SAND2014-1159C

Electrostatically tuned self-assembly of branched amphiphilic peptides

Christina Ting, Amalie Frischknecht, Mark Stevens, and Erik Spoerke
Sandia National Laboratories, Albuquerque, NM

Sandia National Laboratories

U.S. DEPARTMENT OF ENERGY
Office of Science

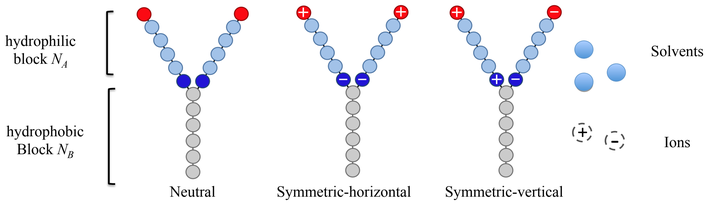
Introduction

The self-assembly of amphiphilic peptides is an active field of research with the potential of impacting critical technological fields such as molecular sensing, catalysis, and biomedical applications. In addition, these molecules provide a model system to study the fundamental science behind supramolecular assembly. Here, driving forces such as electrostatics, hydrogen bonding, and hydrophobicity influence the molecular conformation and subsequent primary and secondary assembly of the peptides into structures such as cylindrical nanofibers, spherical micelles, various sheet-like morphologies.

In a recent experimental study, Gough, et al. [1] observed that the supramolecular assembly of amphiphilic peptides depended on the cooperative influences of hydrogen bonding, amphiphilicity, and electrostatic interactions. In particular, the distribution of charged amino acids affected the assembly into nanofiber gels or multi-layered lamellar structures. Understanding the complex molecular interactions that govern the assembly is key to the success in the development of peptide nanomaterials. Towards this end, simulation and theory can be used to provide some of the desired molecular insights. Here, we employ self-consistent field theory (SCFT) to obtain thermodynamic information in these complex systems, with a focus on the effects of the electrostatic interactions.

[1] D. Van Gough, J.S. Wheeler. S. Cheng. M. J. Stevens and E.D. Spoerke (in review)

Molecular Model



① Peptide (polymer) chain connectivity

$$\mathscr{H} = \sum_{i=1}^{n_P} h_i(\{\mathbf{r}\}) + \int d\mathbf{r}d\mathbf{r}' \left[\hat{\phi}_j(\mathbf{r})u_{jk}(\mathbf{r},\mathbf{r}')\hat{\phi}_k(\mathbf{r}') + \frac{1}{8\pi}\frac{\hat{\rho}_c(\mathbf{r})\hat{\rho}_c(\mathbf{r}')}{\varepsilon(\mathbf{r})|\mathbf{r}-\mathbf{r}'|}\right]$$

② Pairwise interaction potential

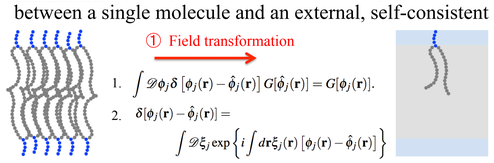
③ Long-ranged electrostatics

$$\Xi = \sum_{n_\alpha\in\{P,S,\pm\}=0}^{\infty} \frac{e^{\mu_\alpha n_\alpha}}{n_\alpha! v_\alpha^{n_\alpha}} \int \prod_{i=0}^{n_P} d\{\mathbf{r}\}_i \prod_{j=0}^{n_S} d\mathbf{r}_j \prod_{k=0}^{n_\pm} d\mathbf{r}_k \times \prod_{\mathbf{r}} \delta[1-\hat{\phi}_A(\mathbf{r})-\hat{\phi}_B(\mathbf{r})-\hat{\phi}_S(\mathbf{r})] e^{-\mathscr{H}}.$$

④ Excluded volume effects (delta functional in the partition function)

Self-consistent (mean) field theory

Basic idea: Decouple the interactions among molecules and replace with the interaction between a single molecule and an external, self-consistent field.



