Società Chimica Italiana
Divisione di Didattica Chimica

VI SCUOLA NAZIONALE DI DIDATTICA DELLA CHIMICA
"GIUSEPPE DEL RE"
XIII SCUOLA DI RICERCA EDUCATIVA E DIDATTICA CHIMICA
"ULDERICO SEGRE"
17 – 30 novembre 2021

Piano Nazionale Lauree Scientifiche

Per le diverse scale
Gerarchia e dinamica dei processi di self-assembly

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nast
Nanoscience
Nanotechnology
Innovative Instrumentation

Università di Roma
Tor Vergata

The Bottom-up Approach

Self-assembly

Definition: **The spontaneous and reversible association of molecular species to form larger, more complex supramolecular entities according to the intrinsic information contained in the components.**

Equilibrium methods

The final structure must be:
- reasonnably stable at room temperature
- weakly enough bound so that the system can explore the large number of configurations needed to find the desired configuration of lowest free energy.

The most stable structure in a given environment originates from a delicate balance between entropy (at a given temperature) and binding enthalpies.

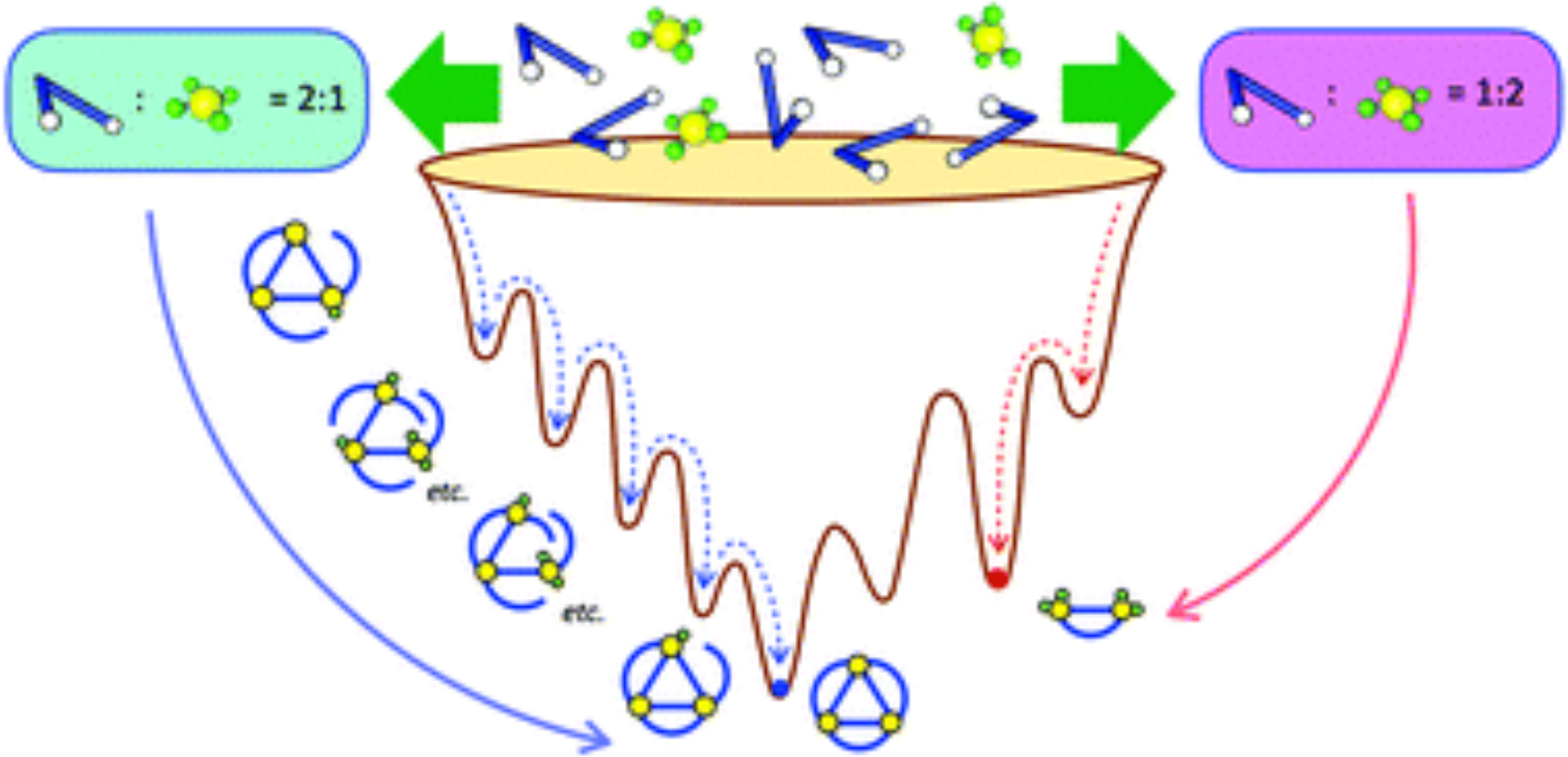
• **Self-healing**: Due to the reversible nature of the assembly process, self-assembling systems are able to correct 'mistakes' during assembly and gradually work their way towards the most thermodynamically stable product.

