Supporting Information: Improved Parameterization of Amine–Carboxylate and Amine–Phosphate Interactions for Molecular Dynamics Simulations Using the CHARMM and AMBER Force Fields

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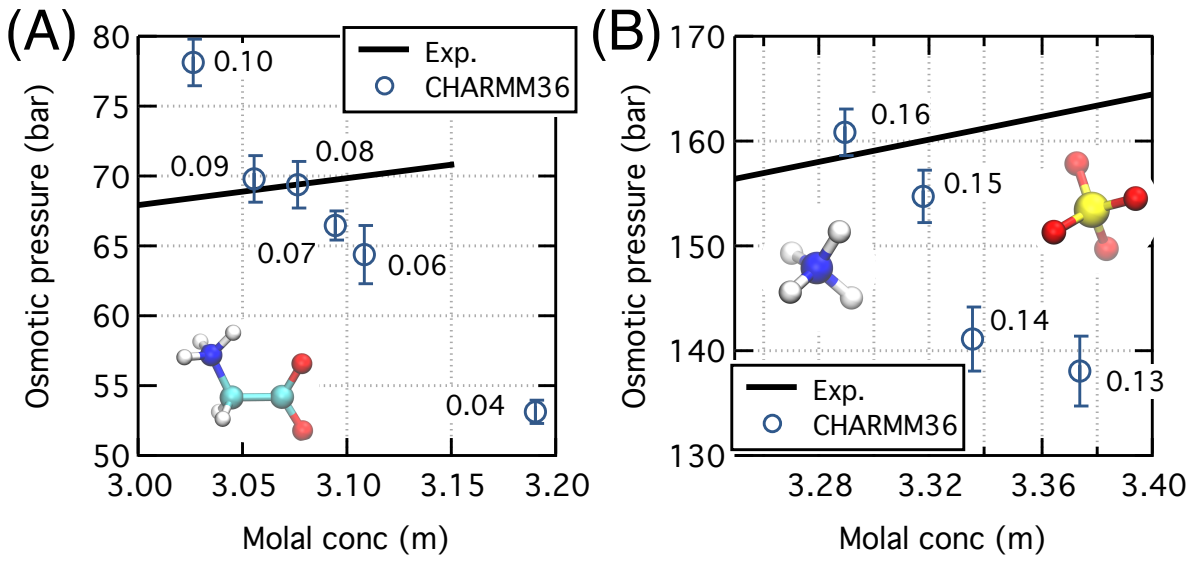

Figure S1: Optimization of the CHARMM LJ $r_{\min}$ parameters against the experimental osmotic pressure data. The osmotic pressure of glycine (panel A) and ammonium sulfate (panel B) solutions is plotted versus the solutions' molality for several values of the LJ $r_{\min}$ parameter describing the vdW interactions between amine nitrogen and carboxylate oxygen (panel A) or amine nitrogen and sulfate oxygen (panel B). The $\Delta r_{\min}$ values are indicated by the numbers next to each data point. Experimental osmotic pressure data (black lines) are recovered using $\Delta r_{\min} = 0.08$ and 0.16 Å for the glycine and ammonium sulfate solutions, respectively. The experimental data were taken from references 1 and 2.