① Field transformation

1. $\int \mathscr{D}\phi_j \delta[\phi_j(\mathbf{r}) - \hat{\phi}_j(\mathbf{r})] G[\hat{\phi}_j(\mathbf{r})] = G[\phi_j(\mathbf{r})].$
2. $\delta[\phi_j(\mathbf{r}) - \hat{\phi}_j(\mathbf{r})] = \int \mathscr{D}\xi_j \exp\left\{i\int d\mathbf{r}\xi_j(\mathbf{r})[\phi_j(\mathbf{r}) - \hat{\phi}_j(\mathbf{r})]\right\}$

$$\Xi = \int \mathscr{D}\omega \exp(-G[\omega])$$

② Mean-field approximation

$$\Xi \approx \exp(G[\omega^*])$$

$$G[\phi,\xi,\psi] = -\frac{e^{\mu_P}}{v_P} Z_P[\xi_A,\xi_B,\psi] - \frac{e^{\mu_S}}{v_S} Z_S[\xi_S] - \frac{e^{\mu_\pm}}{v_\pm} Z_\pm[\psi] + \int d\mathbf{r}\left[\chi_{jk}\phi_j\phi_k + \frac{\kappa_j}{2}|\nabla\phi_j|^2 - \xi_j\phi_j + \psi\frac{\pm\phi_{A_\pm}}{v_A} - \frac{\varepsilon}{2}|\nabla\psi|^2\right]$$

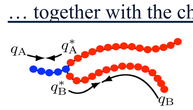
Gives set of self-consistent equations, which are solved iteratively until convergence…

$\frac{\partial G}{\partial \phi}|_{\phi^*} = 0$ → external fields, ξ_I

$\frac{\partial G}{\partial \xi}|_{\xi^*} = 0$ → density fields, ϕ_I

$\frac{\partial G}{\partial \psi}|_{\psi^*} = 0$ → Born augmented Poisson – Boltzmann equation

… together with the chain propagators



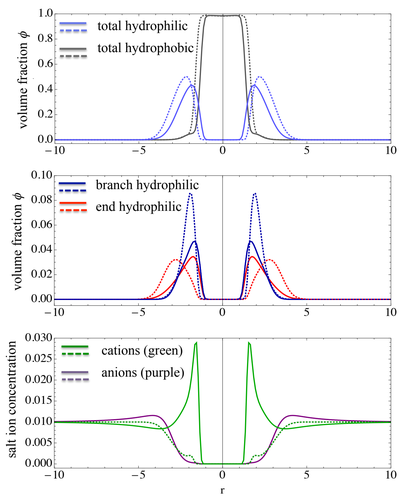
$$q_I(\mathbf{r},1) = e^{-v_I\xi_I(\mathbf{r})}$$

$$q_I(\mathbf{r};i) = e^{-v_I\xi_I(\mathbf{r})} \int d\mathbf{r}'\Gamma(|\mathbf{r}-\mathbf{r}'|) q_I(\mathbf{r}';i-1).$$

Solutions give free energy and density profiles to equilibrium states of the system.

Results

Radial density profiles for the cylindrical micelle



Neutral/symmetric vertical

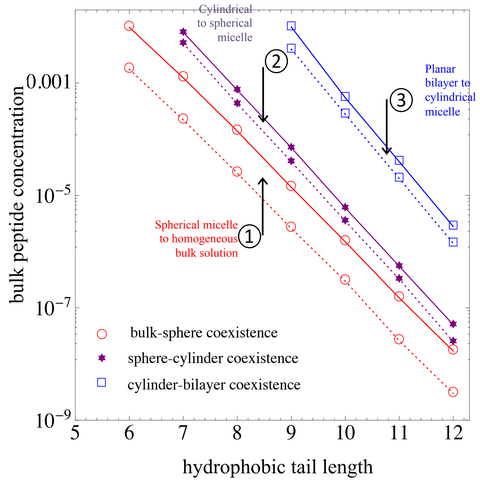
Symmetric horizontal

Parameters:
χ = 35
N_A = 9, N_B = 6
bulk [salt] = 15 mM
bulk [peptide] = 1.11e-4

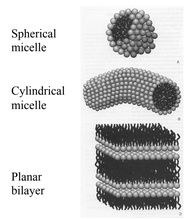
Symmetric-vertical peptides are self-neutralizing and produce the same results as neutral peptides; symmetric horizontal peptides must rearrange and collapse the hydrophilic branch to form charged pairs.

→ Result is a more conical molecule.

