Supporting Information for

Interactions between Ionizable Amino Acid Side Chains at a Lipid Bilayer-Water Interface

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The PMFs for side chains in water and lipid bilayer were determined using CHARMM27 force field[52,53]. Simulations were performed using NAMD[51]. To calculate the PMFs we employed the ABF method[41,42,72]. Dynamics was performed in NPAT ensemble.[57] Smooth particle mesh Ewald[61] was used to treat electrostatic interactions. No counterions were included, instead the net charge of the systems simulated was handled by the neutralizing plazma employed in PME method (see Methods). A cutoff of 10.5 Å was used for Lennard-Jones and electrostatics interactions with smoothing functions activated at 8.5 Å.

This document contains additional PMFs and analysis plots. The latter include a) average number of hydrogen bonds between the two side chains and with water and headgroups, b) average interaction energies between the two side chains and with water and headgroups as well as their LJ component and c) relative interaction energies, i.e. interaction energies relative to those at the farthest distance between the side chains. This allows the direct comparison of energetic contributions to the PMF between different orientation and pairs.

Hydrogen bonds were calculated from the ABF trajectories using sets of Tcl scripting commands available in NAMD with the distance between donor and acceptor set to 3 Å and the angle between donor, hydrogen and acceptor <60 º. Total interaction energies and Lennard-Jones energies were calculated using NAMDEnergy plug-in of VMD. Selections of atoms included side chains, water molecules and head groups of the POPC. Numbers of H-bonds and values of energies were averaged over the trajectory. The X-axis corresponds to the distance between selected atoms of the side chains and which are specified in the H-bonds figure captions. These atoms are the same as the reaction coordinates selected for PMF calculation.

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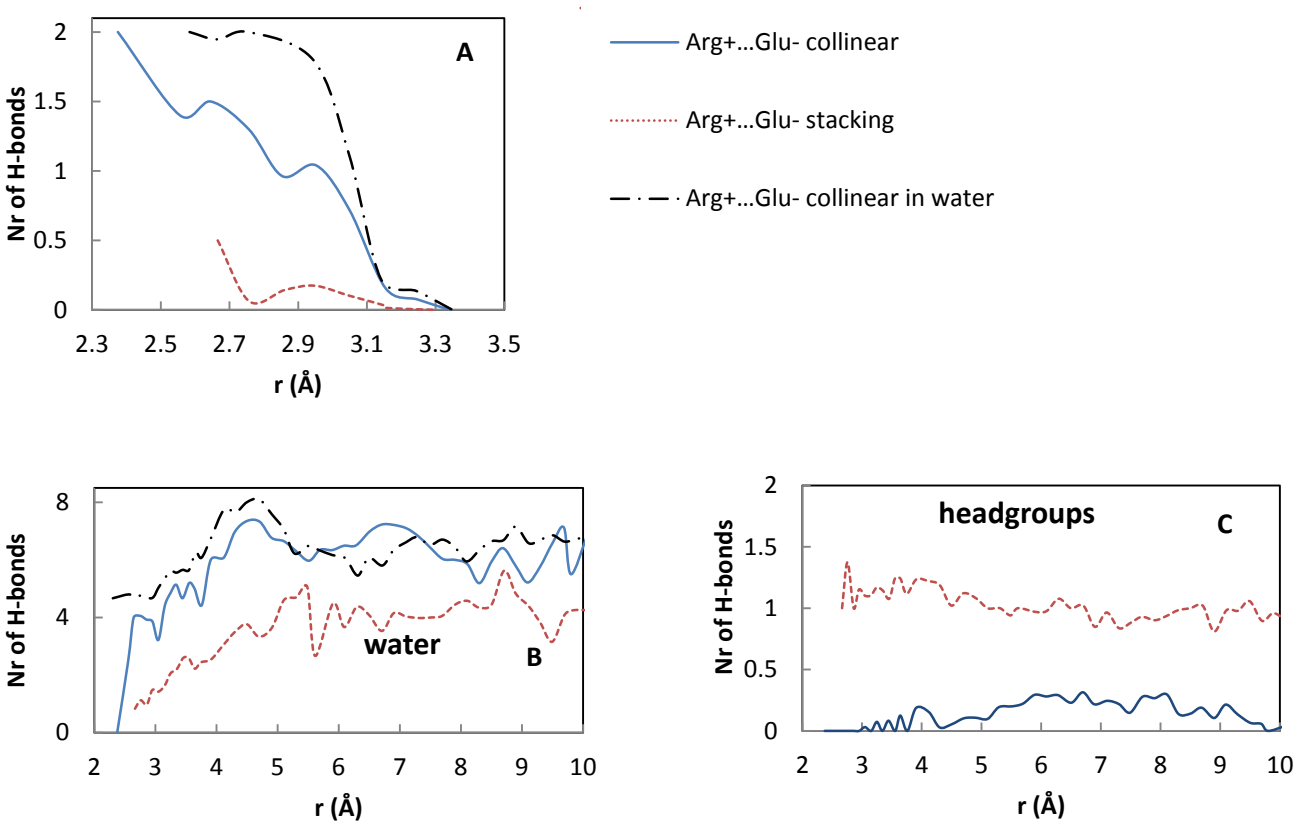

Figure S1. H-bonds between Arg and Glu (A), side chains and water (B) and side chains and headgroups (C). *r* is the distance between COM of NH atoms of Arg and OE atoms of Glu.

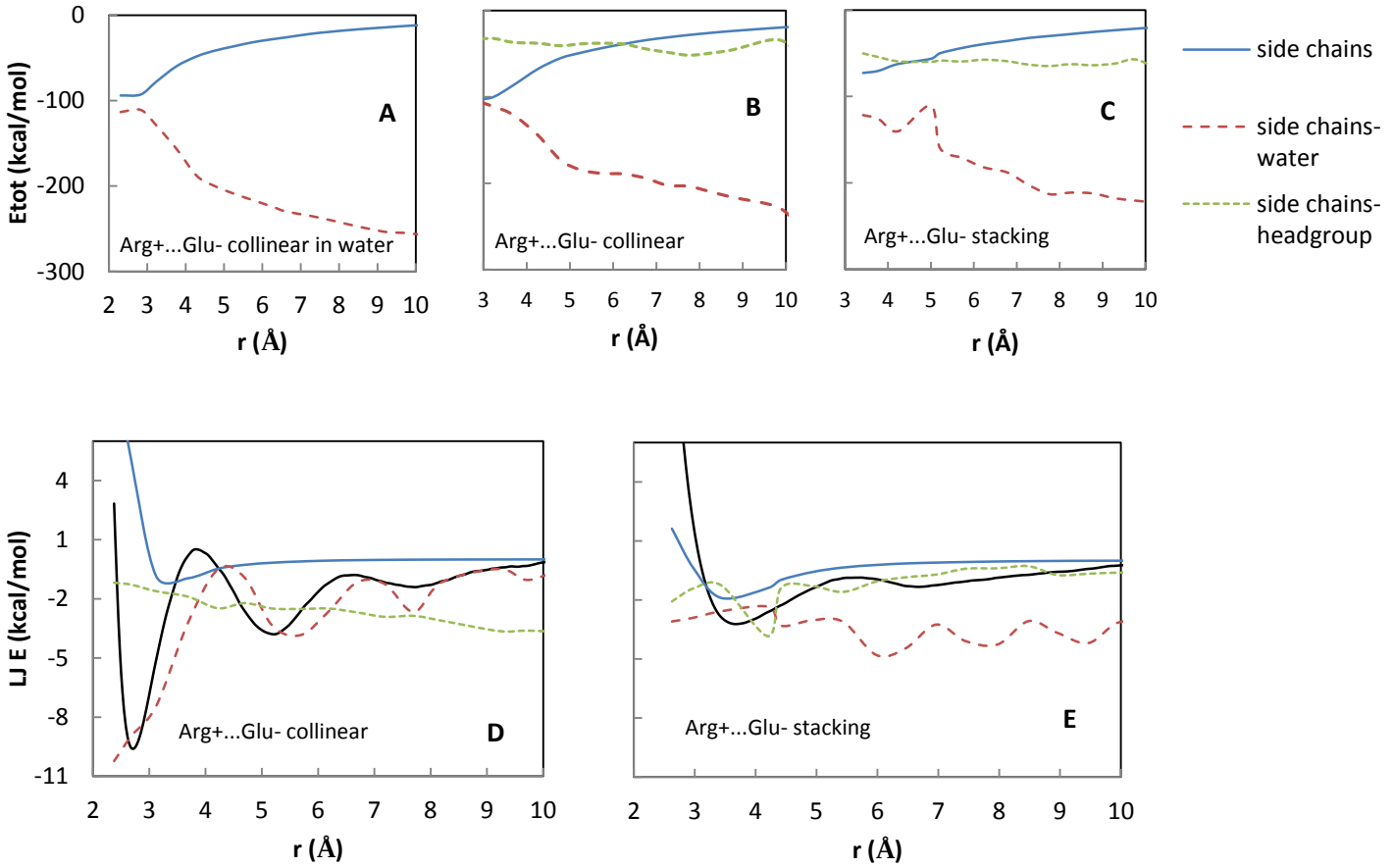

Figure S2. Total interaction energy (A-C) and Lennard-Jones energy (D, E) between the two side chains, side chains and headgroups, side chains and water obtained from ABF simulation trajectories in water (A) and POPC (B-E). PMFs (black) are shown for comparison.

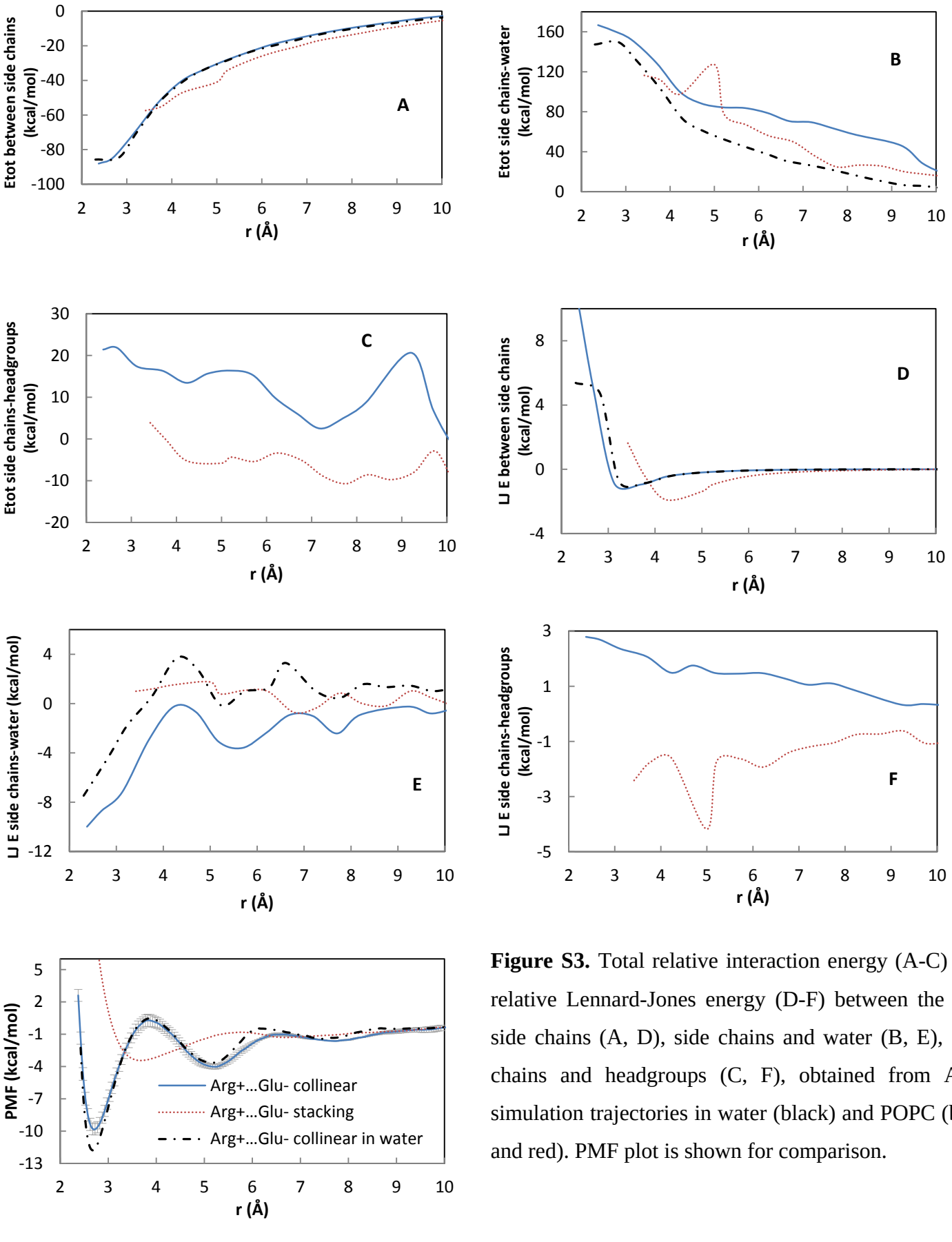

Figure S3. Total relative interaction energy (A-C) and relative Lennard-Jones energy (D-F) between the two side chains (A, D), side chains and water (B, E), side chains and headgroups (C, F), obtained from ABF simulation trajectories in water (black) and POPC (blue and red). PMF plot is shown for comparison.

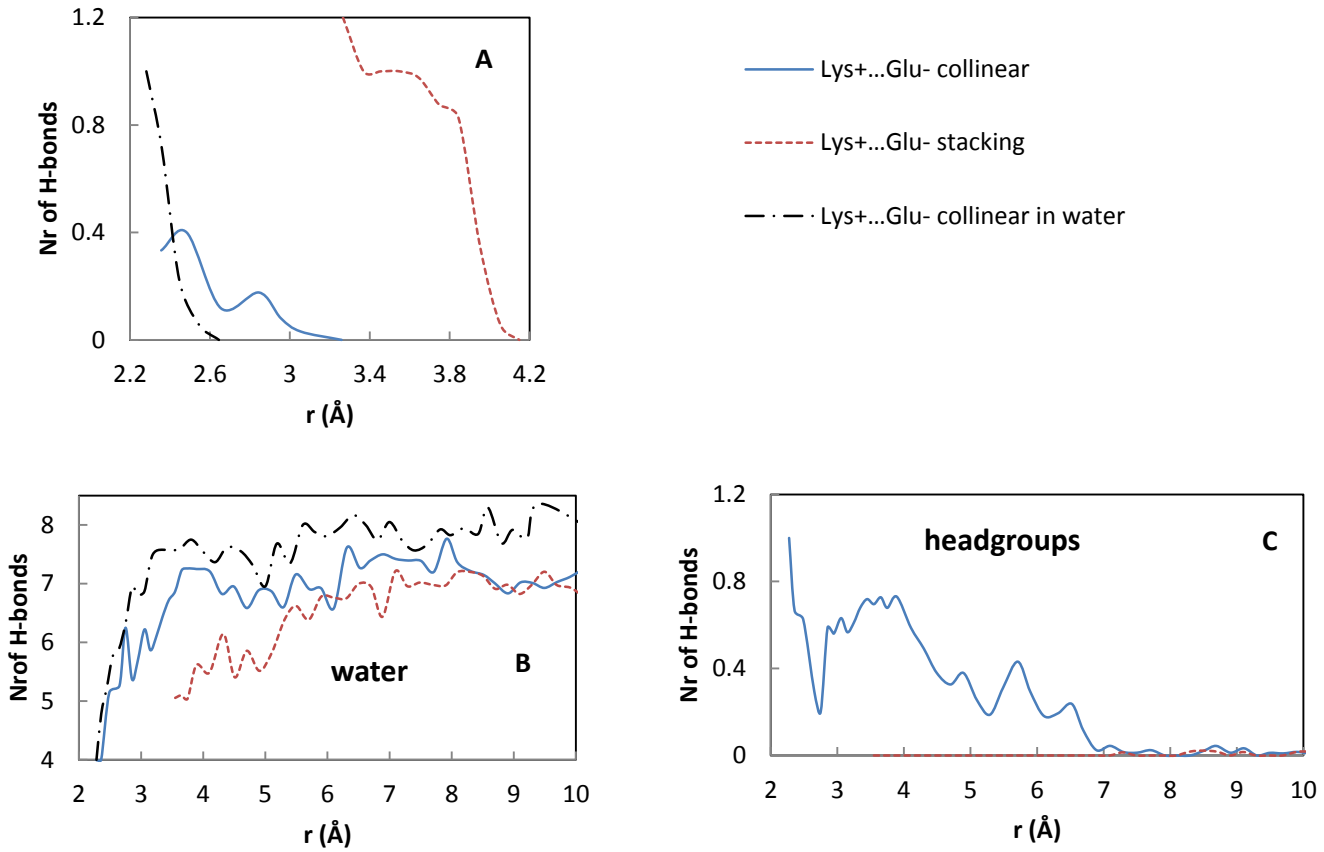

Figure S4. H-bonds between Lys and Glu (A), side chains and water (B) and side chains and headgroups (C). *r* is the distance between: COM of OE atoms of Glu and NZ atoms of Lys and OE atom and NZ atom for collinear and stacking pairs, respectively.