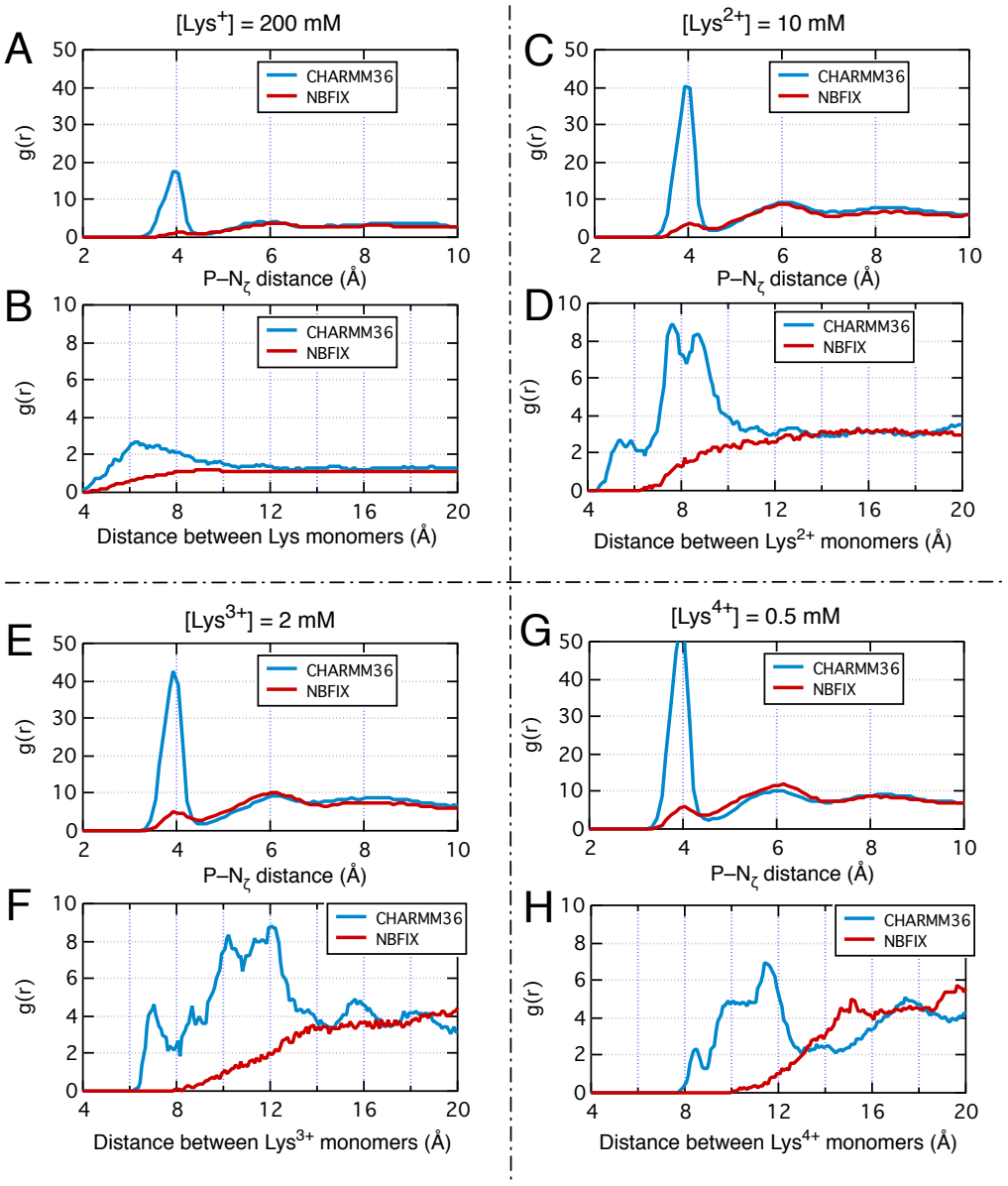

Figure S2: The distribution of lysine solutes in the simulations of pairwise DNA–DNA forces performed using the CHARMM36 force field. (A) The radial distribution function of N_ζ atoms of the lysine residues with respect to the phosphate phosphorus atoms. (B) The radial distribution function of the centers of mass of the lysine solutes. Data in panels A and B correspond to $[Lys^+] = 200$ mM. Red and blue curves correspond to the simulations performed using our NBFIX corrections ($r_{\min}^{N-O=P} = 0.16$ Å and $r_{\min}^{N-O=C} = 0.08$ Å) and the standard CHARMM36 parameter set, respectively. (C,D) Same as in panels A and B but for $[Lys^{2+}] = 10$ mM. (E,F) Same as in panels A and B but for $[Lys^{3+}] = 2$ mM. (G,H) Same as in panels A and B but for $[Lys^{4+}] = 0.5$ mM.

