Supporting Information for

Flower Micelle of Amphiphilic Random Copolymers in Aqueous Media

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System Preparation

In high temperature implicit water MD simulations, fully ionized p(AMPS/C12) with the degree of polymerization of 200 and a random sequence of 50 mol% C12 and taking the most energetically stable (or the all trans) conformation were initially generated using the Insight II software package (Accelrys Inc., San Diego, CA). The atomic charges for each monomer unit were derived from RESP analysis[1] in Gaussian 98[2] with the 6-31G* basis set. The force field parameters of general AMBER force field[3] (GAFF) and atomic charges were assigned using the ANTECHAMBER program as implemented in AMBER7.[4] After 50 ns implicit water MD

simulations at 400 K, the fully ionized p(AMPS/C12) was placed into a periodic water box containing 118 sodium ions, 18 chloride ions, and 19,946 TIP3P water molecules. The initial positions of the ions were determined by the computed electrostatic potential using LEaP.[5]

Simulation Protocol

High temperature implicit water MD simulations. All generalized Born/surface area MD (GB/SA-MD) simulations were performed using the AMBER7 suite programs with the GAFF force field. The fully extended conformations of the polymers were subjected to 1,000 steps each of steepest descent and conjugate gradient minimizations. GB/SA-MD simulations were then initiated using GB implicit water model by Tsui and Case.[6] The surface access area correction was made using linear combinations of pairwise overlap by Still *et. al*.[7] Simulations employed a 2 fs time step for 2.5×10^7 steps corresponding to a total of 50 ns of GB/SA-MD. The final desired temperature of 400 K was obtained by a heating cycle from 0 to 400 K over the course of the first 10 ps with temperature regulation maintained via coupling to an external heat bath using Berendsen scheme.[8] Bond lengths involving bonds to hydrogen atoms were constrained using SHAKE algorithm.[9] Dielectric constants of 1 (interior) and 78.5 (exterior) were employed in all GB-MD simulations. No cutoff (cutoff = 999 Å) was employed during the GB-MD simulations. An ionic strength of 0.05 M was included, and a surface tension parameter of 0.005 kcal/mol $Å^2$ was used. The conformations were saved at every 2 ps.

Explicit Water Molecular Dynamics Simulations. Explicit water MD simulations were performed using the AMBER 8[10] suite programs. The GAFF force field was applied to the polymers, and the AMBER Parm99 force field was applied to sodium and chloride ions. Water was modeled using the TIP3P model. The solvated structures were subjected to 1,000 steps of steepest decent minimization, followed by another 1,000 steps of conjugate gradient

minimization. Harmonic restraints with force constants of 10 kcal/mol $Å^2$ were subsequently applied to maintain the polymer conformations close to their initial structures. The minimized structure was subjected to 100 ps of constant volume-constant temperature (NVT) MD, with a 2 fs time step. During the MD, the system was gradually heated from 0 to 350 K, and the force constants for the harmonic restraints on the polymer atom positions were gradually reduced to zero. Subsequently, 100 ns NPT unrestrained MD simulations were carried out at 350 K, then temperature was incrementally decreased to 300 K, annealing over a period of 1 ns. Finally, 160 ns NPT unrestrained production dynamics was performed at 300 K. During the NPT simulations, the pressure was maintained at 1.0 atom using isotropic scaling with the relaxation time of 1.0 ps while the temperature was maintained at 300 K using Berendsen scheme. The particle-mesh Ewald algorithm[11] was used for handling long-range electrostatic forces, while the short-range van der Waals force was truncated at 8.0 Å. The time step was set to 2.0 fs, and the SHAKE algorithm was used to restrain all bonds containing hydrogen atoms. The trajectory was collected as a series of snapshots saved every 2.0 ps.

References

(1) Bayly, C. I.; Cieplak, P.; Cornell, W. D.; Kollman, P. A. A well-behaved electrostatic potential based method using charge restraints for deriving atomic charges: the RESP model. *J. Phys. Chem.* **1993**, *97*, 10269-10280.