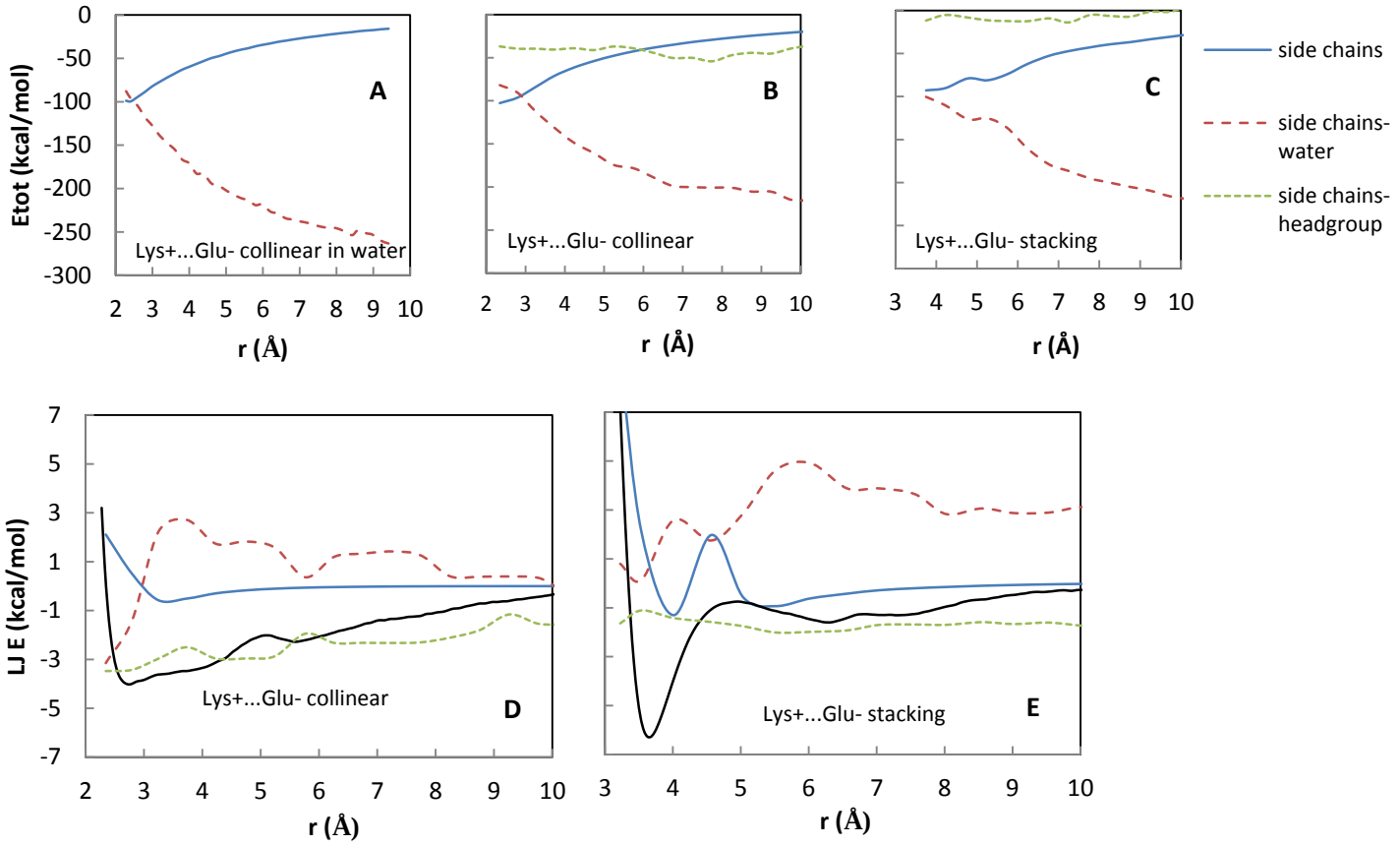

Figure S5. Total interaction energy (A-C) and Lennard-Jones energy (D,E) between the H-bonded Lys and Glu side chains, residues and headgroups, residues and water obtained from ABF simulation trajectories in water (A) and POPC (B-E). PMFs (black) are shown for comparison.

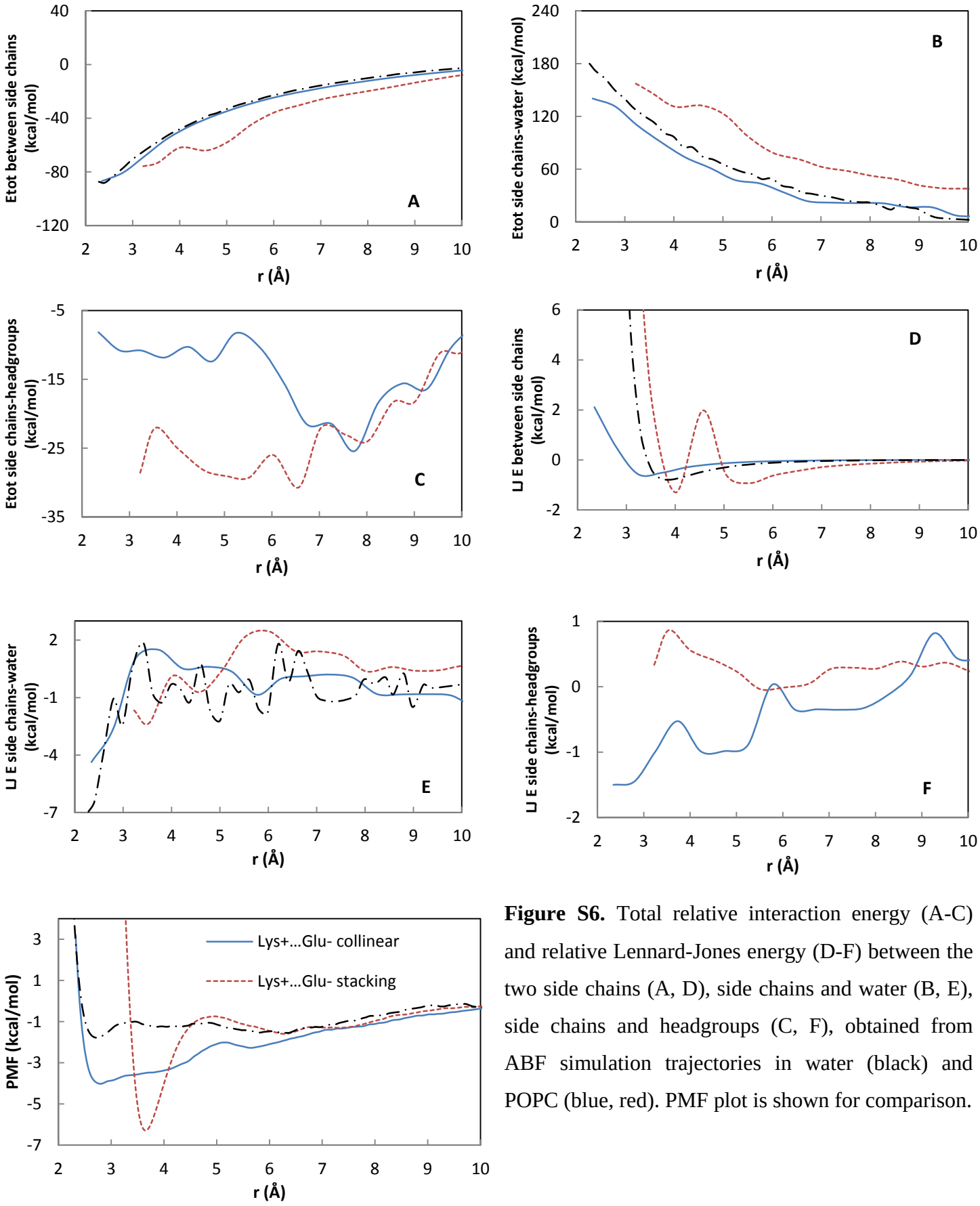

Figure S6. Total relative interaction energy (A-C) and relative Lennard-Jones energy (D-F) between the two side chains (A, D), side chains and water (B, E), side chains and headgroups (C, F), obtained from ABF simulation trajectories in water (black) and POPC (blue, red). PMF plot is shown for comparison.

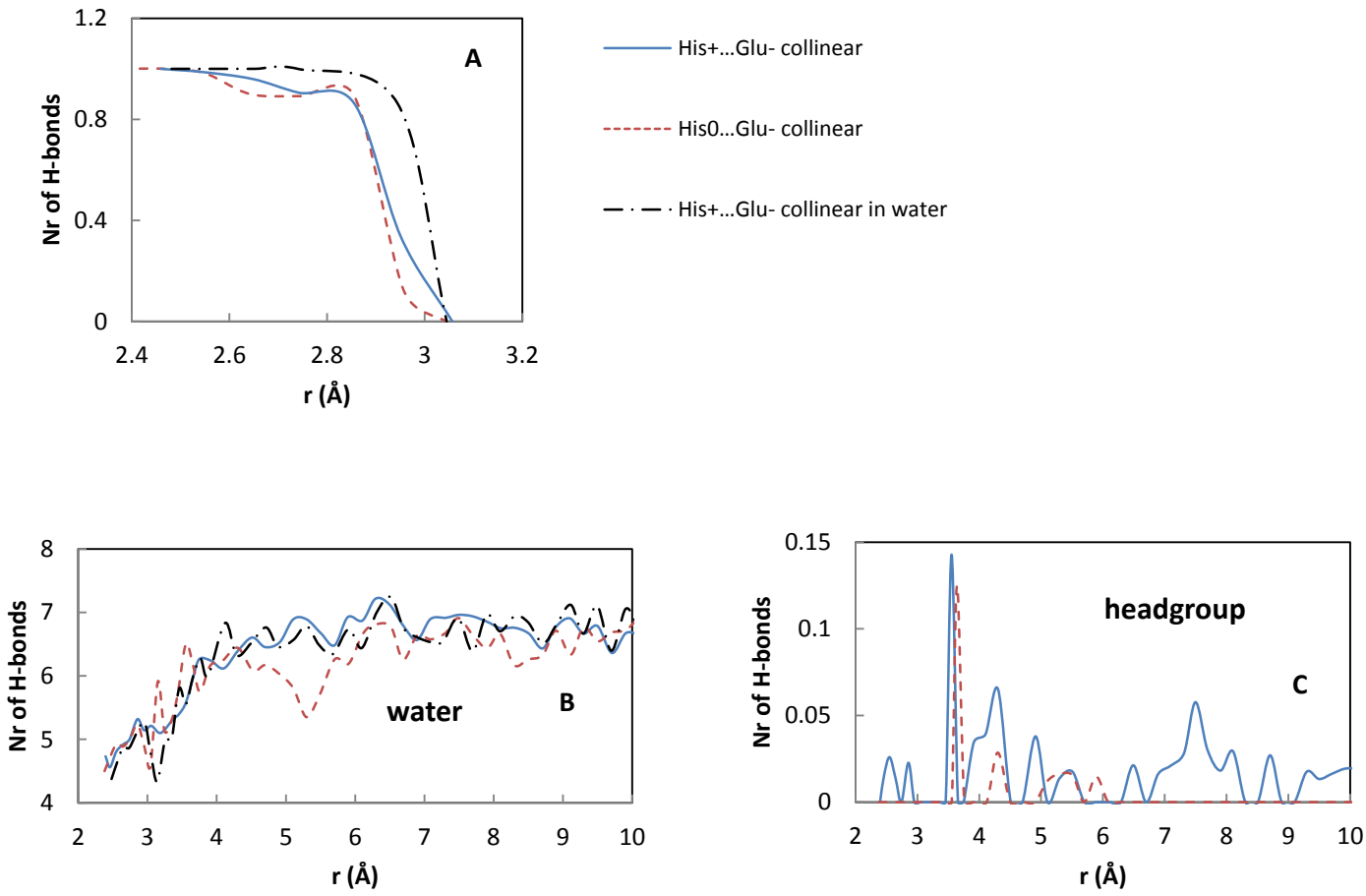

Figure S7. H-bonds between His and Glu (A), side chains and water (B) and side chains and headgroups (S). *r* is the distance between ND atom of His and OE2 of Glu.

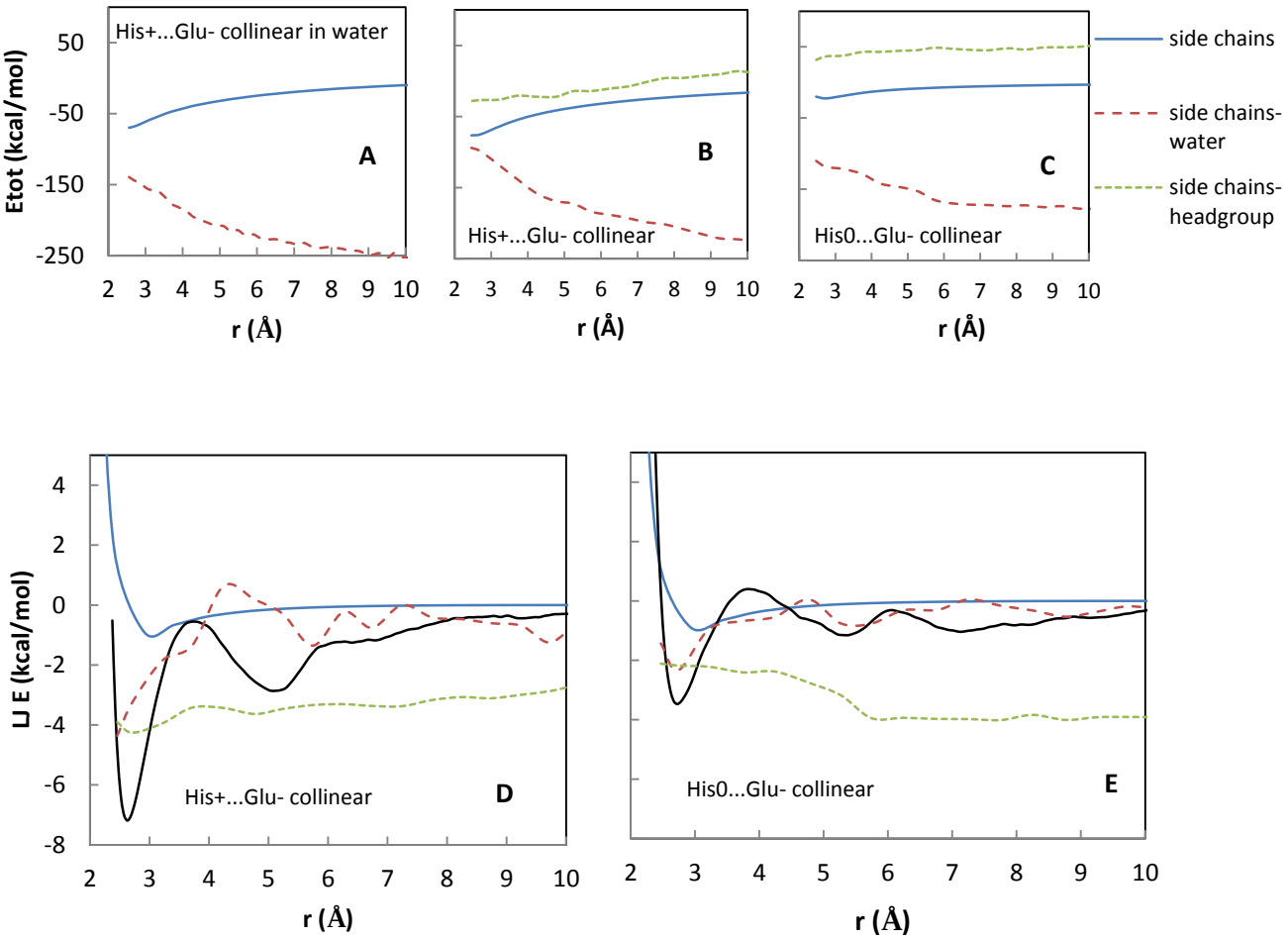

Figure S8. Total interaction energy (A-C) and Lennard-Jones energy (D, E) between the H-bonded His and Glu side chains, residues and headgroups, residues and water obtained from ABF simulation trajectories in water (A) and POPC (B-E). PMFs (black) are shown for comparison.