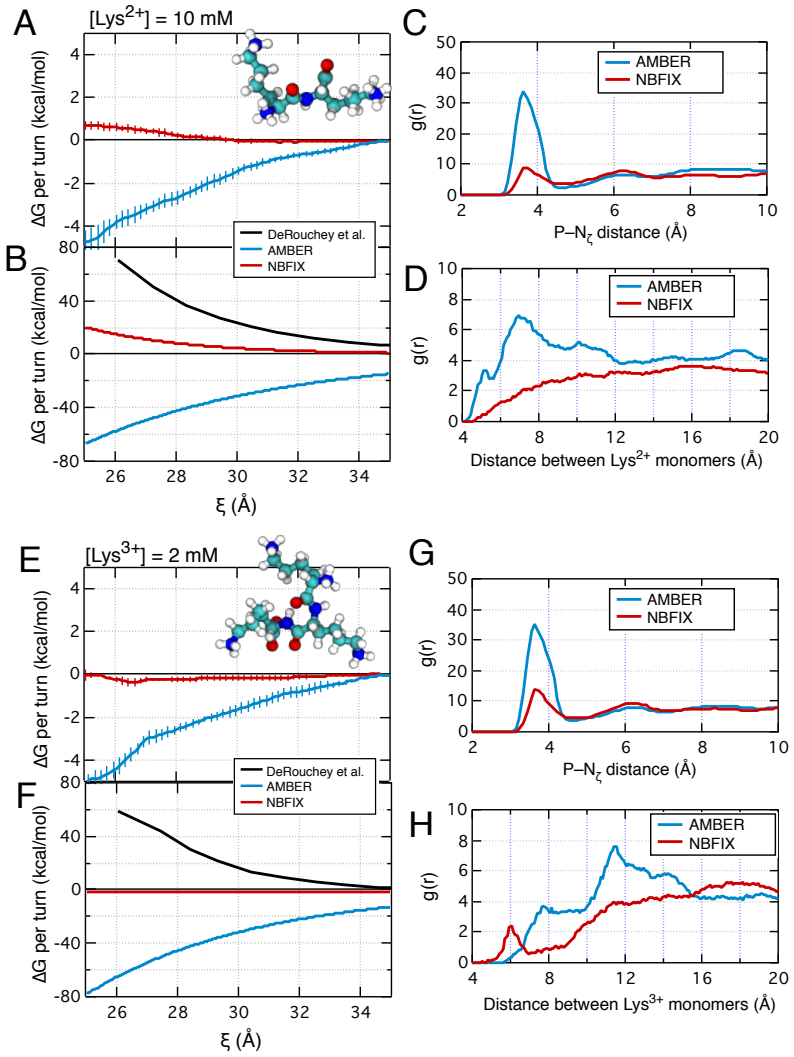

Figure S3: The effects of NBFIX corrections on DNA–DNA interactions mediated by 10 mM Lys^{2+} (A–D) and 2 mM Lys^{3+} (E–H) in the simulations performed using the AMBER force field. (A,B) The interaction free energy, ΔG (panel A), and the effective DNA–DNA force, F (panel B), between two dsDNA molecules as a function of the inter-DNA distance, ξ, at $[Lys^{2+}] = 10$ mM. The ΔG and F values computed using our NBFIX corrections ($\sigma^{N-O=P} = 0.14$ Å and $\sigma^{N-O=C} = 0.08$ Å) and the standard AMBER parameter set are shown as red and blue lines, respectively. The experimental DNA–DNA force (black) was taken from Ref. 3. The interaction free energy was computed from a set of umbrella sampling simulations; the duration of the MD trajectory in each umbrella sampling window was 40 ns. The error bars in the ΔG curves indicate the standard deviations among four ΔG estimates obtained using independent 10 ns fragments of the umbrella sampling trajectories. To compute the DNA–DNA forces, the corresponding interaction free energy was fitted to a double exponential function;[4] numerical differentiation of the fitting function with respect to ξ yielded the effective force as $F = -dG/d\xi$. (C) The radial distribution functions of N_ζ atoms of lysine with respect to phosphate phosphorus atoms. (D) The radial distribution functions of the centers of mass of lysine solutes. (E–H) Same as in panels A–D but for $[Lys^{3+}] = 2$ mM.

