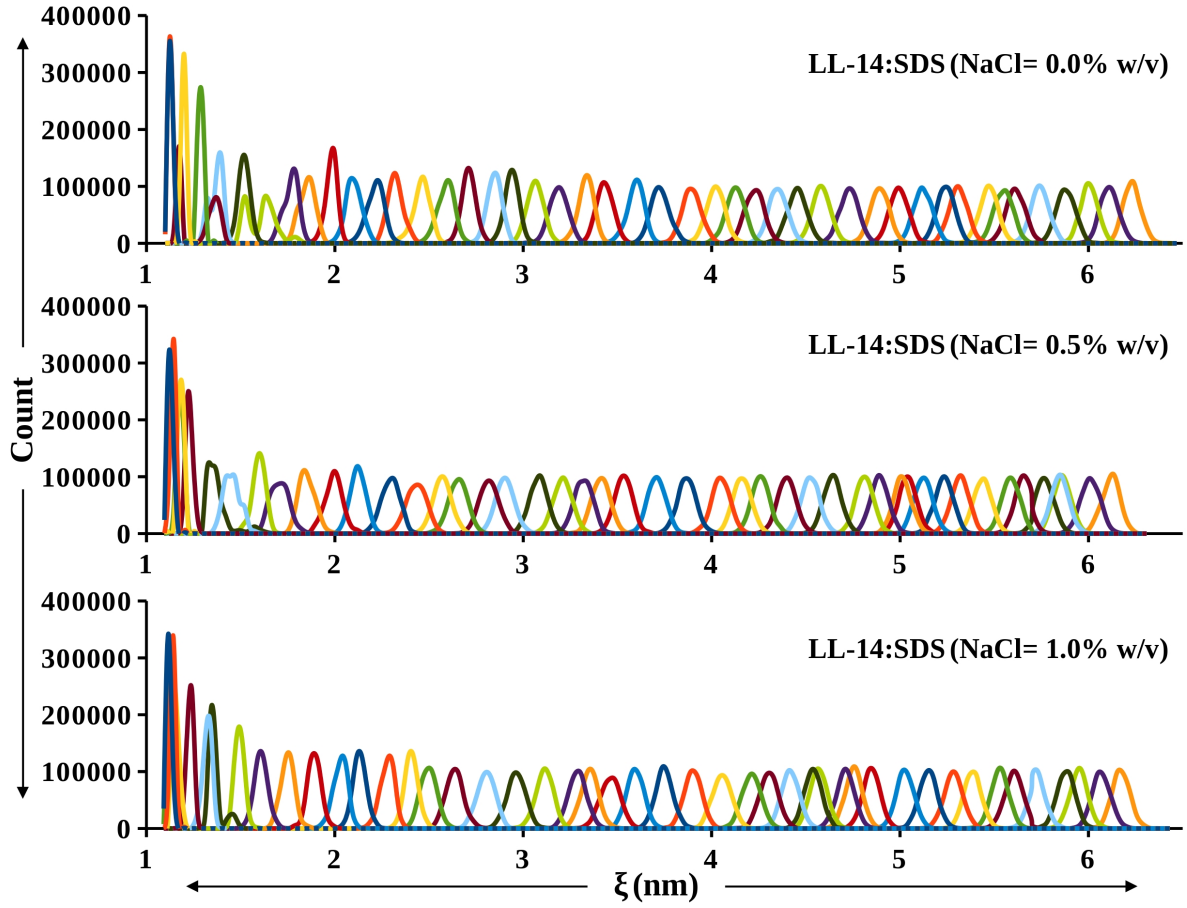

Fig. S3 Probability distribution at each umbrella sampling window (Total windows = 43, shown in different colours) from the LL-14:SDS PMF profile at various salt-concentrations (NaCl = 0%, 0.5%, and 1.0% w/v). The overlap of probability distribution (between two neighbouring windows) was evident.