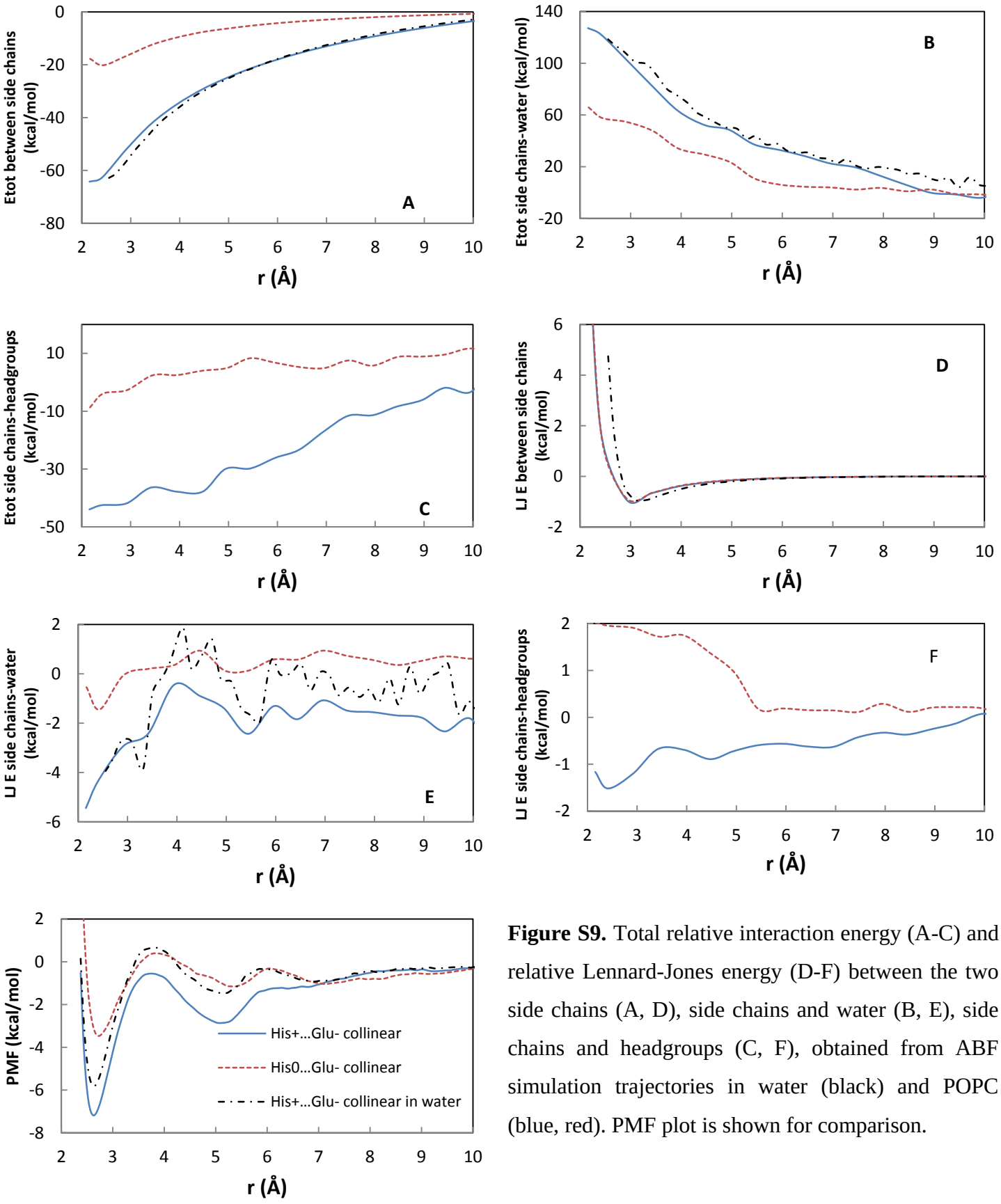

Figure S9. Total relative interaction energy (A-C) and relative Lennard-Jones energy (D-F) between the two side chains (A, D), side chains and water (B, E), side chains and headgroups (C, F), obtained from ABF simulation trajectories in water (black) and POPC (blue, red). PMF plot is shown for comparison.

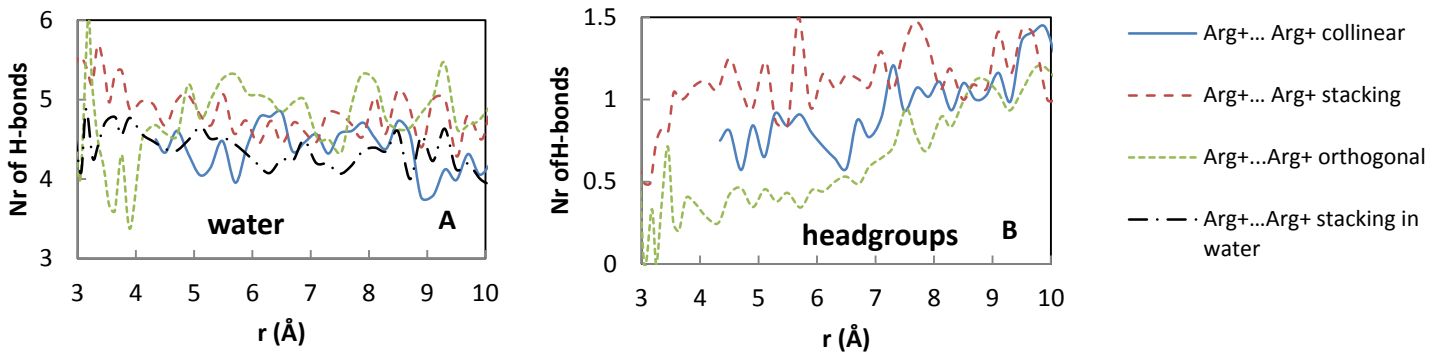

Figure S10. H-bonds between Arg side chains and water (A), Arg side chains and headgroups (B). *r* is the distance between COM of NH atoms of two Arg residues. H-bonds with water at long distance vary due to the different orientation of side chains with respect to the membrane.

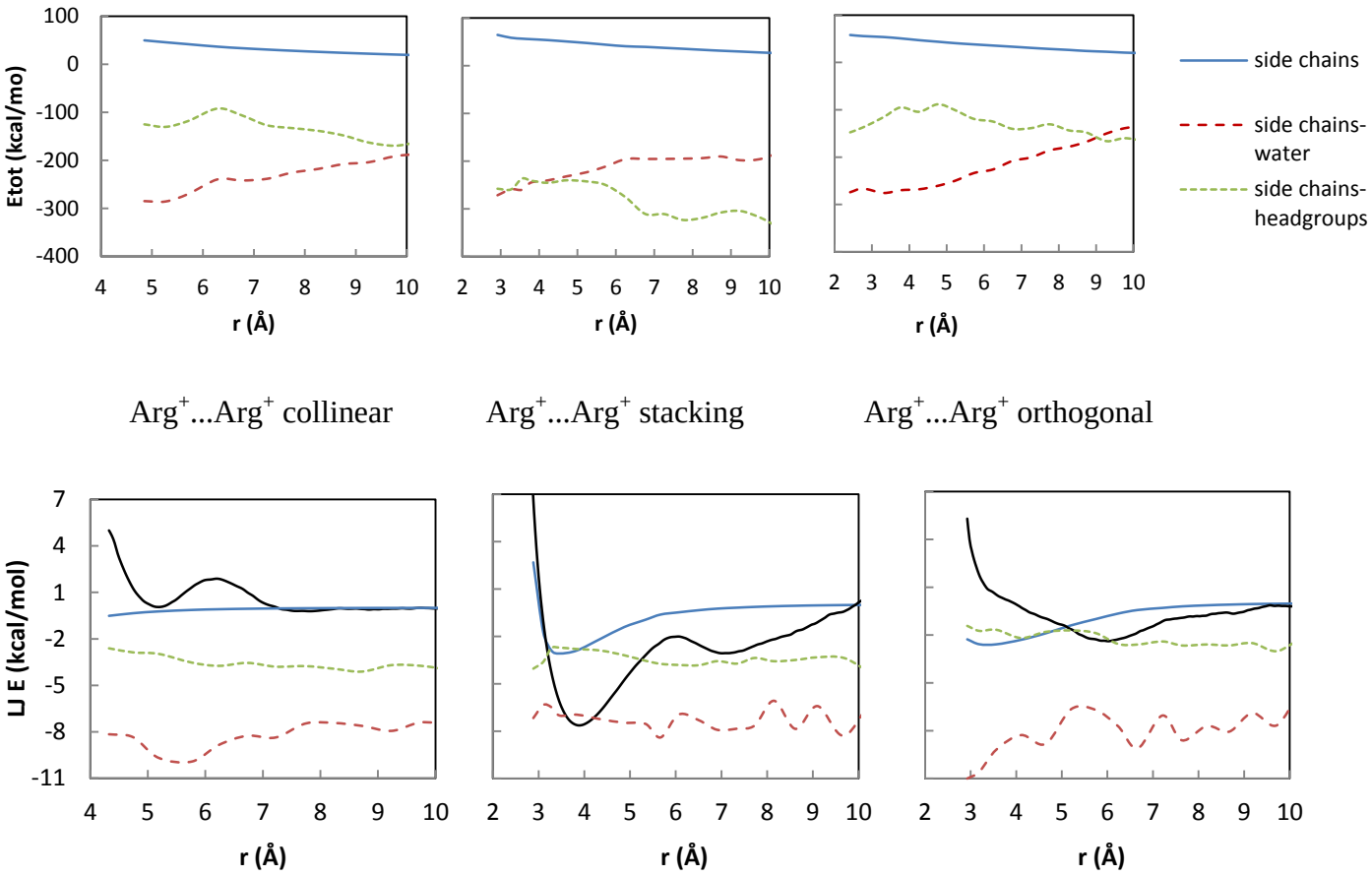

Figure S11. Total interaction energy (top) and Lennard-Jones energy (bottom) between the like-charged Arg side chains, side chains and headgroups, side chains and water obtained from ABF simulation trajectories. PMFs (black) are shown for comparison.

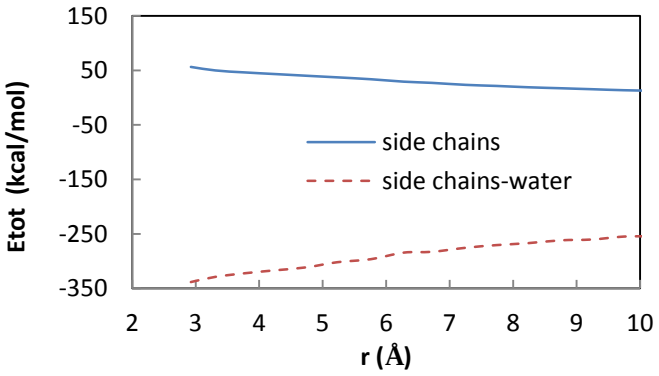

Figure S12. Total interaction energy between the two stacking Arg^+ side chains, side chains and water obtained from ABF simulation trajectories in water box.

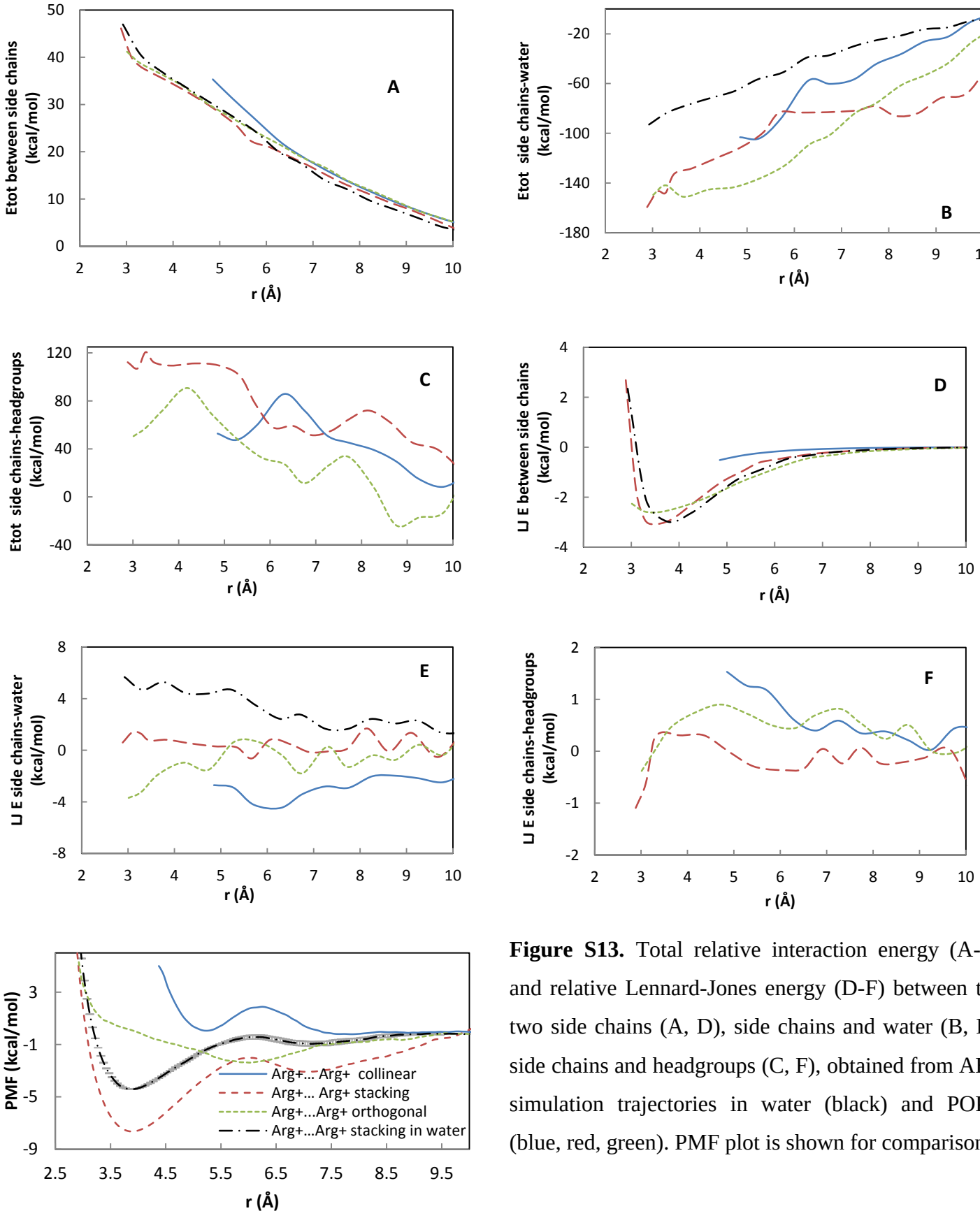

Figure S13. Total relative interaction energy (A-C) and relative Lennard-Jones energy (D-F) between the two side chains (A, D), side chains and water (B, E), side chains and headgroups (C, F), obtained from ABF simulation trajectories in water (black) and POPC (blue, red, green). PMF plot is shown for comparison.