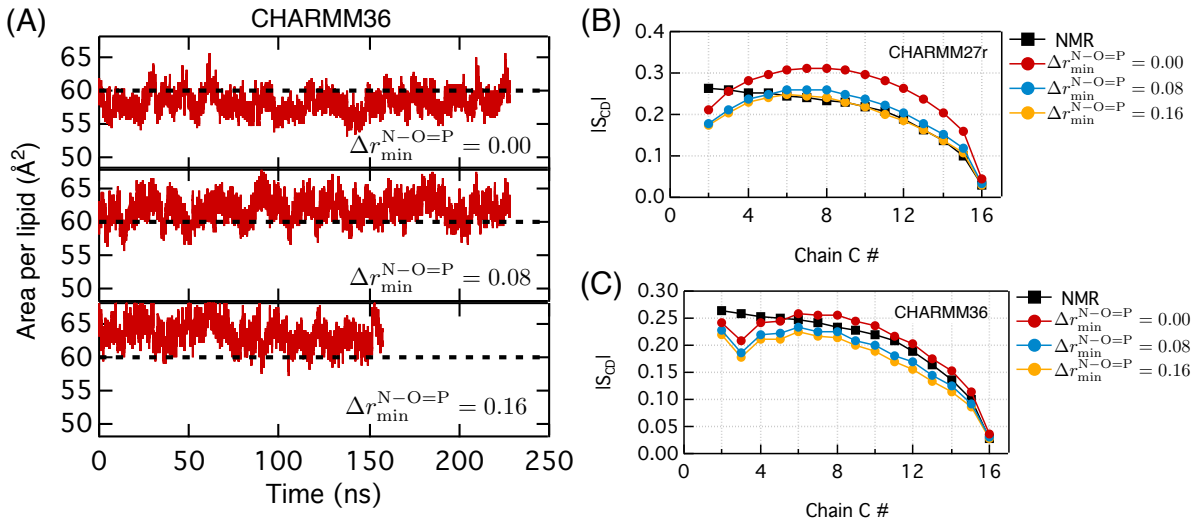

Figure S4: Simulated area per lipid (A) and deuterium order parameters, $|S_{\mathrm{CD}}|$, (B,C) of a POPE lipid bilayer at 30°C. (A) The simulated area per lipid as a function of simulation time computed using the CHARMM36 lipid parameter set for the following three values of $\Delta r_{\min}^{\mathrm{N-O=P}}$: 0.00, 0.08, and 0.16 Å; the $\Delta r_{\min}^{\mathrm{N-O=P}}$ correction was applied to the amine nitrogen–phosphate oxygen atom pairs. Experimental area per lipid is shown using dashed lines.[5] Similar data for the CHARMM27r parameter set are shown in Figure 8C of the main text. (B,C) The simulated deuterium order parameters of the POPE lipid tails obtained using the CHARMM27r (panel B) and CHARMM36 (panel C) lipid parameter sets. In panels B and C, data for the three values of $\Delta r_{\min}^{\mathrm{N-O=P}}$ (0.00, 0.08, 0.16 Å) are shown in red, blue, and orange, respectively. Experimental data (black) was taken from Ref. 6.