(2) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Zakrzewski, V. G.; Montgomery, J. A., Jr.; Stratmann, R. E.; Burant, J. C.; Dapprich, S.; Millam, J. M.; Daniels, A. D.; Kudin, K. N.; Strain, M. C.; Farkas, O.; Tomasi, J.; Barone, V.; Cossi, M.; Cammi, R.; Mennucci, B.; Pomelli, C.; Adamo, C.; Clifford, S.; Ochterski, J.; Petersson, G. A.; Ayala, P. Y.; Cui, Q.; Morokuma, K.; Malick, D. K.; Rabuck, A. D.;

Raghavachari, K.; Foresman, J. B.; Cioslowski, J.; Ortiz, J. V.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Gonzalez, C.; Challacombe, M.; Gill, P. M. W.; Johnson, B. G.; Chen, W.; Wong, M. W.; Andres, J. L.; Head-Gordon, M.; Replogle, E. S.; Pople, J. A. *Gaussian 98*; Gaussian, Inc.: Pittsburgh, PA, 1998.

(3) Wang, J.; Wolf, R. M.; Caldwell, J. W.; Kollman, P. A.; Case, D. A. Development and Testing of a General Amber Force Field. *J. Comput. Chem.* **2004**, *25*, 1157-11742.

(4) Case, D. A.; Pearlman, D. A.; Caldwell, J. W.; Cheatham, T. E., III; Wang, J.; Ross, W. S.; Simmering, C. L.; Darden, T. A.; Merz, K. M.; Stanton, R. V.; Cheng, A. L.; Vincent, J. J. Crowley, M.; Tsui, V.; Gohlke, H.; Radmer, R. J.; Duan, Y.; Pitera, J.; Massova, I. Seibel, G. L.; Singh, U. C.; Weiner, P. K.; Kollman, P. A. *AMBER7*; University of California: San Francisco, 2002.

(5) Case, D.; Cheatham, T.; Darden, T.; Gohlke, H.; Luo, R.; Merz, K.; Onufriev, A.; Simmerling, C.; Wang, B.; Woods, R. *J. Comput. Chem.* **2000**, *21*, 1049-1074.

(6) Tsui, V.; Case, D. A. Theory and applications of the generalized Born salvation model in macromolecular simulations. *Bioplymers (Nucl. Acids. Sci.)* **2001**, *56*, 275-291.

(7) Weiser, J.; Shenkin, P. S.; Still, W. C. *J. Comput. Chem.* **1999**, *20*, 217.

(8) Berendsen, H. J. C.; Postma, J. P. M.; Vangunsteren, W. F.; Dinola, A; Haak, J. R. Molecular-Dynamics with Coupling to an External Bath. *J. Chem. Phys.* **1984**, *81*, 3684-3690.

(9) Ryckaert, J. P.; Ciccotti, G.; Berendsen, H. J. C. Numerical-Integration of Cartesian Equations of Motion of a System with Constraints – Molecular-Dynamics of N-Alkanes. *J. Comput. Phys.* **1977**, *23*, 327-341.

(10) Case, D. A., Darden, T. A., Cheatham, I. T. E., Simmerling, C. L., Wang, J., Duke, R. E., Luo, R., Merz, K. M., Wang, B., Pearlman, D. A., Crowley, M., Brozell, S., Tsui, V., Gohlke, H., Mongan, J., Hornak, V., Cui, G., Beroza, P., Schafmeister, C., Caldwell, J. W., Ross, W. S., and Kollman, P. A. (2004) *AMBER 8*, Scripps Research Institute, La Jolla, CA.

(11) Darden, T., York, D., and Pedersen, L. (1993) Particle Mesh Ewald: An N.Log(N) Method for Ewald Sums in Large Systems. *J. Chem. Phys.***1993**, *98*, 10089-10092.