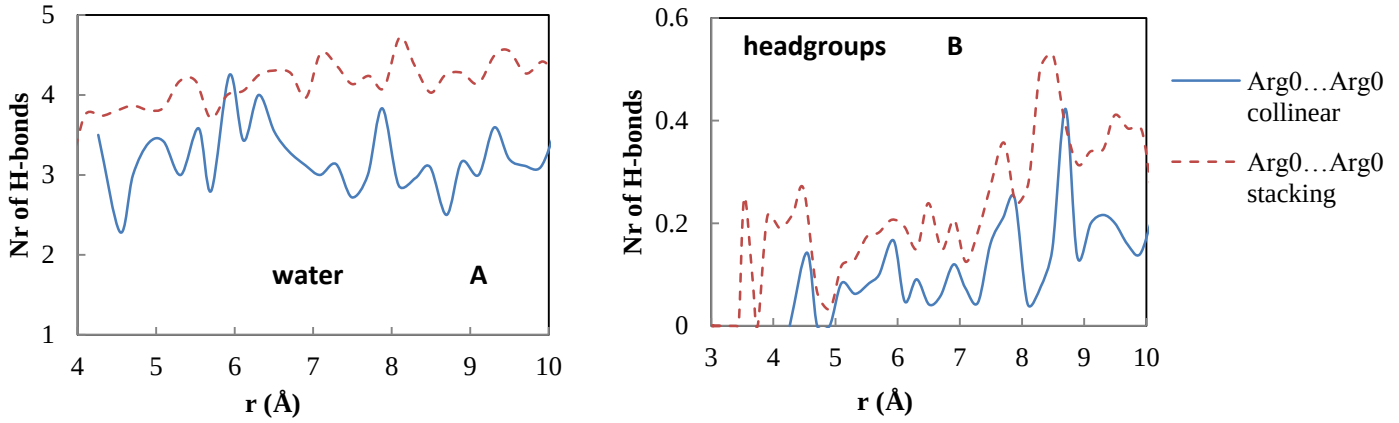

Figure S14. H-bonds between Arg side chains and water (A), side chains and headgroups (B). *r* is the distance between COM of NH atoms of two Arg residues.

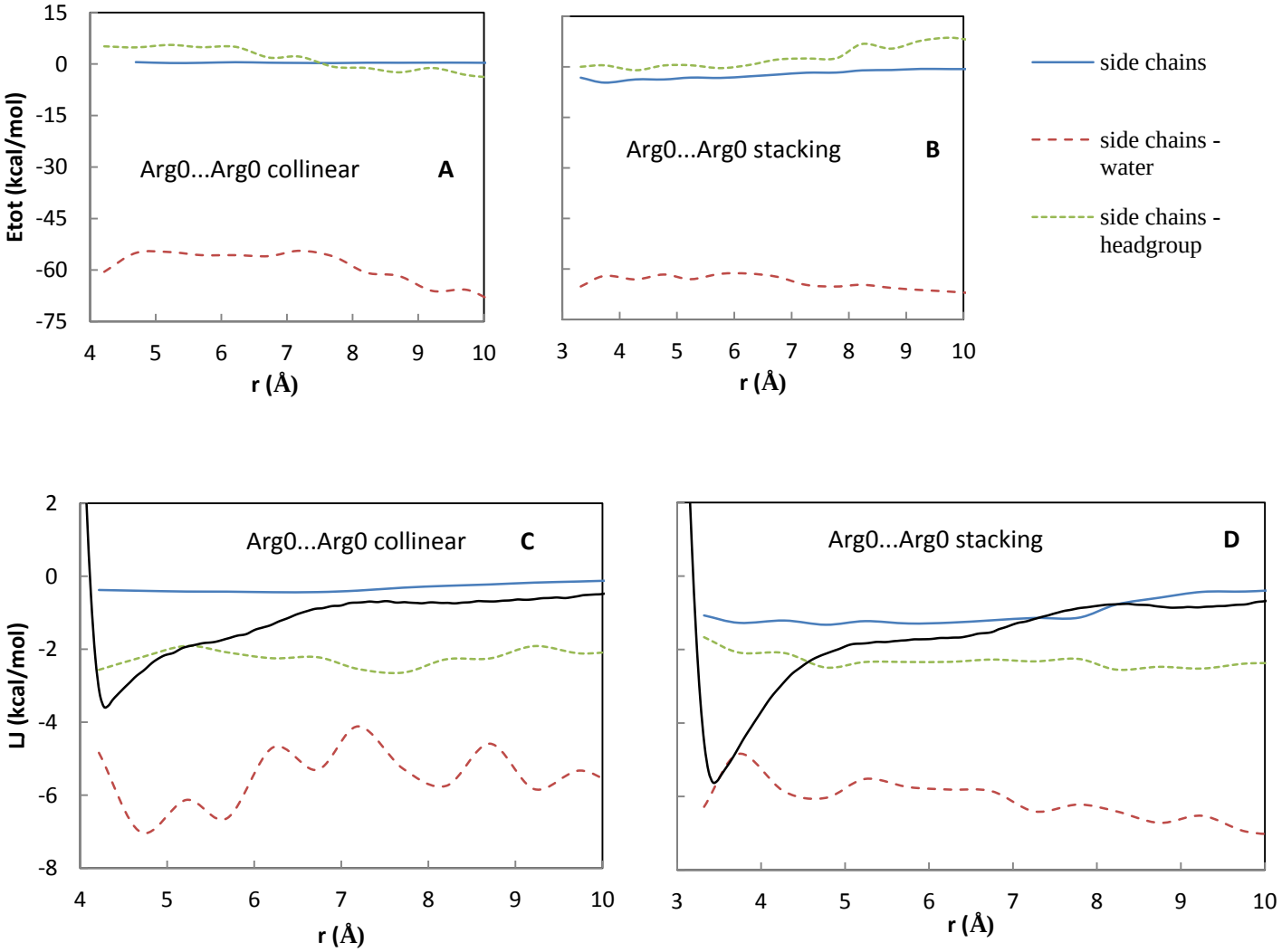

Figure S15. Total interaction energy (top) and Lennard-Jones energy (bottom) between the neutral Arg side chains, side chains and headgroups, side chains and water obtained from ABF simulation trajectories. PMFs (black) are shown for comparison

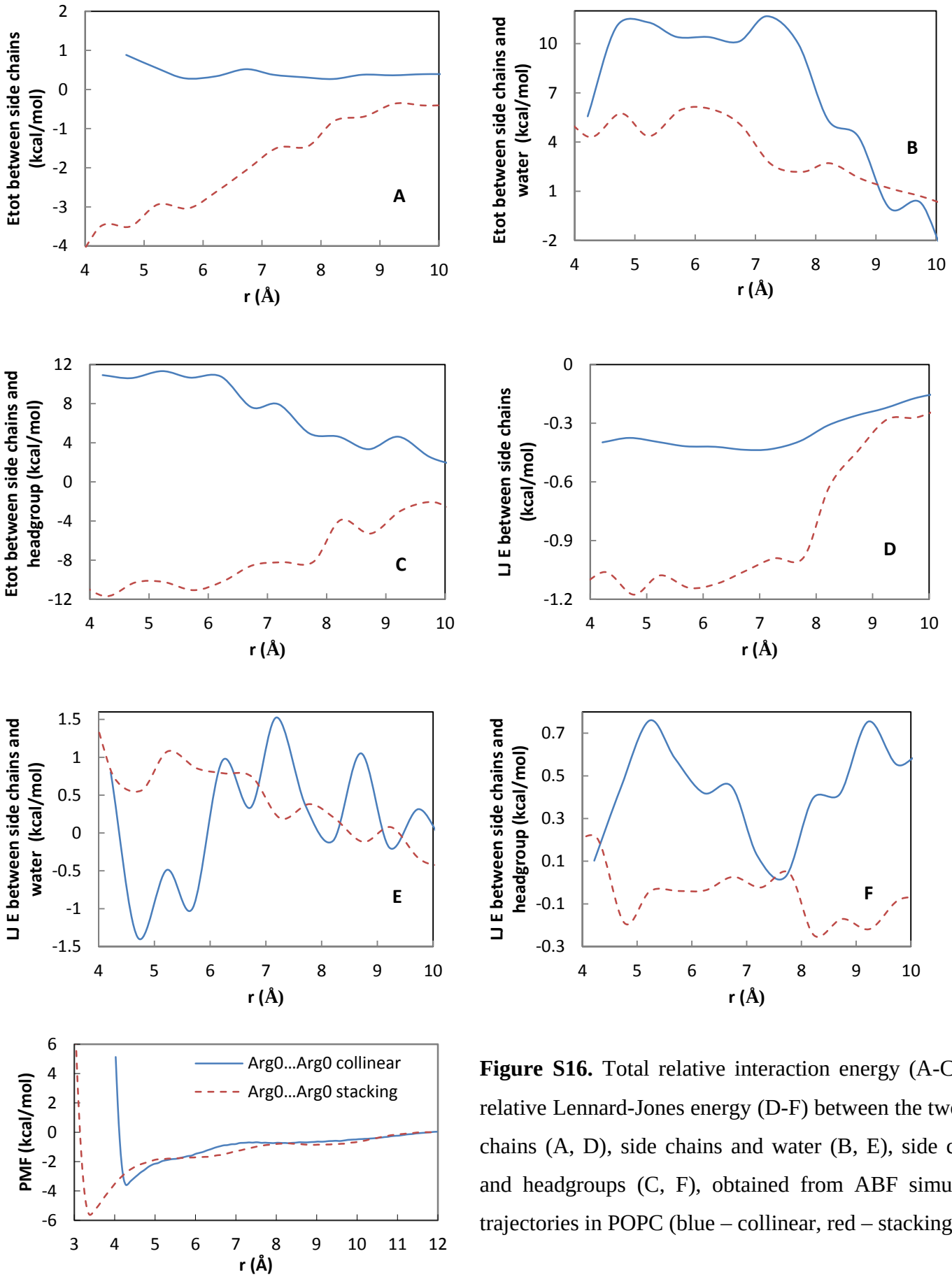

Figure S16. Total relative interaction energy (A-C) and relative Lennard-Jones energy (D-F) between the two side chains (A, D), side chains and water (B, E), side chains and headgroups (C, F), obtained from ABF simulation trajectories in POPC (blue – collinear, red – stacking).

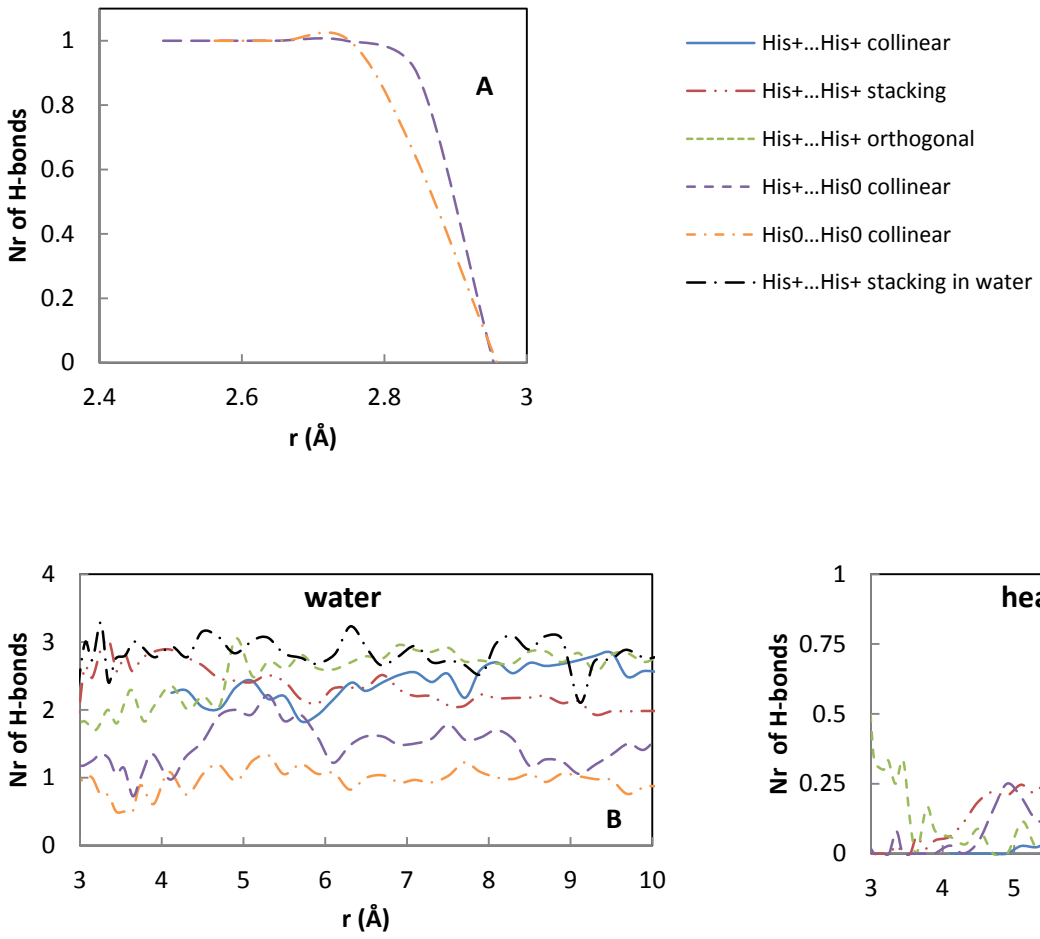

Figure S17. H-bonds between residues (A), side chains and water (B), side chains and headgroups (C). *r* is the distance between: collinear, His^{+}...His^{0} and His^{0}...His^{0} - ND atoms of His; stacking – COM of the ring; orthogonal - NE and ND atoms of His.

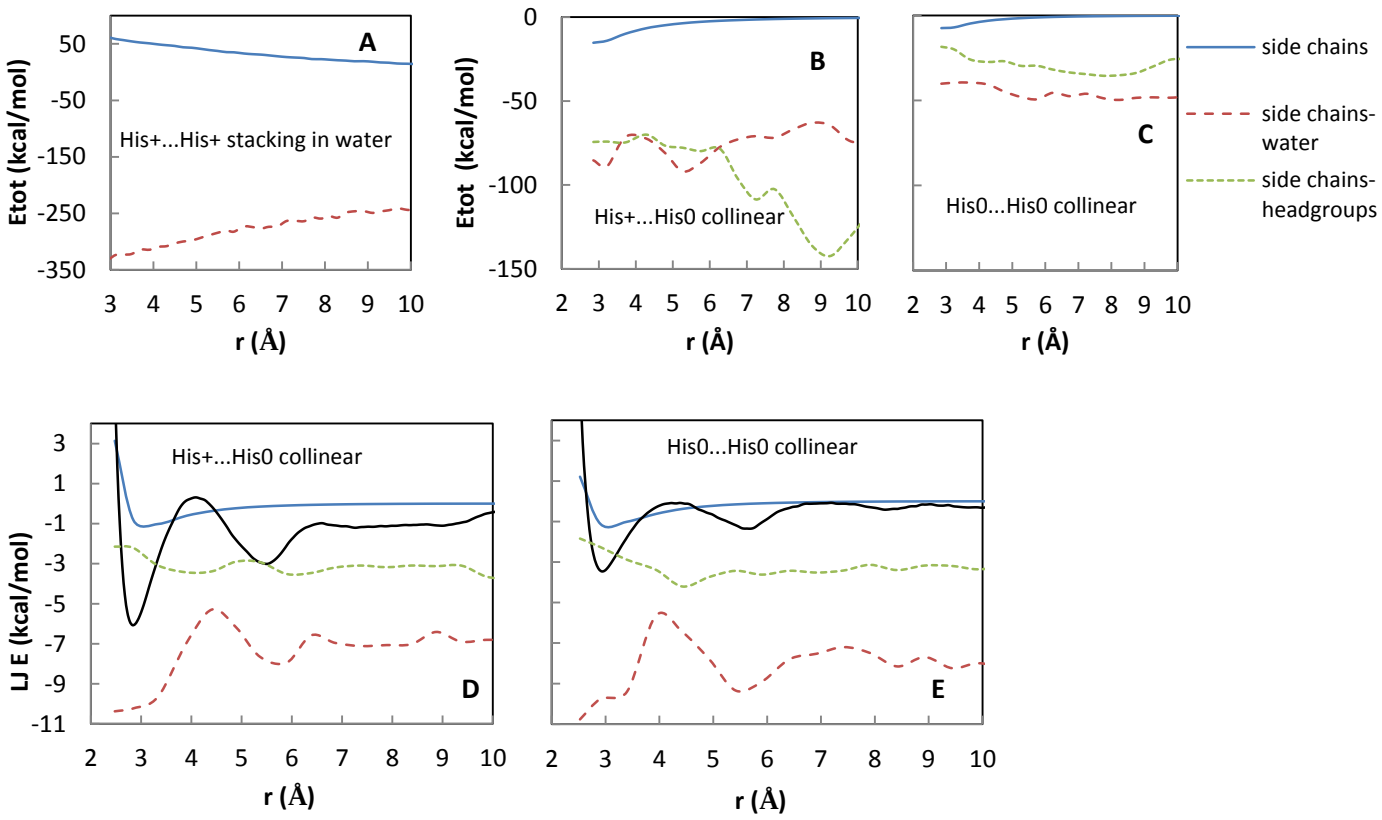

Figure S18. Total interaction energy (A-C) and Lennard-Jones energy (D, E) between the H-bonded His side chains, residues and headgroups, residues and water obtained from ABF simulation trajectories in water (A) and POPC (B-E). PMFs (black) are shown for comparison. For A, *r* is the distance between COM of the His ring; for B-E *r* is the distance between ND atoms of His.