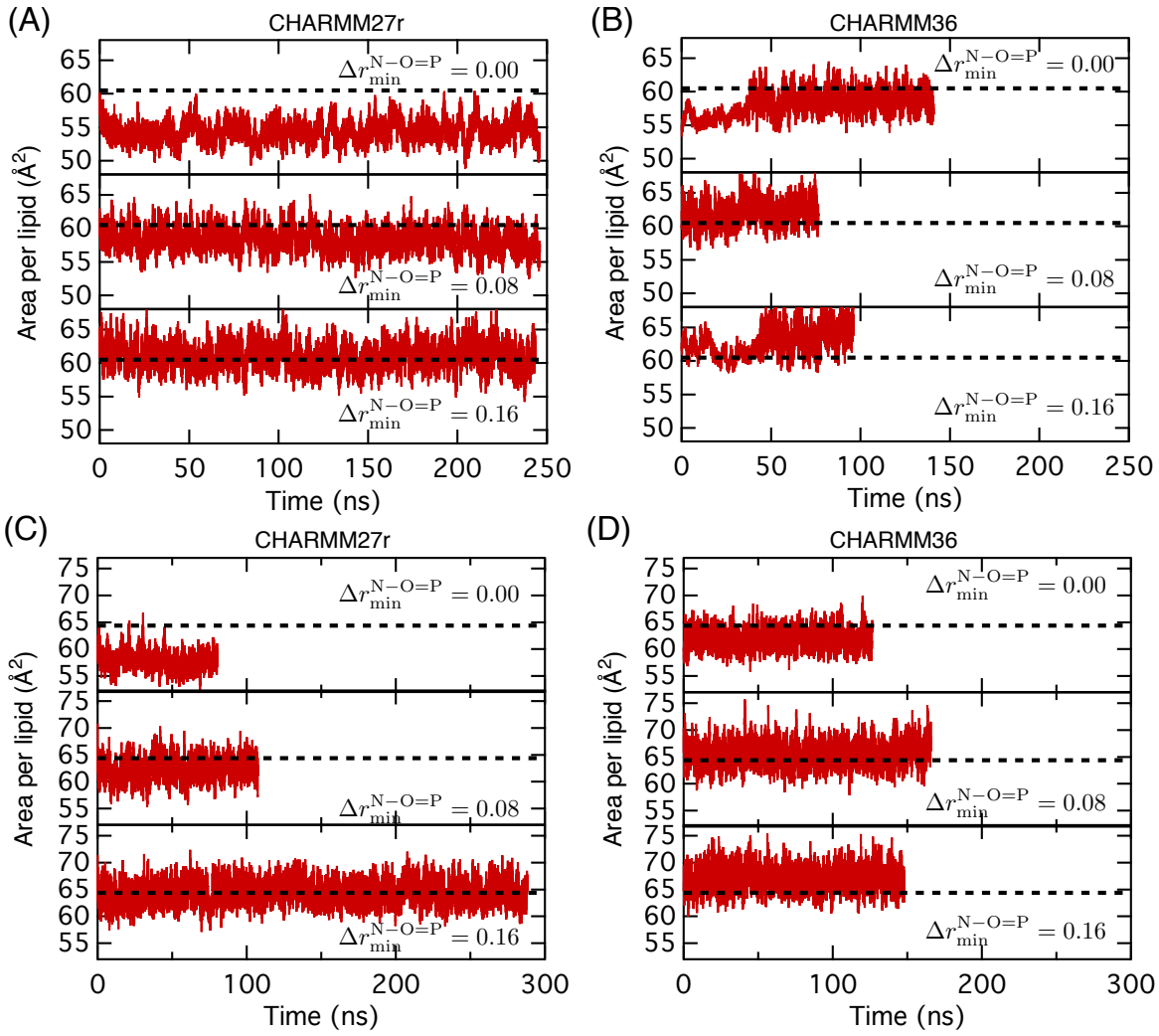

Figure S5: The simulated area per lipid of a DPPE bilayer as a function of simulation time computed using the CHARMM27r (panels A and C) and CHARMM36 (panels B and D) lipid parameter sets at 69°C (panels A and B) and 85°C (panels C and D) for the following three values of $\Delta r_{\mathrm{min}}^{\mathrm{N-O=P}}$: 0.00, 0.08, and 0.16 Å; the $\Delta r_{\mathrm{min}}^{\mathrm{N-O=P}}$ correction was applied to the amine nitrogen–phosphate oxygen atom pairs. Experimental area per lipid is shown using dashed lines.[7]

