Factors that Drive Peptide Assembly from Native to Amyloid Structures: Experimental and Theoretical Analysis of [Leu-5]-Enkephalin Mutants

Thanh D. Do, [‡±] *Nichole E. LaPointe,* [‡†] *Smriti Sangwan,* [‡§] *David B. Teplow,*[#] *Stuart C. Feinstein,*[†] *Michael R. Sawaya,*[§] *David S. Eisenberg*[§] *and Michael T. Bowers*[±*]

± Department of Chemistry and Biochemistry and † Neuroscience Research Institute and Department of Molecular, Cellular and Developmental Biology, University of California, Santa Barbara, California 93106, United States

§ Departments of Chemistry and Biochemistry and Biological Chemistry, Howard Hughes Medical Institute, UCLA-DOE Institute for Genomics and Proteomics, and # Department of Neurology, David Geffen School of Medicine at UCLA, Mary S. Easton Center for Alzheimer's Disease Research at UCLA, and Brain Research Institute and Molecular Biology Institute, University of California, 635 Charles Young Drive South, Los Angeles, California 90095, United States.

SUPPORTING INFORMATION

S1. Replica exchange molecular dynamics

S1.1 Simulation Protocol

Explicit solvent simulations for tetramer of YGGFL, YVVFV, YVIFL, YVVVL, YVVFL and YVGVL were performed using the GROMACS 4.5.3 package[1-2] and all-atom Optimized Potentials for Liquid Simulations (OPLS-AA) force field[3] in TIP3P water with periodic condition boundary condition. The LINCS algorithm was employed to constrain bonds between heavy atoms and hydrogens, and the SETTLE algorithm was used for water molecules. These constraints allow an integration time step of 2.0 fs. Electrostatic and dispersion forces were computed with a real space cutoff of 1.2 nm and the particle mesh Ewald method[4] was used to treat long-range electrostatics. All simulations were performed at neutral pH in which the temperature was maintained by the Nose-Hoover thermostat. The temperature and pressure coupling constants were 0.1 ps and 1.0 ps, respectively. The equations of motion were integrated accordingly to the leap-frog algorithm.

Initial configurations were set up so that each peptide chain is 6 angstroms away from the closest adjacent chain. The initial structure was minimized using the steepest decent method, followed by a solvent and volume equilibration simulation in NPT ensemble (T = 300K and P = 1 bar) to optimize the box size. The number of water molecules in each system is approximately 5330 molecules. The box size after equilibration was 5.47, 5.47 and 5.47 ± 0.02 nm. Another equilibration run was performed in NVT ensemble for 6 ns after the optimized volume is obtained. Initial guess for temperature in T-REMD simulations with 32 replicas was taken from Patriksson and Spoel's temperature predictor[5] (http://folding.bmc.uu.se/remd/index.php) and then adjusted to obtain the exchange rate of approximately 20%. Each replica is equilibrated at the desired temperature for 6 ns before the production run for T-REMD was begun. Exchanges between replicas were attempted at every 3 ps. The production run is 200-ns long per replica, but only the last 100-ns data were subjected to analysis.

S1.2 DSSP analysis

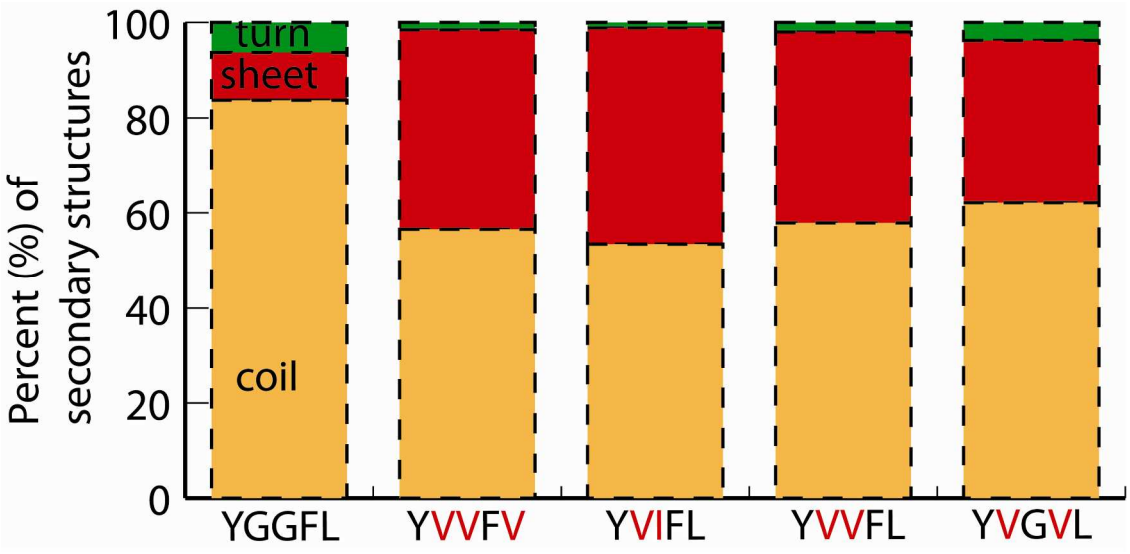

Figure S1. DSSP analysis for the last 100-ns T-REMD data.