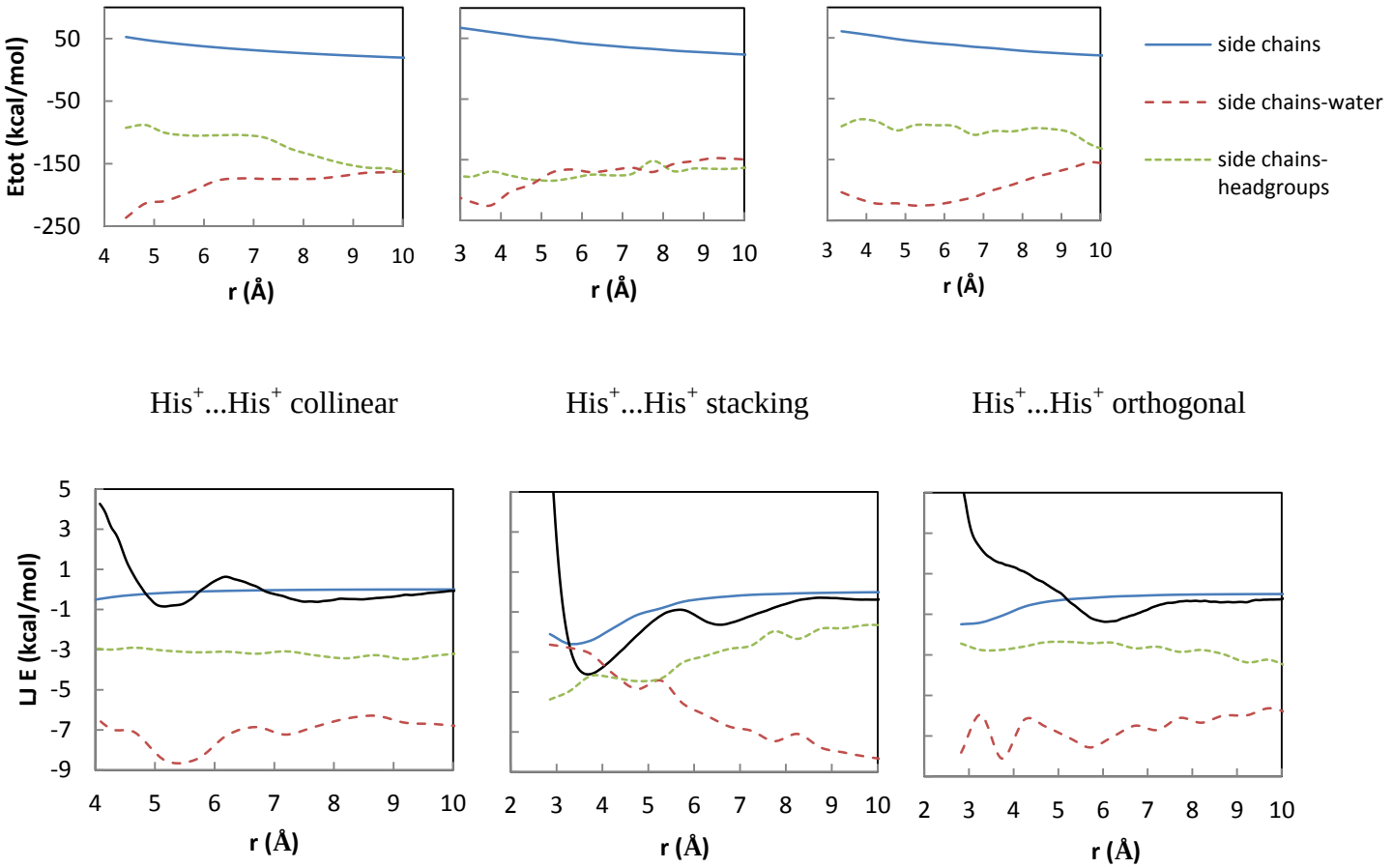

Figure S19. Total interaction energy (top) and Lennard-Jones energy (bottom) between the like-charged His side chains, residues and headgroups, residues and water obtained from ABF simulation trajectories. PMFs (black) are shown for comparison. *r* is the distance between: collinear - ND atoms of His; stacking – COM of the ring; orthogonal - NE and ND atoms of His.

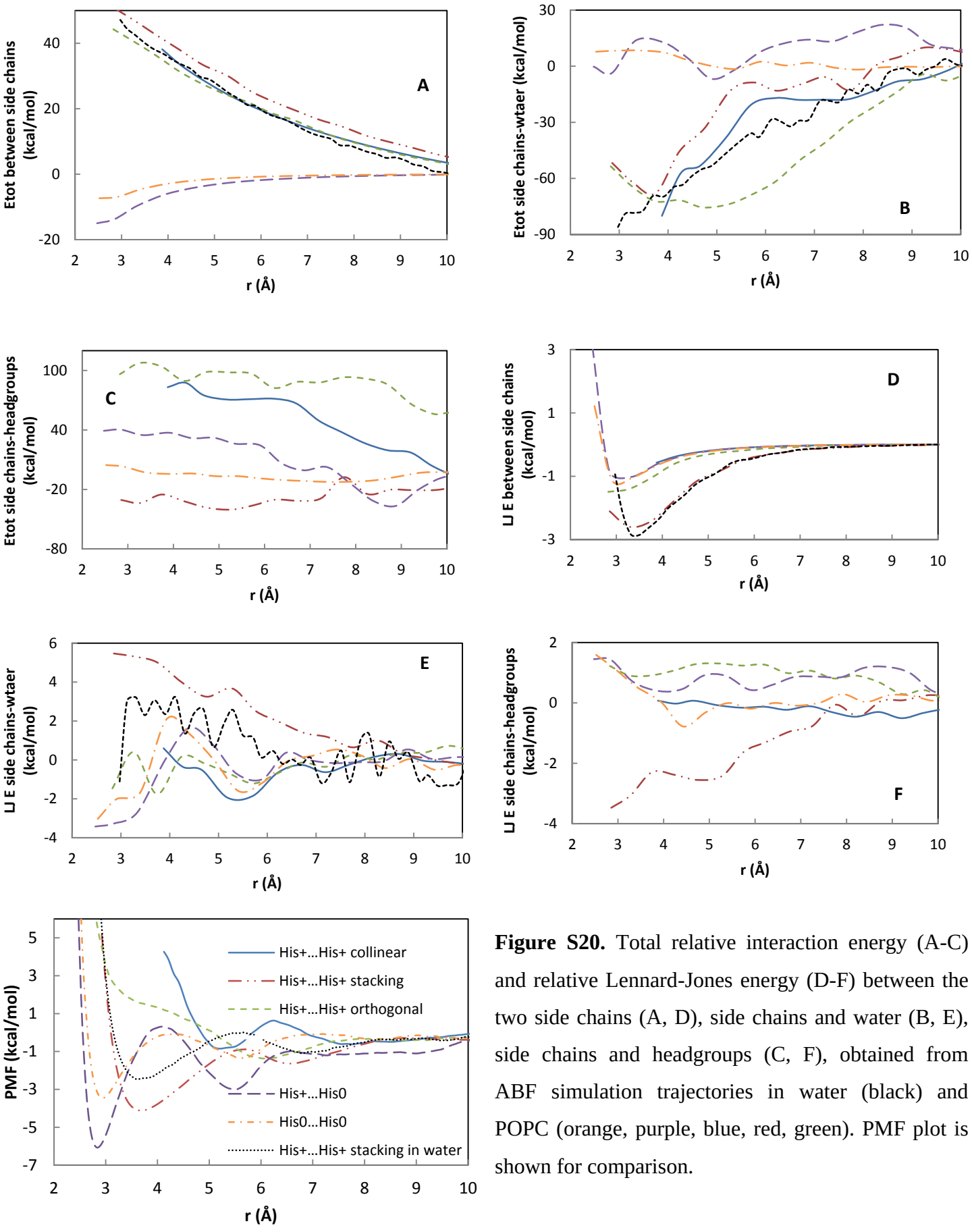

Figure S20. Total relative interaction energy (A-C) and relative Lennard-Jones energy (D-F) between the two side chains (A, D), side chains and water (B, E), side chains and headgroups (C, F), obtained from ABF simulation trajectories in water (black) and POPC (orange, purple, blue, red, green). PMF plot is shown for comparison.

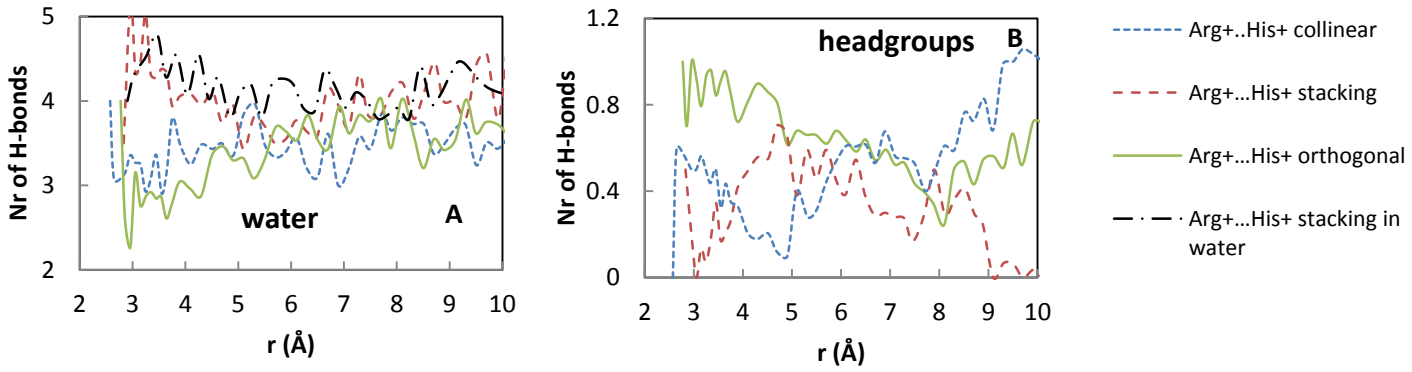

Figure S21. H-bonds between side chains and water (A), side chains and headgroups (B). *r* is the distance between COM of NH atoms of Arg and COM of His ring.

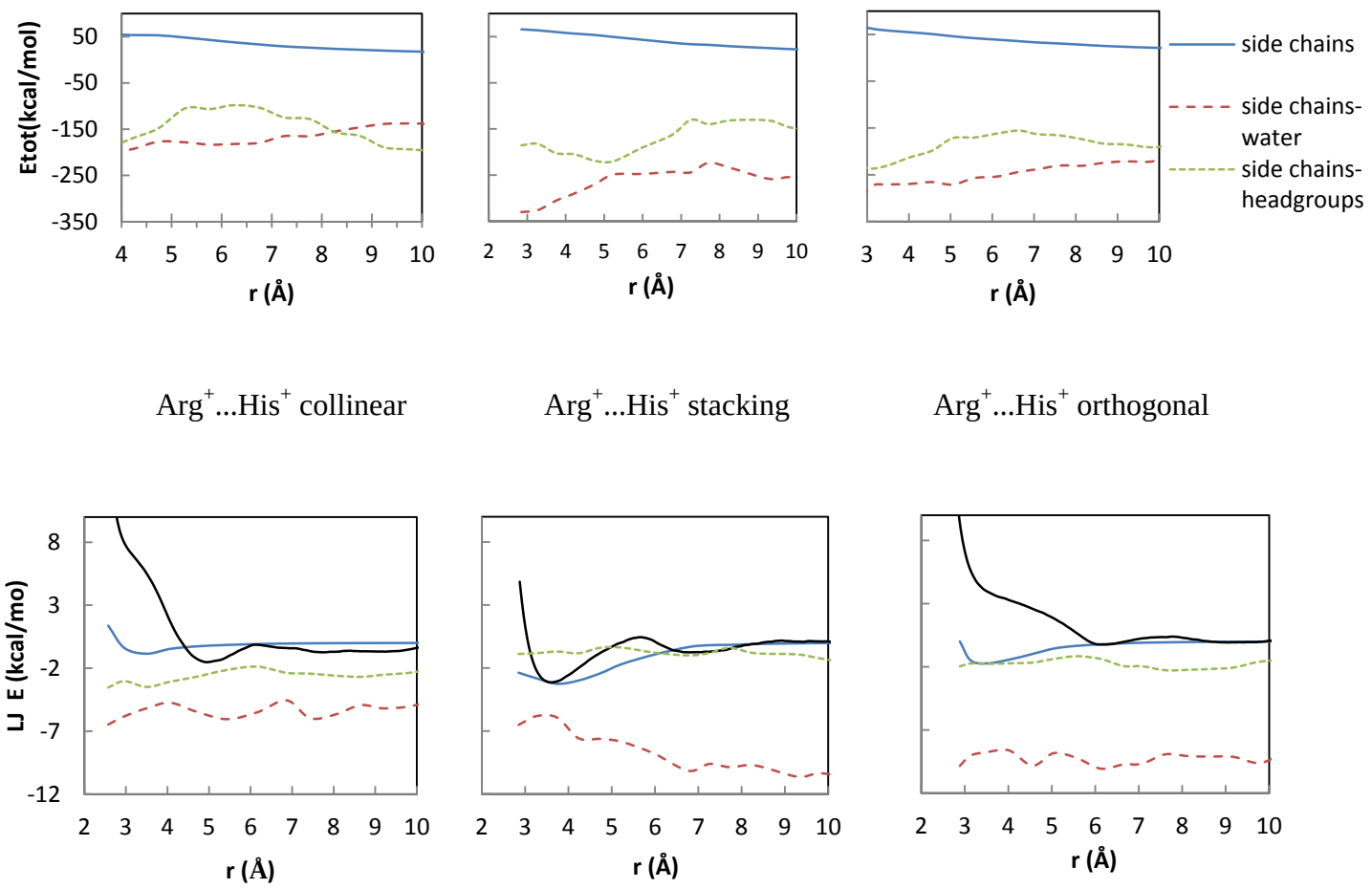

Figure S22. Total interaction energy (top) and Lennard-Jones energy (bottom) between the like-charged Arg and His side chains, residues and headgroups, residues and water obtained from ABF simulation trajectories. PMFs (black) are shown for comparison.