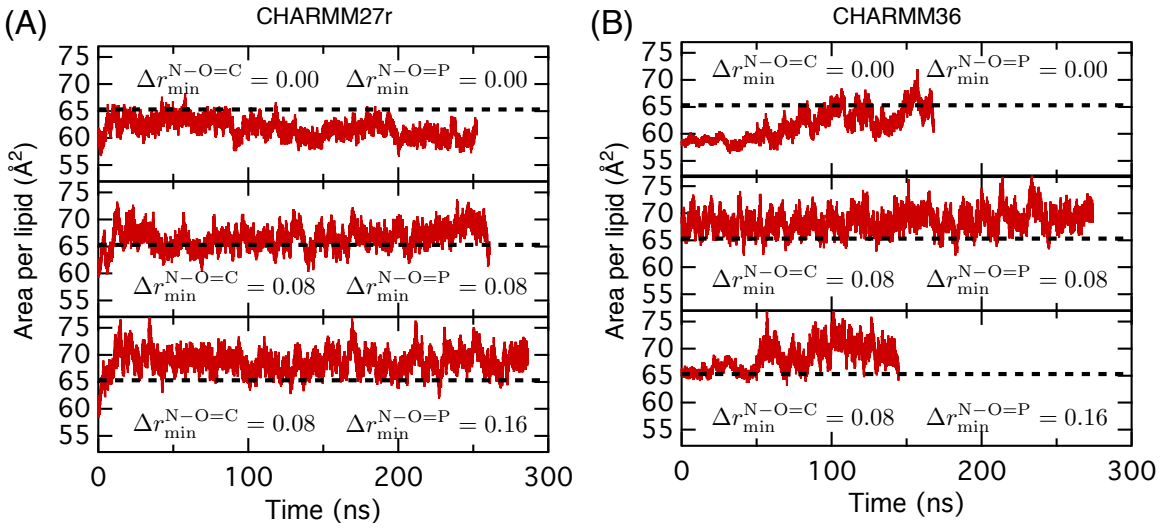

Figure S6: The simulated area per lipid of a DOPS bilayer as a function of simulation time computed using the CHARMM27r (panel A) and CHARMM36 (panel B) lipid parameter sets at 30°C for the following three values of $\Delta r_{\min}^{\mathrm{N-O=P}}$: 0.00, 0.08, and 0.16 Å. The non-zero $\Delta r_{\min}^{\mathrm{N-O=P}}$ correction was applied to the amine nitrogen–phosphate oxygen atom pairs simultaneously with the $\Delta r_{\min}^{\mathrm{N-O=C}} = 0.08$ Å correction applied to the amine nitrogen–carboxylate oxygen atom pairs. Experimental area per lipid is shown using dashed lines.[8]