Phase diagram for spherical, cylindrical and planar geometries obtained from excess free energy per molecule:



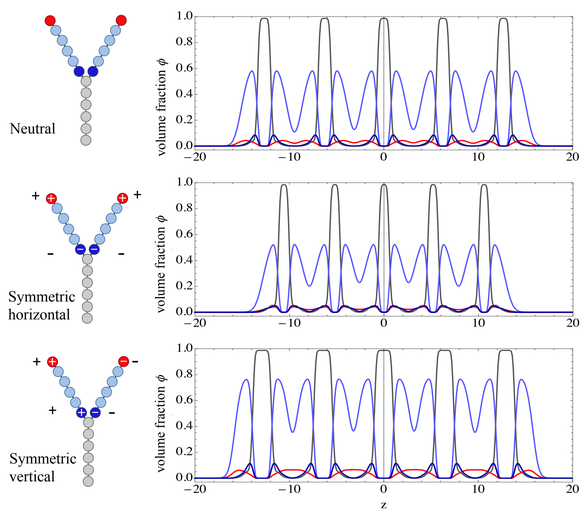
$$\Delta g = (G - G_{bulk})/n_{agg}$$



The above change in molecular shape affects the packing into spherical micelles, cylindrical micelles, or planar bilayers.

→ coexistence curves in the phase diagram shifted towards higher concentrations.

Multi-lamellar planar bilayers

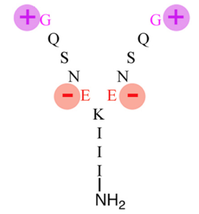


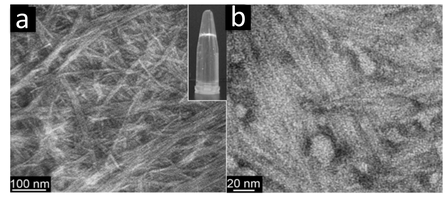
	$\Delta\varrho^{stacked}$	$\Delta\varrho^{isolated}$
neutral:	-3.19	-2.33
sym-hor:	-1.93	-1.83
sym-vert:	-5.27	-3.17

Electrostatics also affects secondary assembly. Symmetric-vertical favors extended multilayer aggregate formation; symmetric-horizontal favors more compact bilayer formation.

Experimental observations

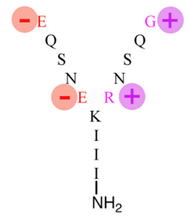
Symmetric-horizontal: self assembles into nanofibers

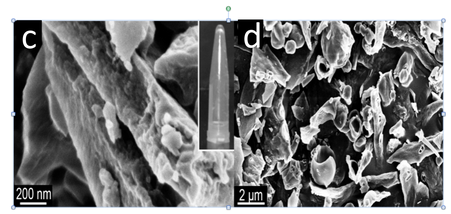




a) SEM images showing nanofibers assembled from the symmetric-horizontal peptides and b) negatively-stained TEM image of a self-supporting gel

Symmetric-vertical: self assembles into sheetlike structures

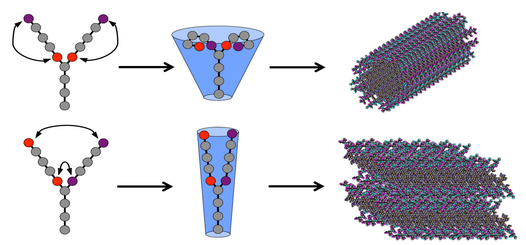




Multilamellar sheets formed from symmetric vertical peptides at high and low magnification. Sheets curled into hollow spheres are visible in d).

Conclusions

- *By varying the distribution of charged groups, electrostatic interactions may be used to dictate self-assembly into spherical, cylindrical or planar geometries.*



- Secondary (inter-aggregate) assembly of these molecules is also affected by the charge distribution.
- Results consistent with experimental observations.
- Important implications for the design and utility of functional self-assembling peptides, lipids, dendrimers, and other molecular building blocks.
- For example, in therapeutic applications, branched architecture can be used to enhance bioaccessibility of ligand-receptor interactions. Understanding how charge distribution may affect peptide conformation and assembled morphology should thus influence molecular design.

This work was supported by the Harry S. Truman Fellowship in National Security Science and Engineering, a Laboratory Directed Research and Development program, and by the U.S. Department of Energy, Office of Basic Energy Sciences, Division of Materials Sciences and Engineering, Project KC0203010.