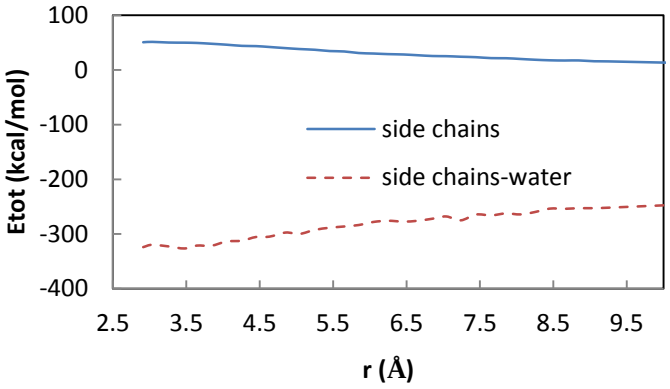

Figure S23. Total interaction energy between the two stacking Arg^{+}…His^{+} side chains, side chains and water obtained from ABF simulation trajectories in water box.

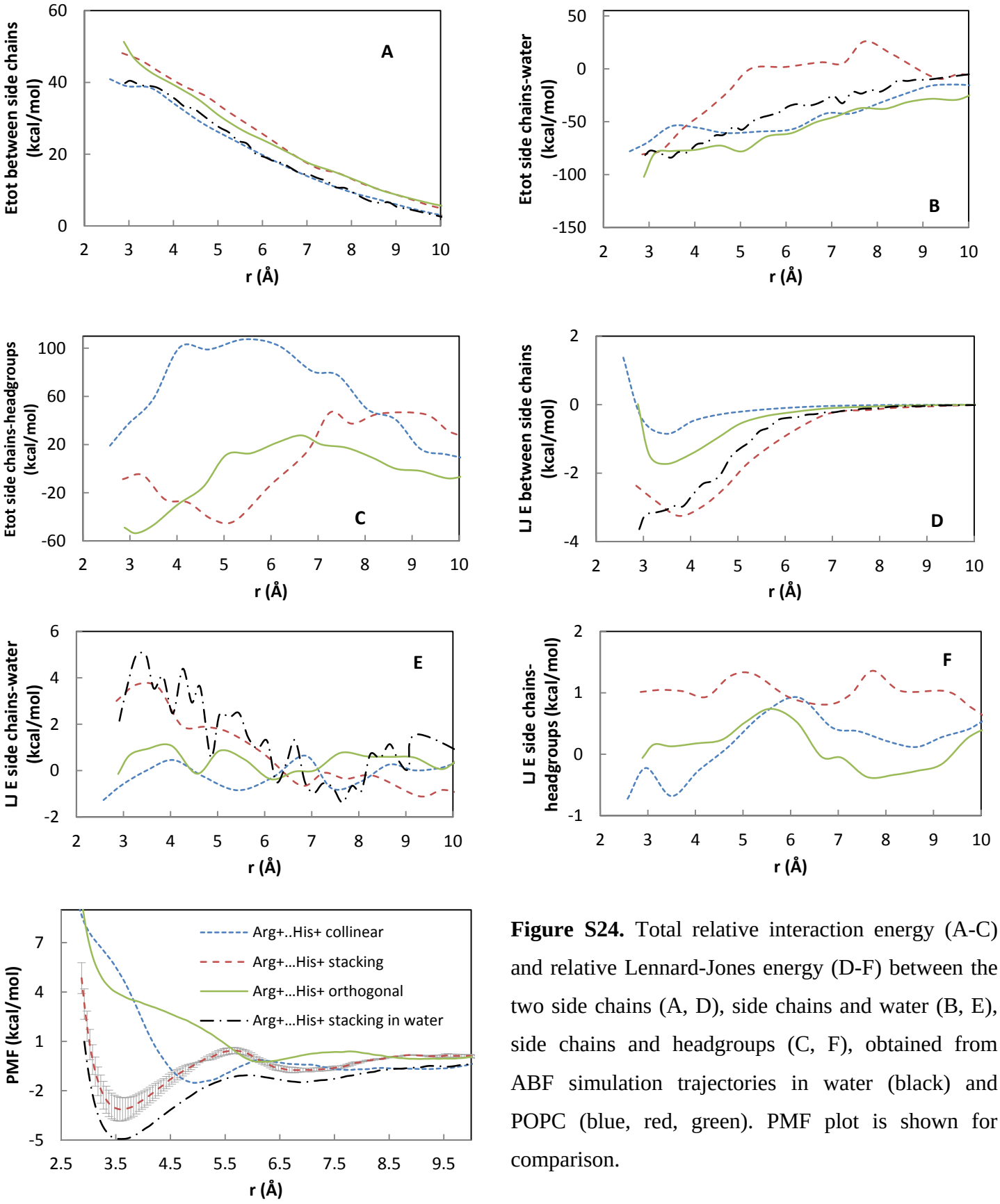

Figure S24. Total relative interaction energy (A-C) and relative Lennard-Jones energy (D-F) between the two side chains (A, D), side chains and water (B, E), side chains and headgroups (C, F), obtained from ABF simulation trajectories in water (black) and POPC (blue, red, green). PMF plot is shown for comparison.

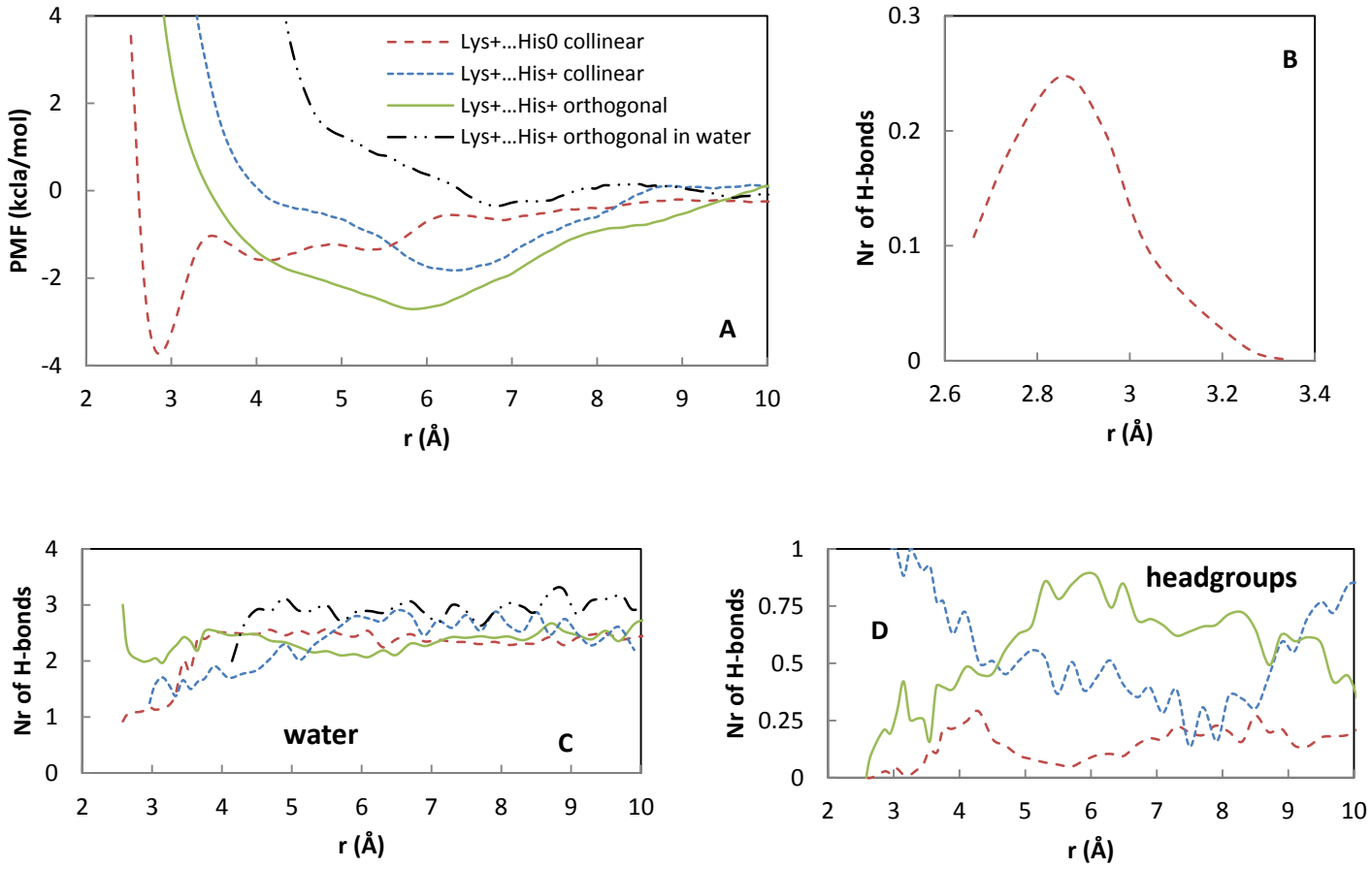

Figure S25. PMF curves for the Lys...His pairs in POPC and water (A). H-bonds between side chains and water (B), side chains and headgroups (C). *r* is a distance between: $Lys^{+}…His^{0}$ - NZ atom of Lys and NE atom of His; $Lys^{+}…His^{+}$ - NZ atom of Lys and ND atom of His.

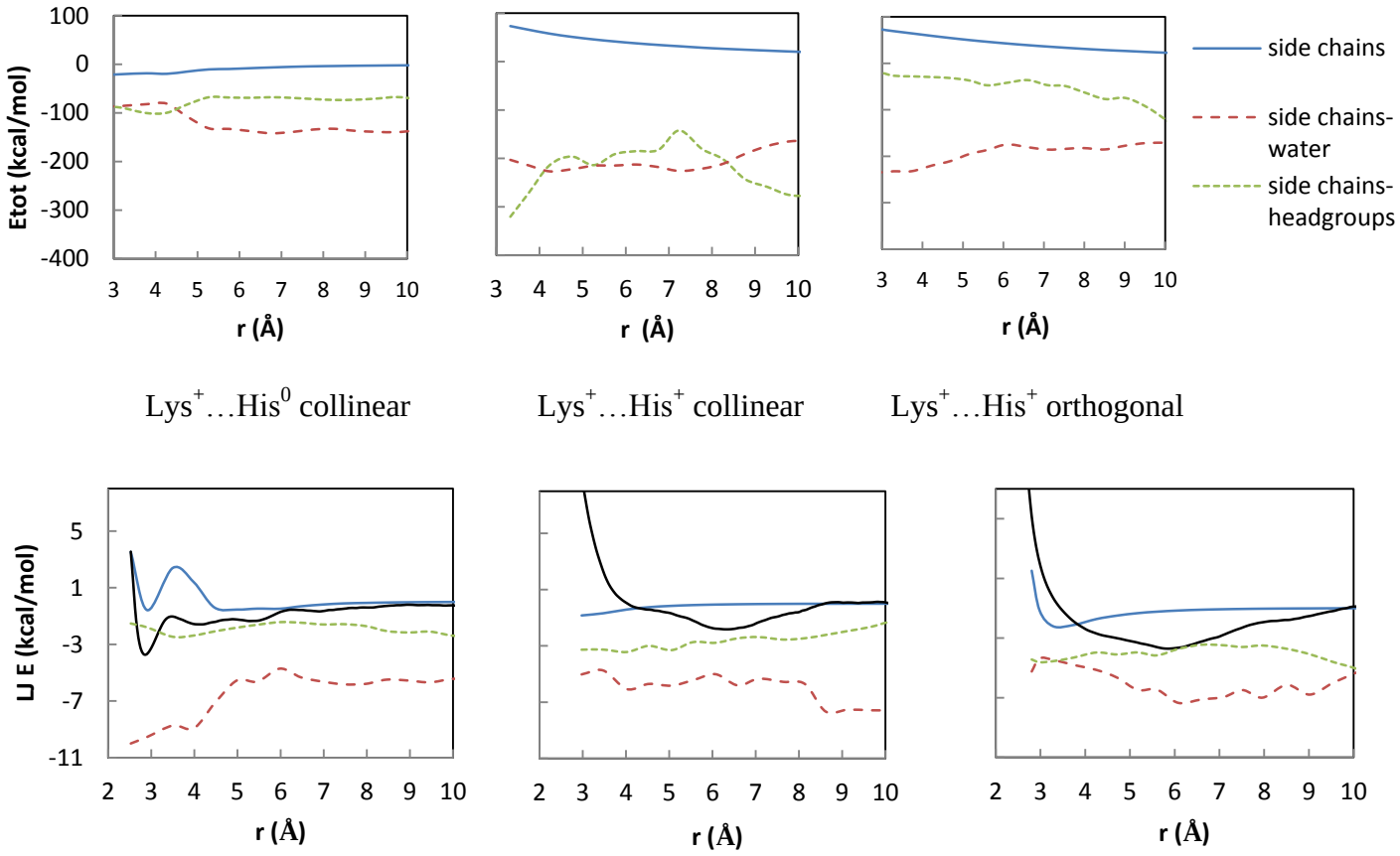

Figure S26. Total interaction energy (top) and Lennard-Jones energy (bottom) between Lys and His side chains, residues and headgroups, residues and water obtained from ABF simulation trajectories. PMFs (black) are shown for comparison.

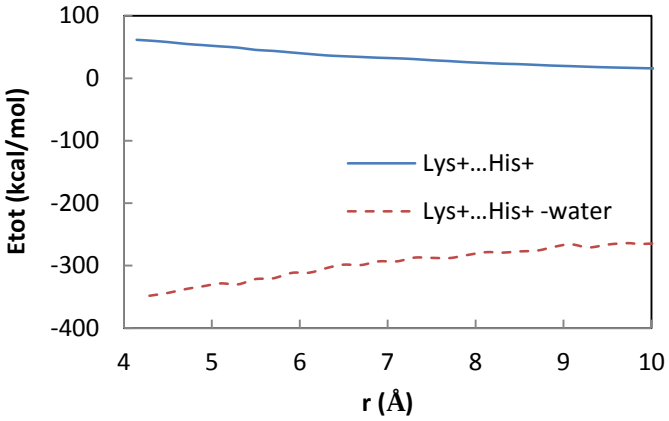

Figure S27. Total interaction energy between the two orthogonal $Lys^{+}…His^{+}$ side chains, side chains and water obtained from ABF simulation trajectories in water box.