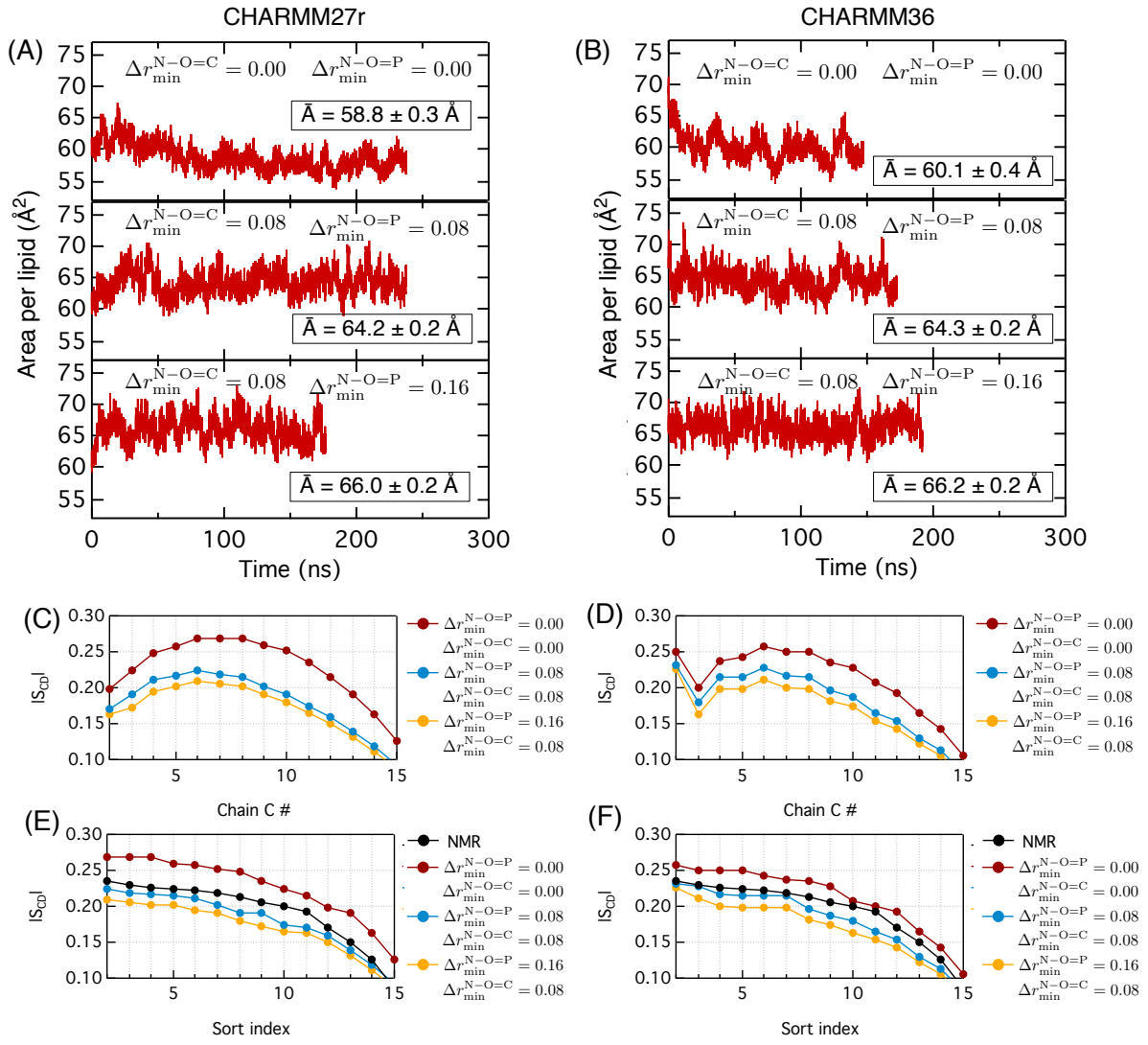

Figure S7: The simulated area per lipid and deuterium order parameters, $|S_{\mathrm{CD}}|$, of a POPS bilayer at 30°C. (A,B) The simulated area per lipid as a function of simulation time computed using the CHARMM27r (panel A) and CHARMM36 (panel B) lipid parameter sets for the following three values of $\Delta r_{\mathrm{min}}^{\mathrm{N-O=P}}$: 0.00, 0.08, and 0.16 Å. The average value of the area per lipid ($\bar{A}$) for each simulation condition is given in the corresponding panel. (C–F) The simulated deuterium order parameters of the lipid tails obtained using the CHARMM27r (panels C and D) and CHARMM36 (panels E and F) lipid parameter sets. Data for the three values of $\Delta r_{\mathrm{min}}^{\mathrm{N-O=P}}$ (0.00, 0.08, 0.16 Å) are shown in red, blue, and orange, respectively. Note that the carbon index in (E,F) is sorted by the magnitude of $|S_{\mathrm{CD}}|$ for direct comparison with the experimental data (black).[6] For panels A–D, no experimental data were found. In all simulations described in this figure, the non-zero $\Delta r_{\mathrm{min}}^{\mathrm{N-O=P}}$ correction was applied to the amine nitrogen–phosphate oxygen atom pairs simultaneously with the $\Delta r_{\mathrm{min}}^{\mathrm{N-O=C}} = 0.08$ Å correction applied to the amine nitrogen–carboxylate oxygen atom pairs.

References

(1) Tsurko, E.; Neueder, R.; Kunz, W. *J. Solut. Chem.* **2007**, *36*, 651–672.

(2) Robinson, R. A.; Stokes, R. H. *Electrolyte Solutions*; Butterworths scientific publications, 1959.

(3) DeRouchey, J.; Hoover, B.; Rau, D. C. *Biochemistry* **2013**, *52*, 3000–3009.

(4) Rau, D. C.; Lee, B.; Parsegian, V. A. *Proc. Natl. Acad. Sci. U.S.A.* **1984**, *81*, 2621–2625.

(5) Klauda, J. B.; Venable, R. M.; Freites, J. A.; O'Connor, J. W.; Tobias, D. J.; Mondragon-Ramirez, C.; Vorobyov, I.; MacKerell, Jr., A. D.; Pastor, R. W. *J. Phys. Chem. B* **2010**, *114*, 7830–7843.

(6) Shaikh, S. R.; Brzustowicz, M. R.; Gustafson, N.; Stillwell, W.; Wassall, S. R. *Biochemistry* **2002**, *41*, 10593–10602.

(7) Petrache, H. I.; Dodd, S. W.; Brown, M. F. *Biophys. J.* **2000**, *79*, 3172–92.

(8) Petrache, H. I.; Tristram-Nagle, S.; Gawrisch, K.; Harries, D.; Parsegian, V. A.; Nagle, J. F. Structure and Fluctuations of Charged Phosphatidylserine Bilayers in the Absence of Salt. 2004.