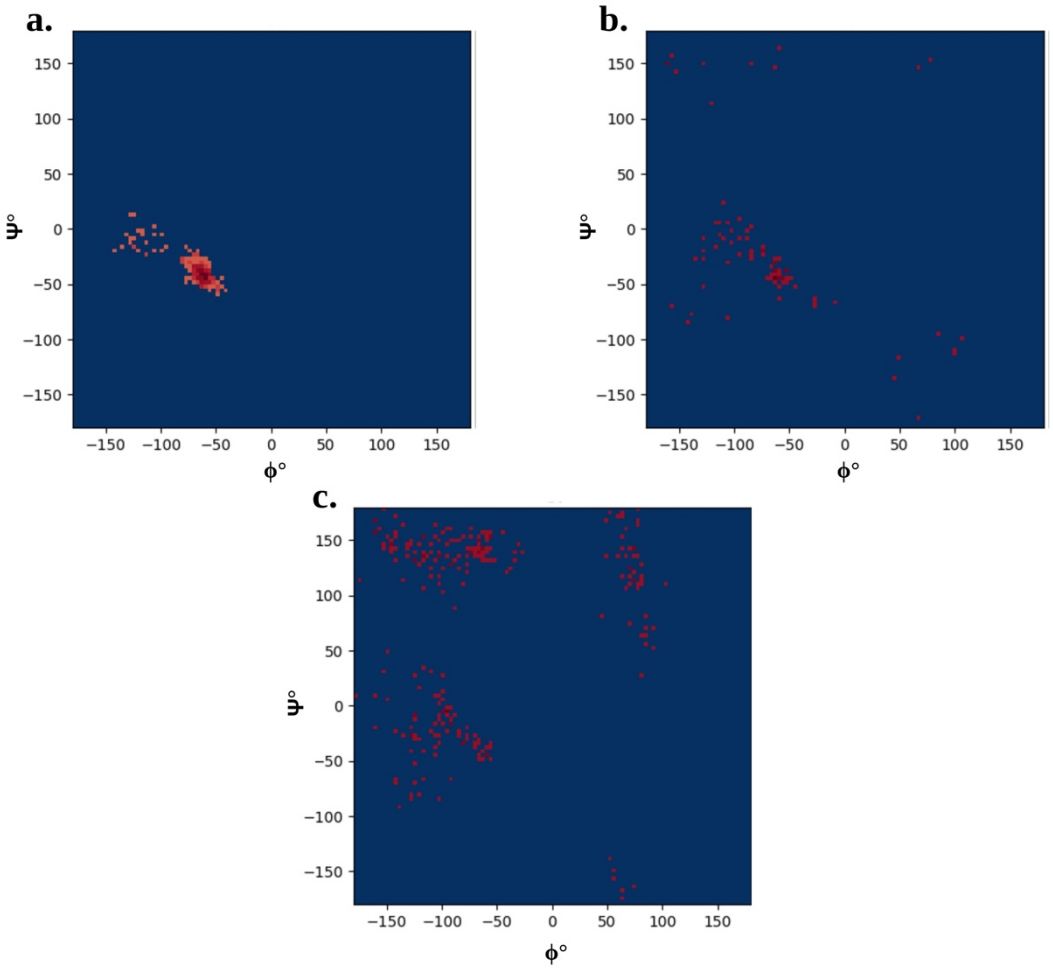

Fig. S4 Ramachandran Plot of LL-14 peptide obtained from different trajectory segment during the centre-of-mass pulling (SMD, pull rate= 0.01 nm/ps, NaCl = 0% w/v). SMD trajectory segment (a) 0 - 263 ps, (b) 264 – 351 ps, and (c) 352 - 500 ps. ϕ and Ψ angles were plotted from -180° to 180°. Dispersion of red points from "a" → "c" indicates helical → random-coil transition. Blue regions exhibit either zero or little likelihood of the peptide adopting such a conformation.