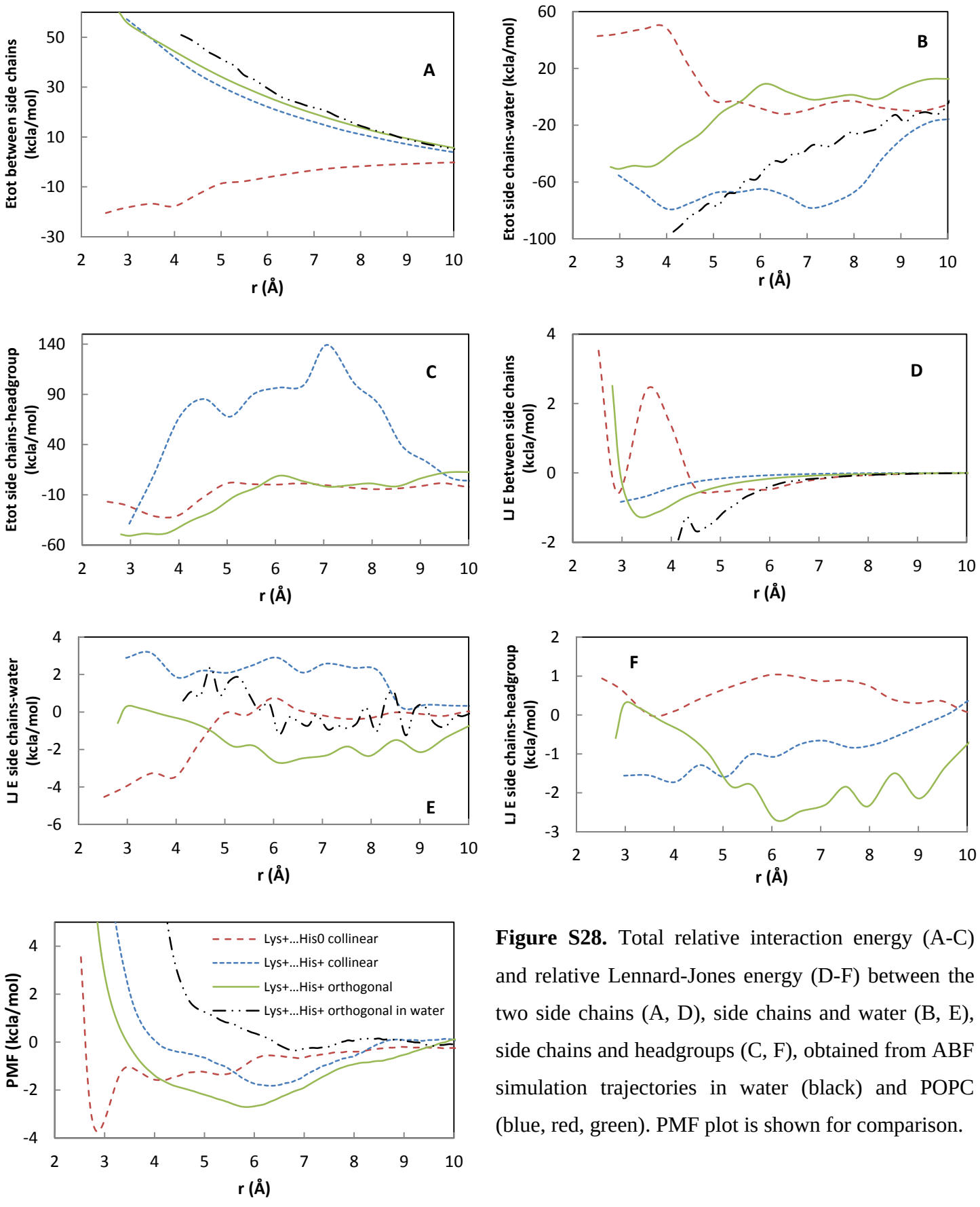

Figure S28. Total relative interaction energy (A-C) and relative Lennard-Jones energy (D-F) between the two side chains (A, D), side chains and water (B, E), side chains and headgroups (C, F), obtained from ABF simulation trajectories in water (black) and POPC (blue, red, green). PMF plot is shown for comparison.

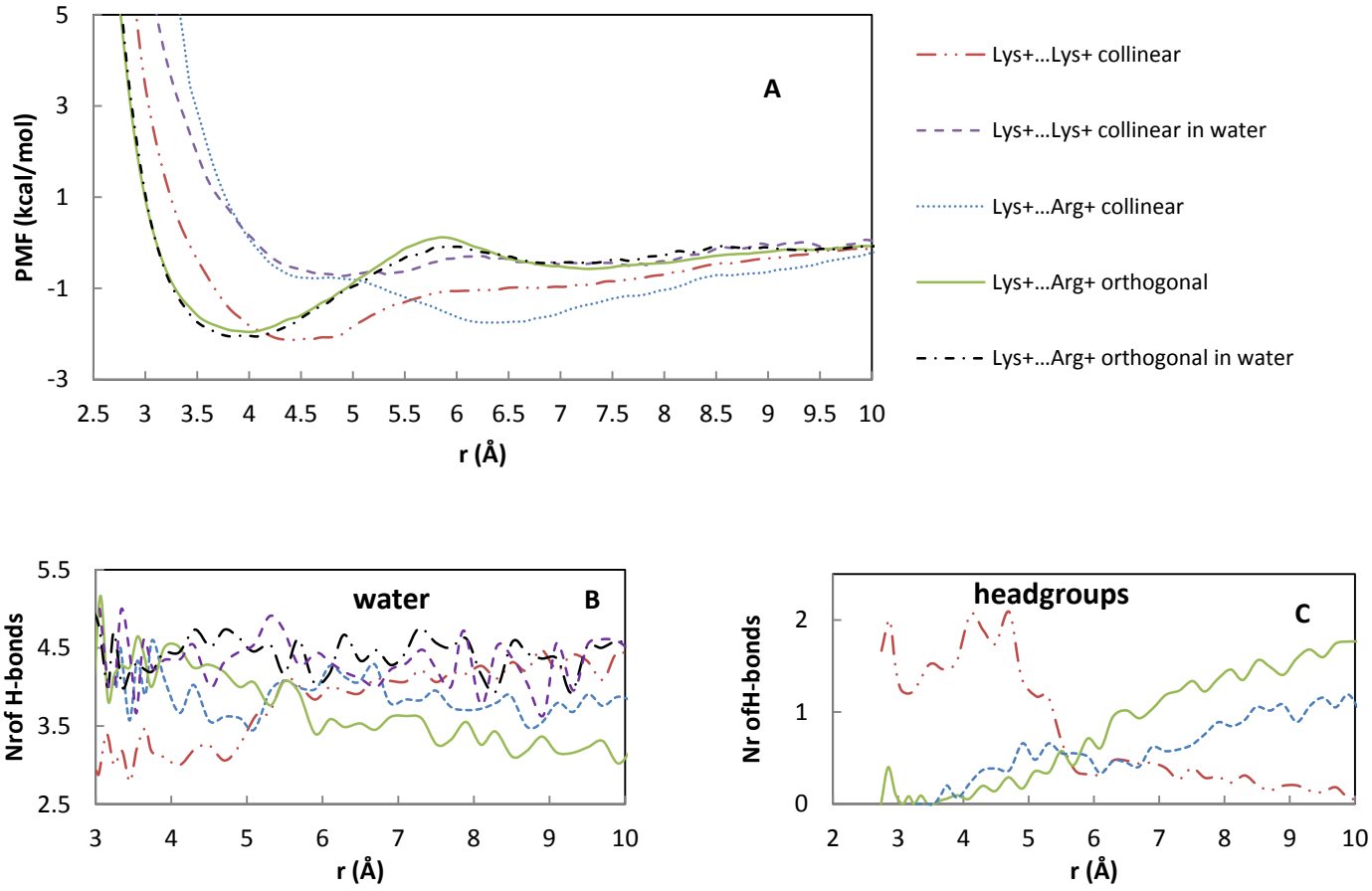

Figure S29. PMF curves for the Lys^+...Lys^+ and Lys^+...Arg^+ ion pairs in POPC and water (A). H-bonds between side chains and water (B), side chains and headgroups (C). *r* is the distance between: Lys^+...Lys^+ - NZ atoms of Lys; Lys^+...Arg^+ - NZ atom of Lys and COM of NH atoms of Arg.

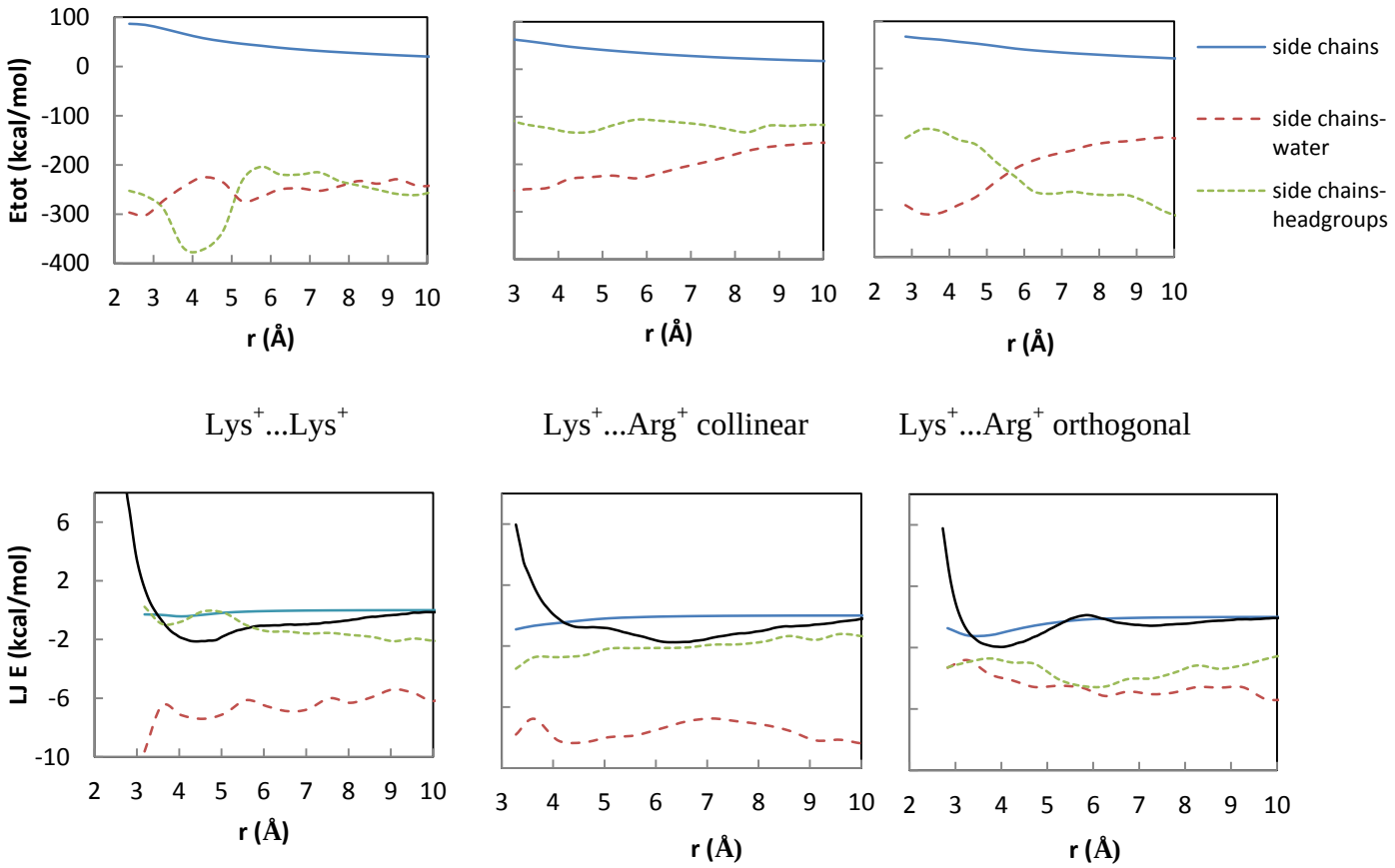

Figure S30. Total interaction energy (top) and Lennard-Jones energy (bottom) between the like-charged Lys and Arg side chains, residues and headgroups, residues and water obtained from ABF simulation trajectories PMFs (black) are shown for comparison.

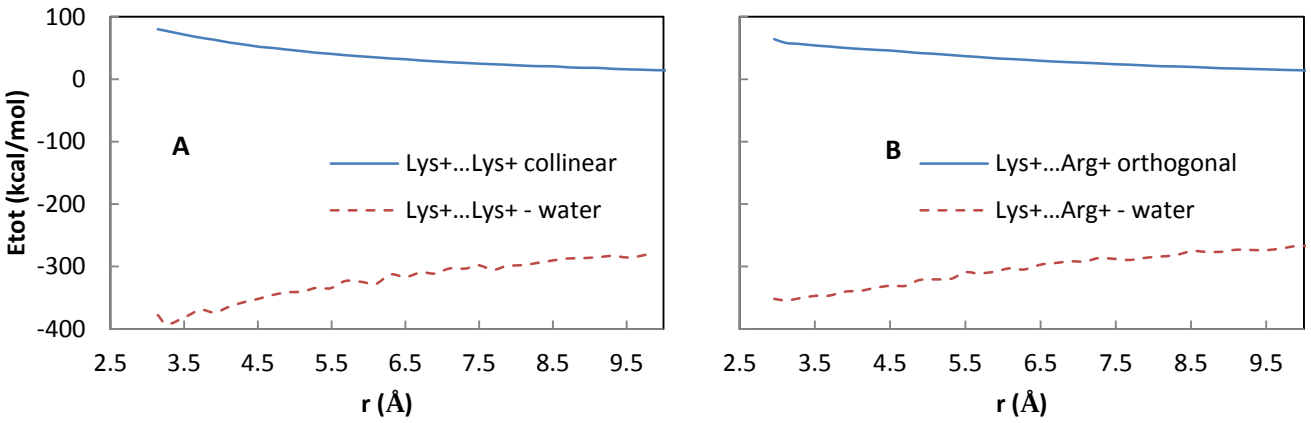

Figure S31. Total interaction energy between the two side chains, side chains and water obtained from ABF simulation trajectories in water box.

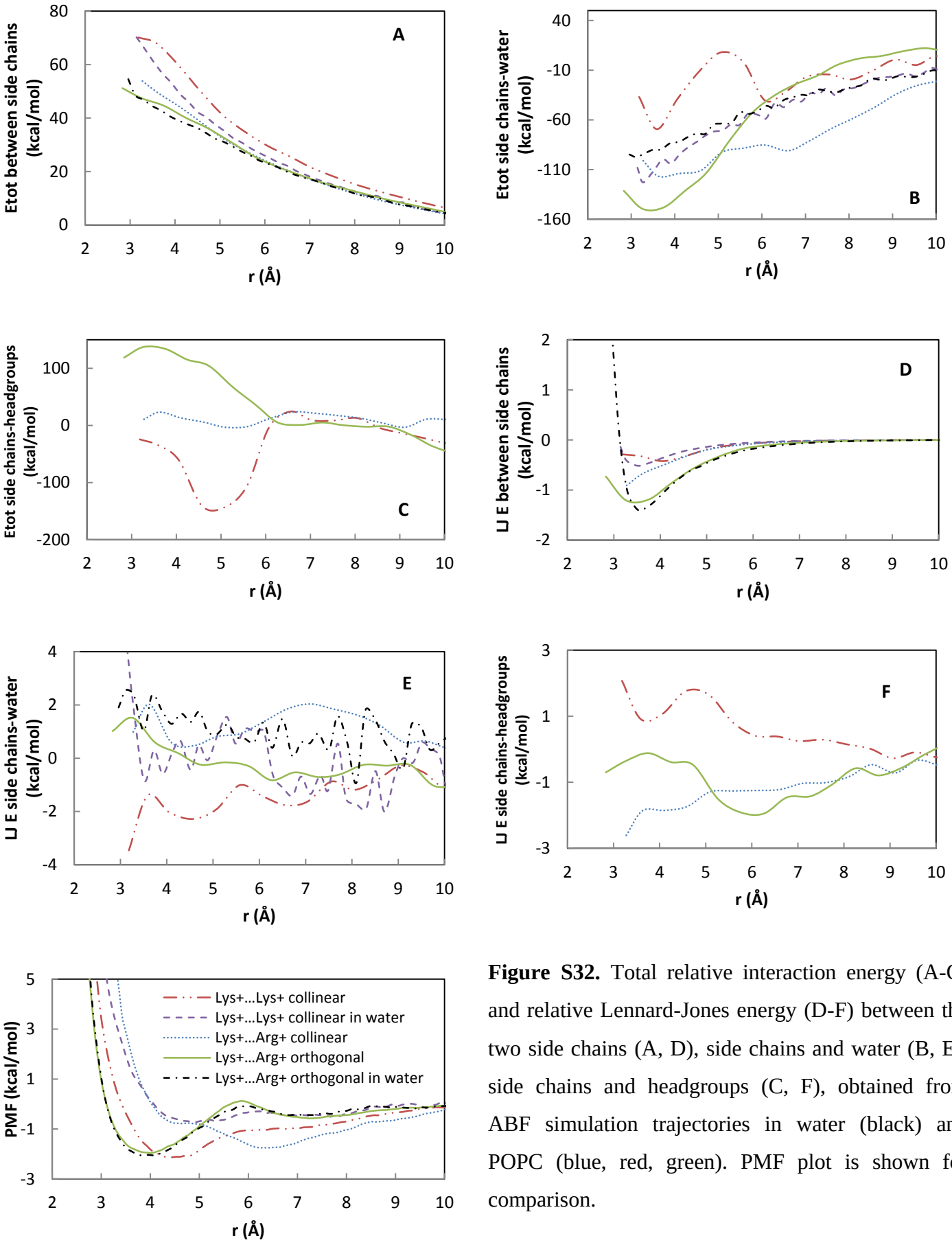

Figure S32. Total relative interaction energy (A-C) and relative Lennard-Jones energy (D-F) between the two side chains (A, D), side chains and water (B, E), side chains and headgroups (C, F), obtained from ABF simulation trajectories in water (black) and POPC (blue, red, green). PMF plot is shown for comparison.