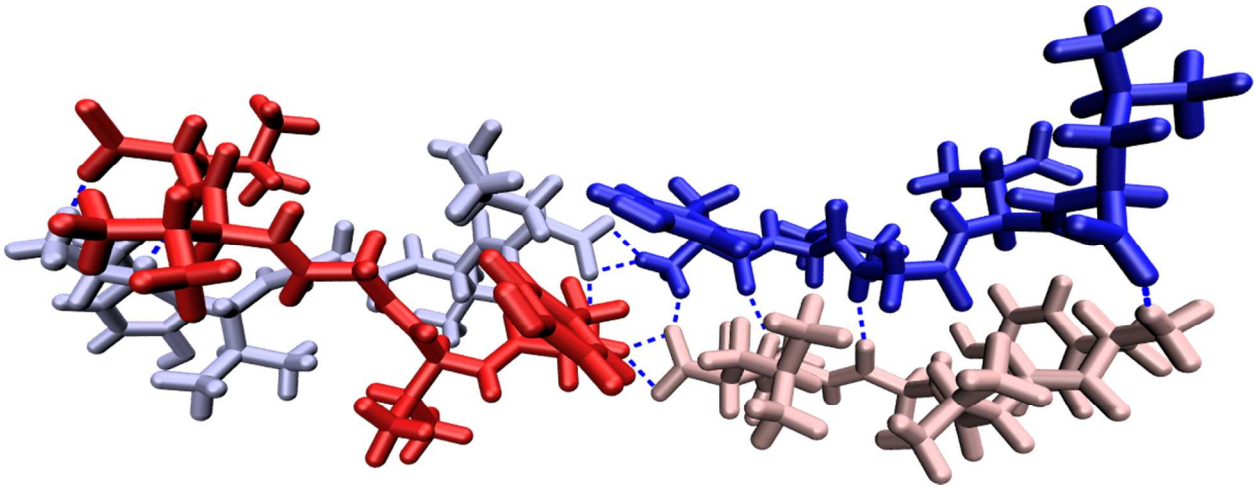

Figure S2. YVGVL tetramer where anti-parallel dimers forming salt-bridges at terminal residues.

S2. Ion-mobility mass spectrometry

The flux of ions exiting the drift tube can be calculated and is used to fit the experimental arrival time distributions. It is assumed that the ion packet takes the form of a periodic delta function and the flux is given by equation 1.1.

(1.1)

$$\Phi\left(0,z,t\right)=\frac{s\cdot a\cdot e^{-\alpha\cdot t}}{4\left(\pi D_L t\right)^{1/2}}\cdot\left(v_d+\frac{z}{t}\right)\cdot\left[1-e^{\left(-r_0^2/4D_L t\right)}\right]\cdot e^{\left(-\left(z-v_d\cdot t\right)^2/4D_L t\right)}$$

Here z is the distance the ions travel, r_0 is the radius of the initial ion packet, a is the area of the exit aperture, D_L and D_T are the longitudinal and transverse diffusion coefficients, s is the initial ion density and α is the loss of ions due to reactions in the drift tube.[6-7]