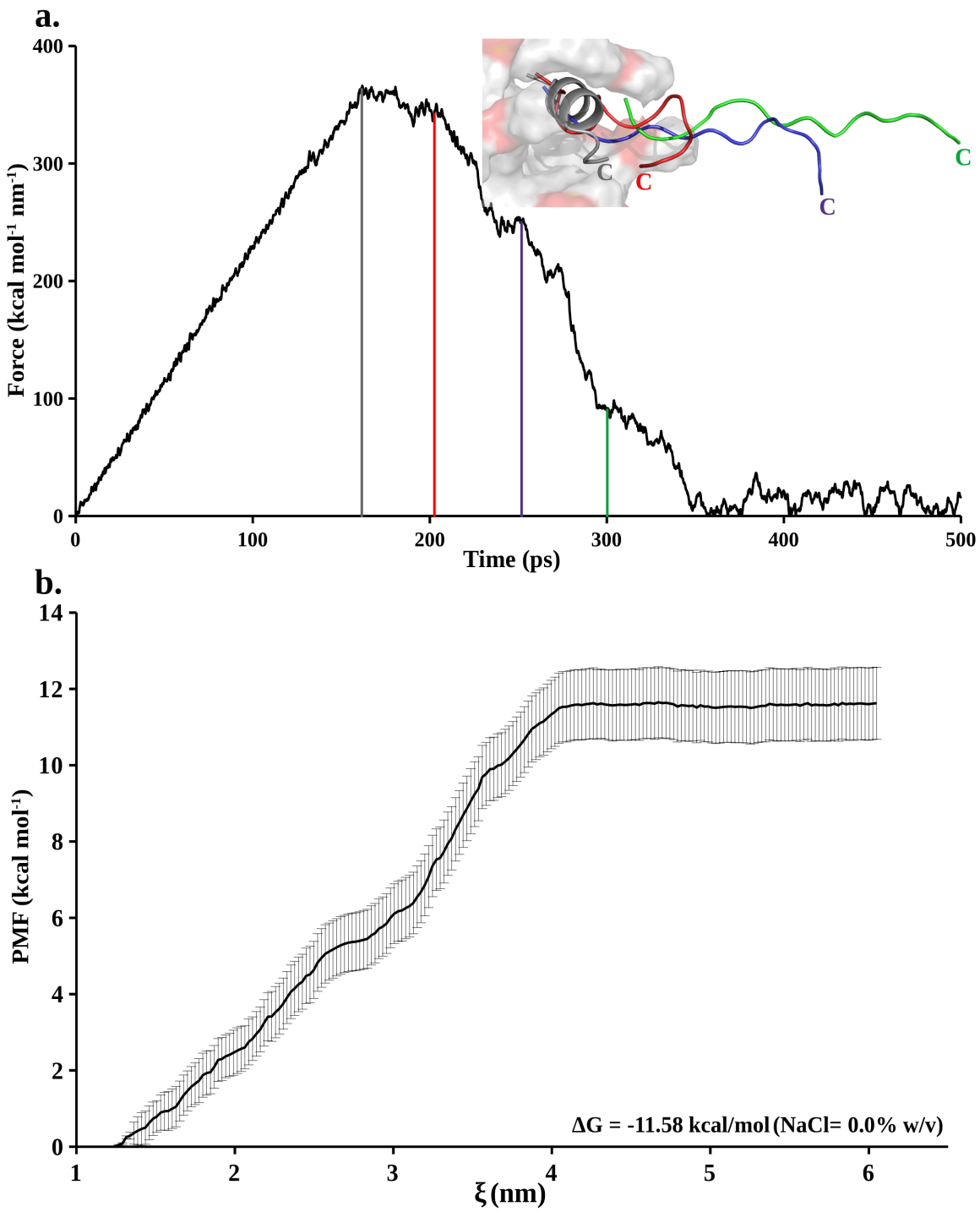

Fig. S5 (a) Force vs. time plots of LL-14:DPC micelle complex (pull rate 0.01nm/ps, NaCl = 0% w/v). Structures at different time-points (grey, red, blue, and green) were overlaid (shown in surface-cartoon representations). (b) LL-14:DPC binding free energy (ΔG) estimated from the potential of mean force (PMF) versus reaction coordinate "ξ" plot. Simulation details were given in Table S3.