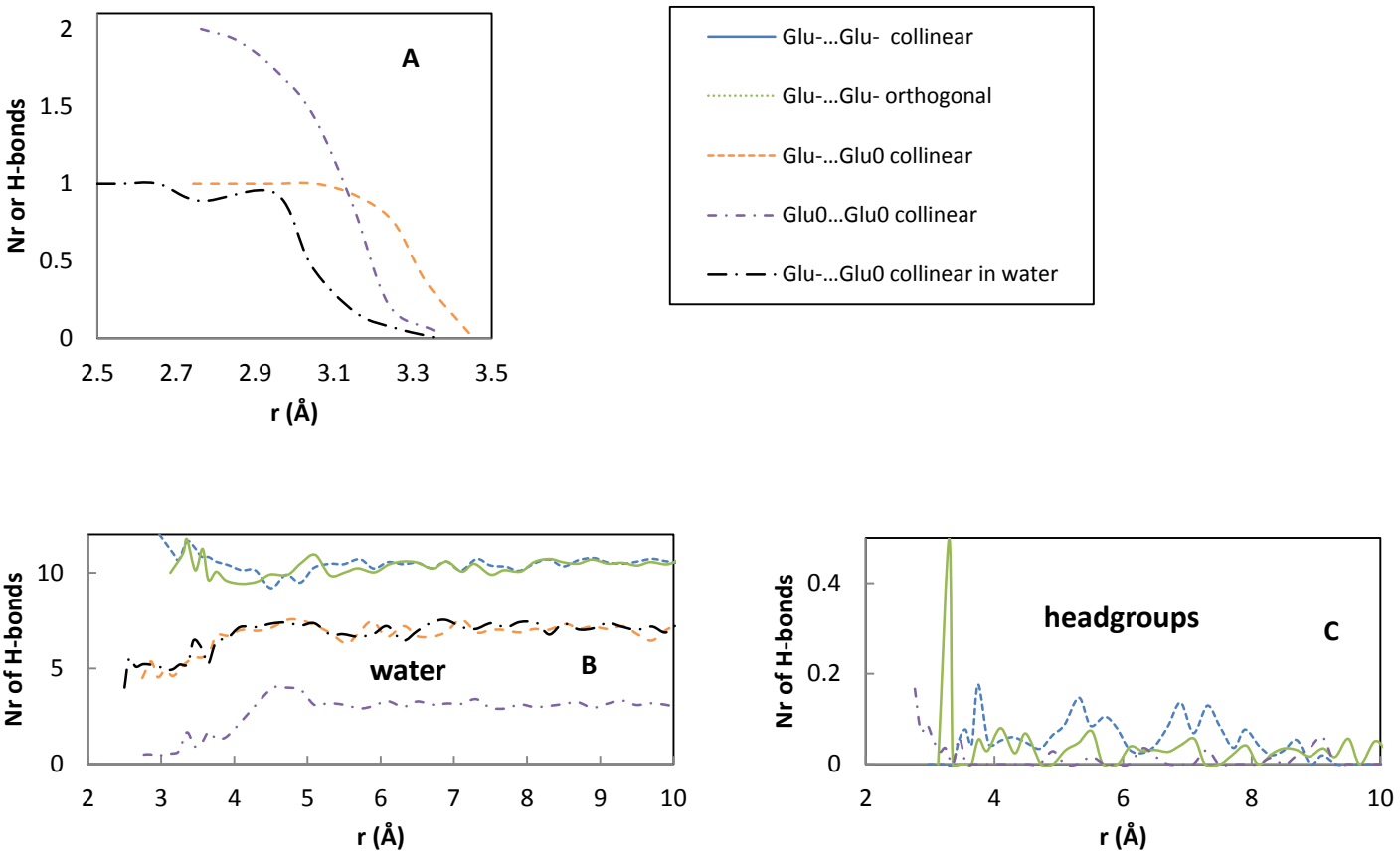

Figure S33. H-bonds between Glu residues (A), side chains and water (B) and side chains and headgroups (C).

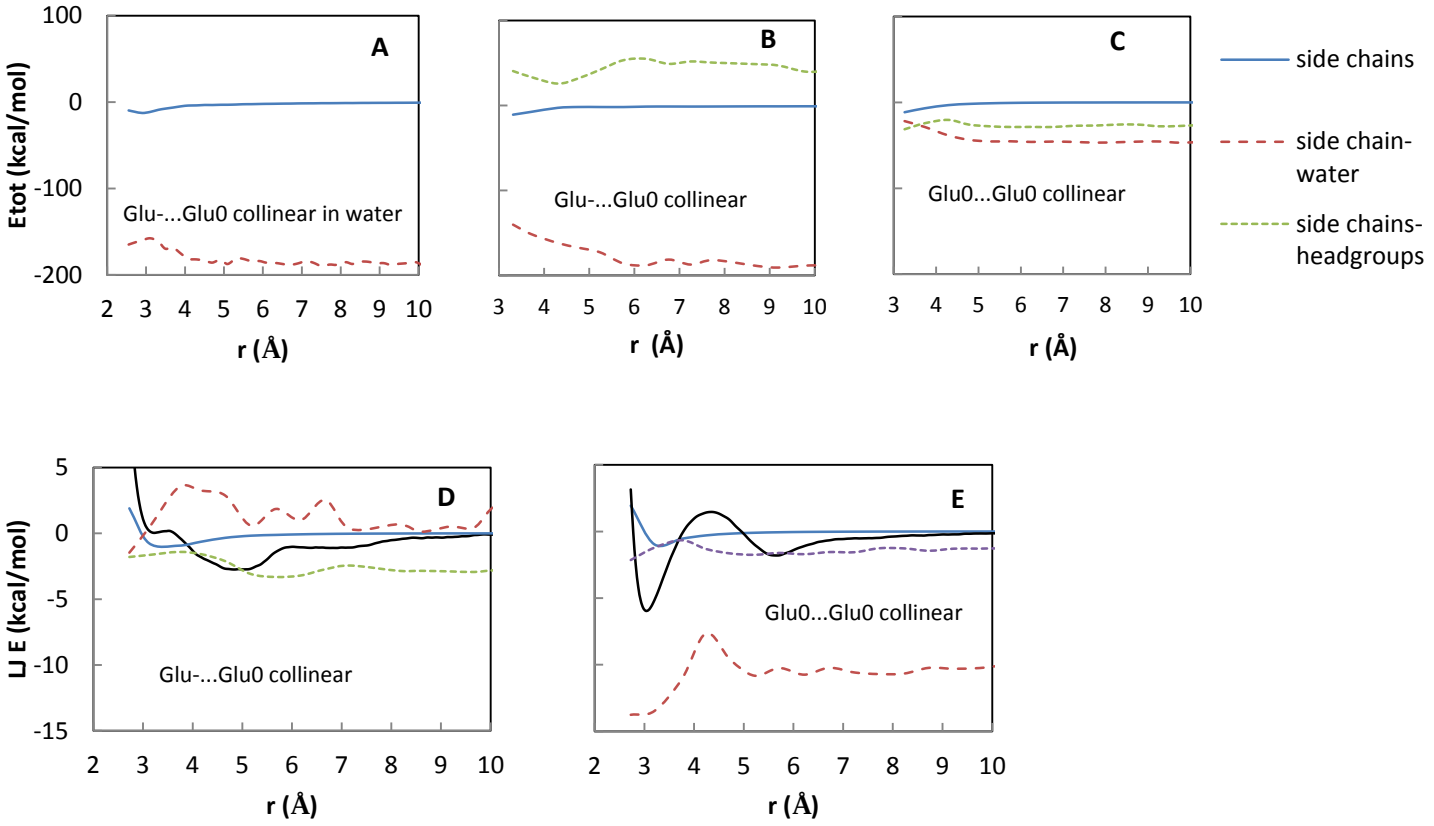

Figure S34. Total interaction energy (A-C) and Lennard-Jones energy (D, E) between the H-bonded Glu side chains, residues and headgroups, residues and water obtained from ABF simulation trajectories in water (A) and POPC (B-E). PMFs (black) are shown for comparison.

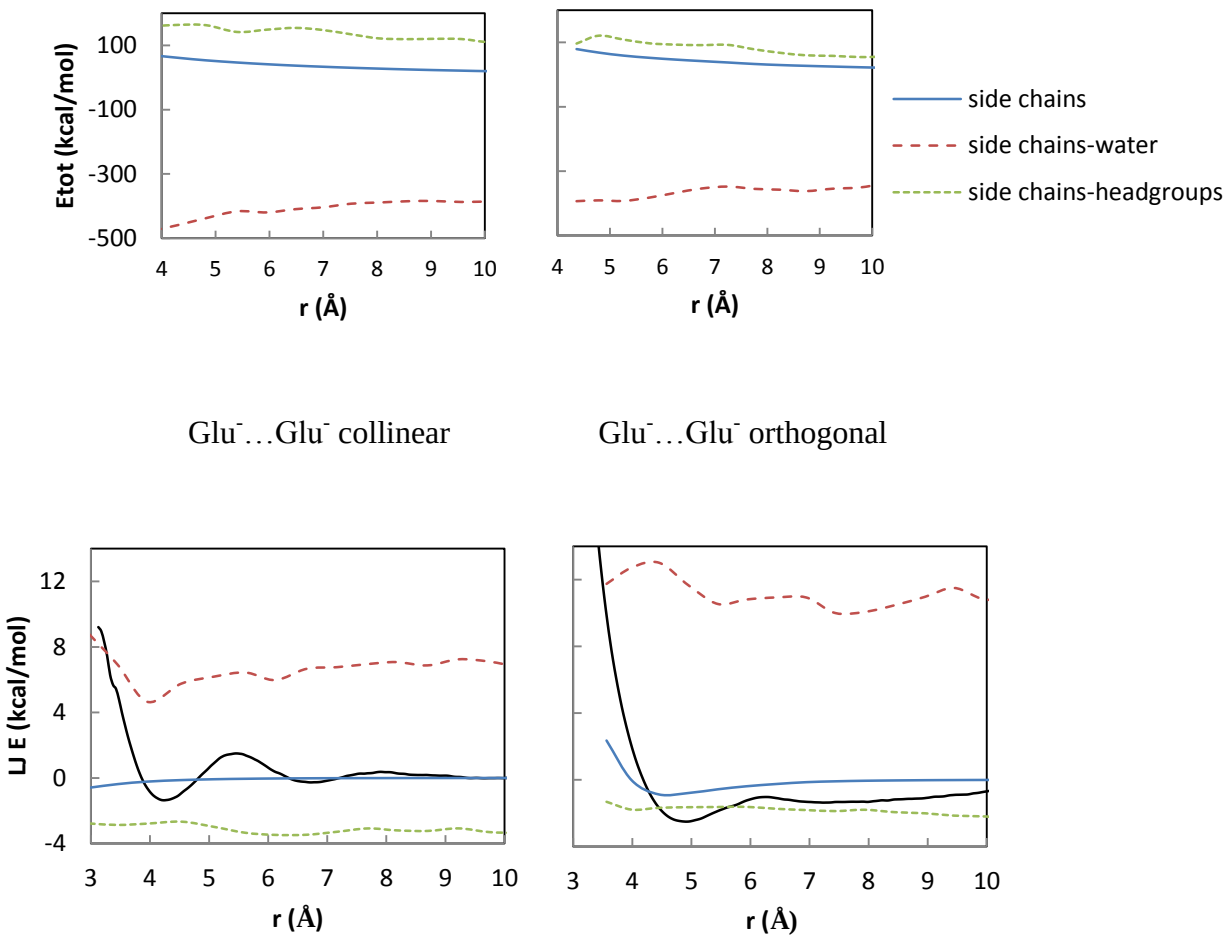

Figure S35. Total interaction energy (top) and Lennard-Jones energy (bottom) between the like-charged Glu side chains, residues and headgroups, residues and water obtained from ABF simulation trajectories. PMFs (black) are shown for comparison.

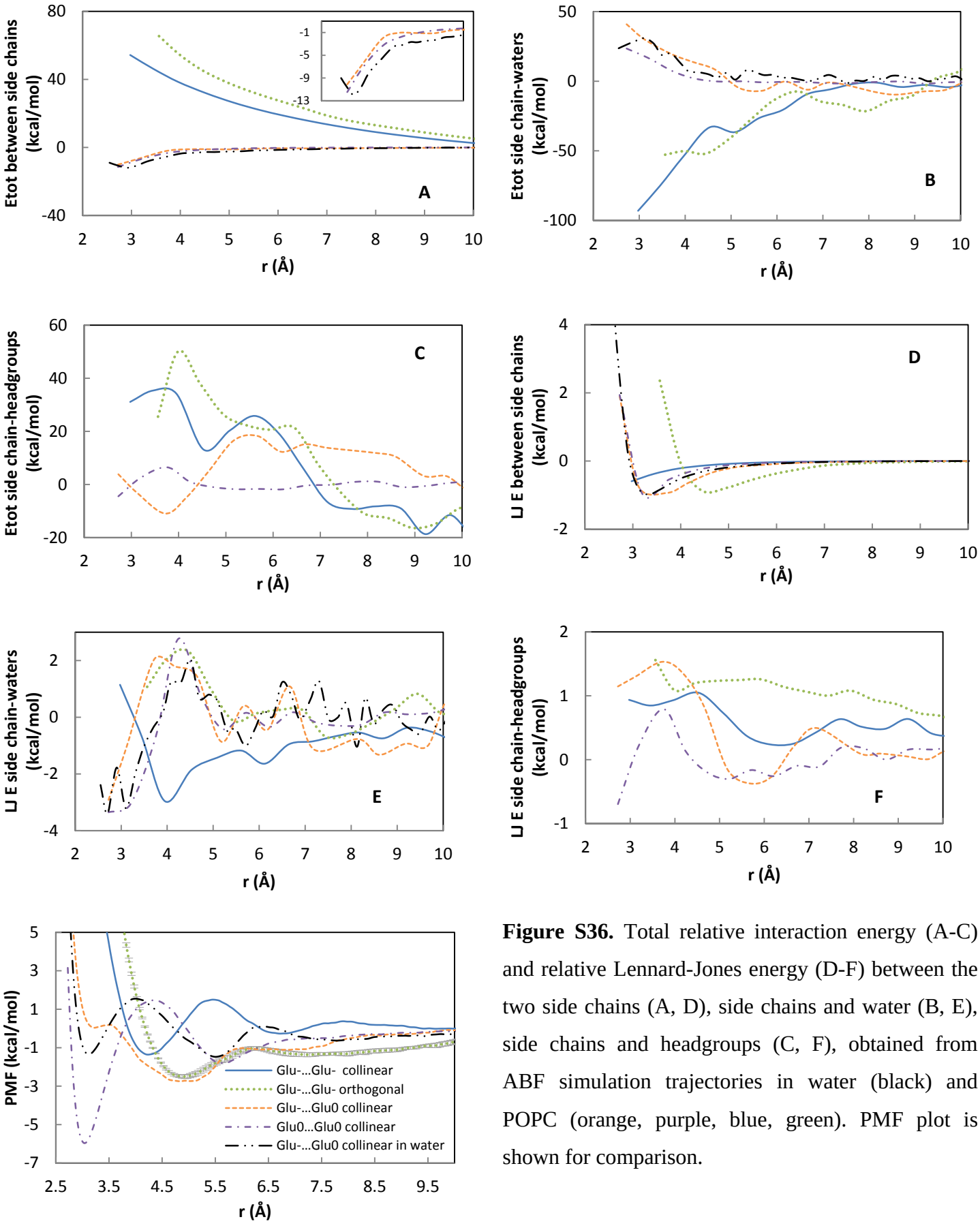

Figure S36. Total relative interaction energy (A-C) and relative Lennard-Jones energy (D-F) between the two side chains (A, D), side chains and water (B, E), side chains and headgroups (C, F), obtained from ABF simulation trajectories in water (black) and POPC (orange, purple, blue, green). PMF plot is shown for comparison.