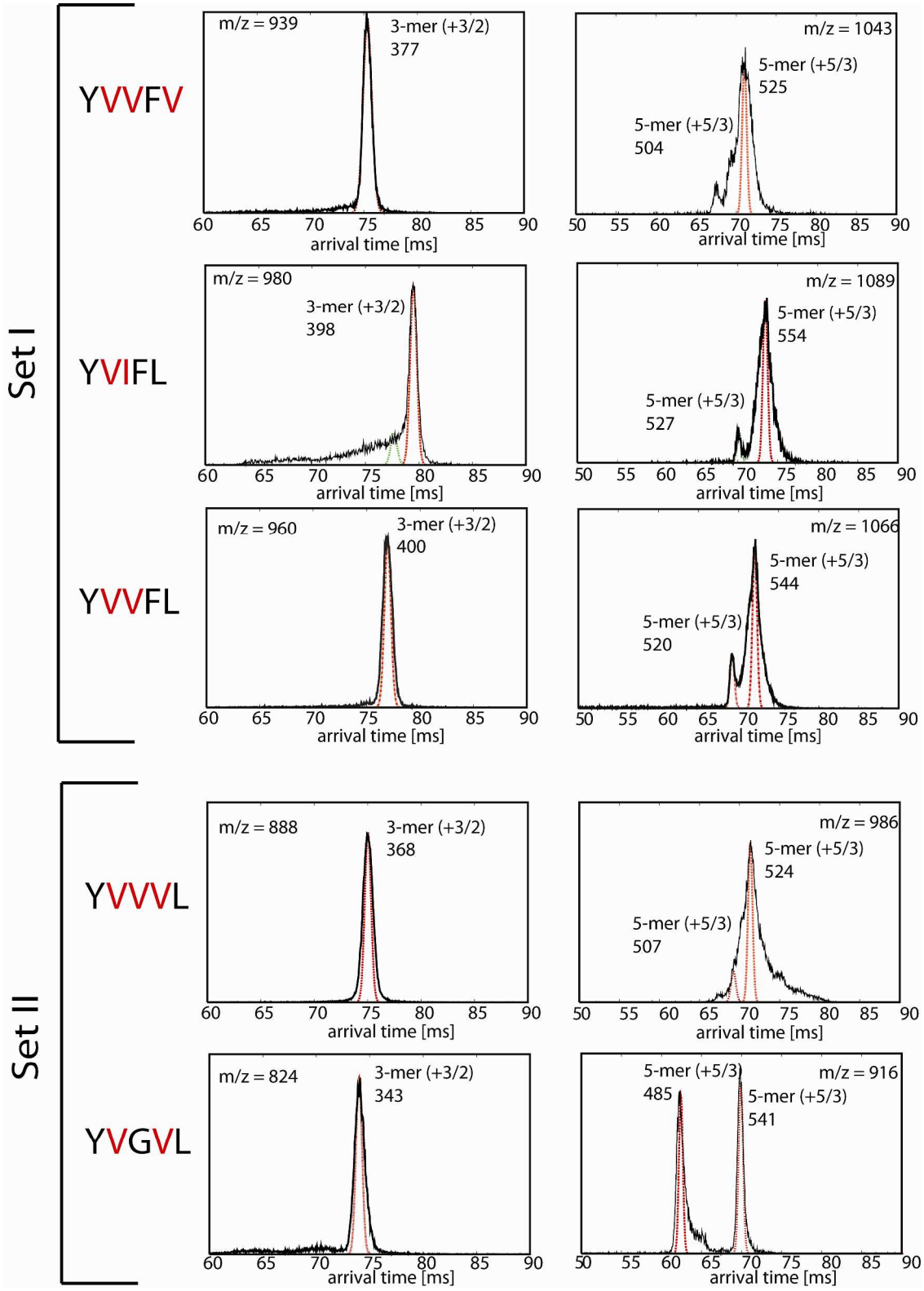

Figure S3. Representative ATDs of *n/z* 3/2 (left) and *n/z* 5/3 (right) of all five peptides. Peaks are annotated with *n/z* where *n* is oligomer size and *z* is charge, and the experimental cross sections.

S3. X-ray Crystallography

Table S1. Data Collection and refinement statistics for YVVFV and YVVFL

Data collection	**YVVFV**	**YVVFL**
Beam line	APS 24-ID-E	APS 24-ID-E
Resolution Å	1.1	1.9
Total unique reflections	3184	522
Total reflections observed	21226	3101
Space group	$P2_1$	P1
I/σ	14.5 (1.5)	19.1(1.1)
Completeness (%)	98.5	93.9
Wavelength Å	0.9791	0.9791
Unit Cell dimensions a b c (Å) α β γ (°)	 9.750 21.380 19.050 90.00 93.17 90.00	 9.613 13.827 14.835 90.61 103.12 108.30
Resolution Å	19.0-1.1	9.3-1.9
Rfree/Rwork (%)	14.9/18.7	15.1/19.9
Molecules in the Asymmetric unit	2	2
Rmsd bond length (Å)	0.010	0.006
Rmsd angles (°)	1.37	0.84
Ramachandran plot: Allowed Generous Disallowed	 100 0 0	 100 0 0

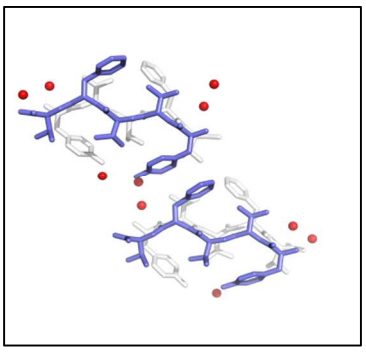

Figure S4. The second interface of the YVVFV structure with π stacking between opposing stacks of tyrosine 1 and phenylalanine 4.

References

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