• The entropic penalty is somewhat offset by the release of solvent molecules that were previously interacting with the binding areas of the assembly components.

Entropy driven aggregation!

Kinetic trapping

Trapping the system in some non-equilibrium configuration.

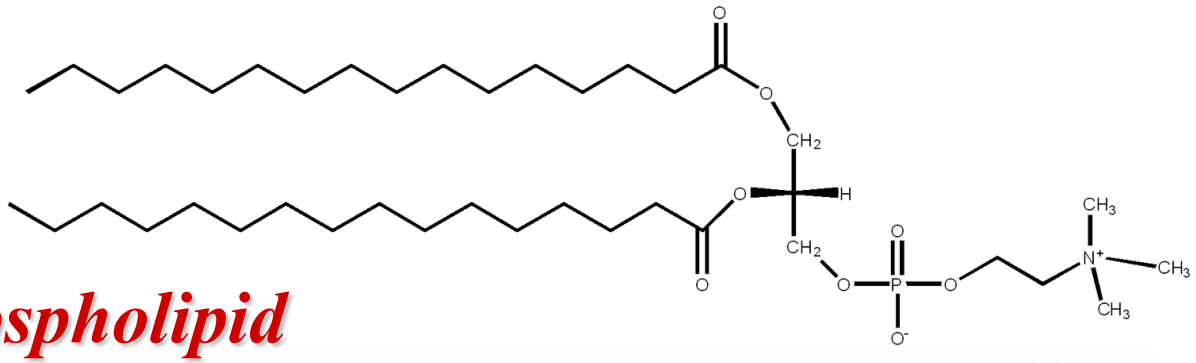


Self-assembly driving force

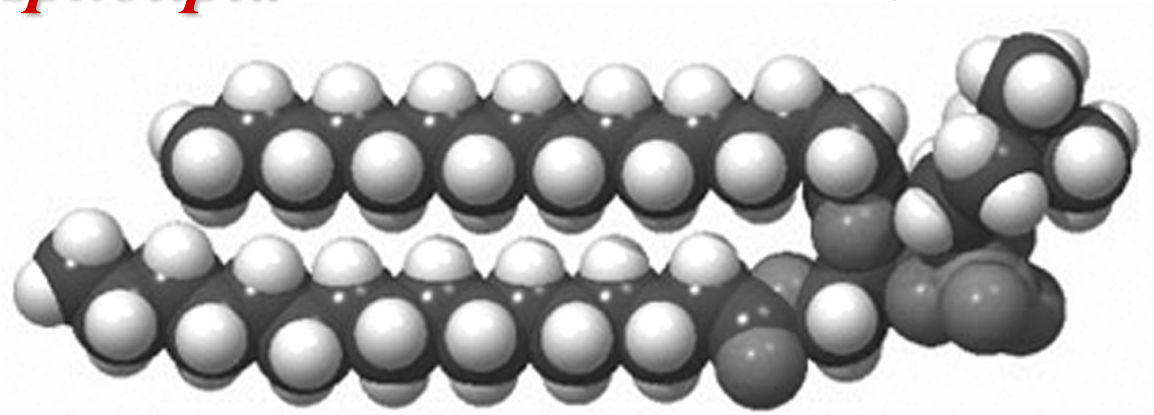
- **electrostatic, Van der Waals, HB interactions**
- **π-π interaction**
- **comparative solvation of monomers and aggregates**
- **Aggregation is an interfacial phenomenon**

- size and molecular shape

Amphiphiles



Phospholipid

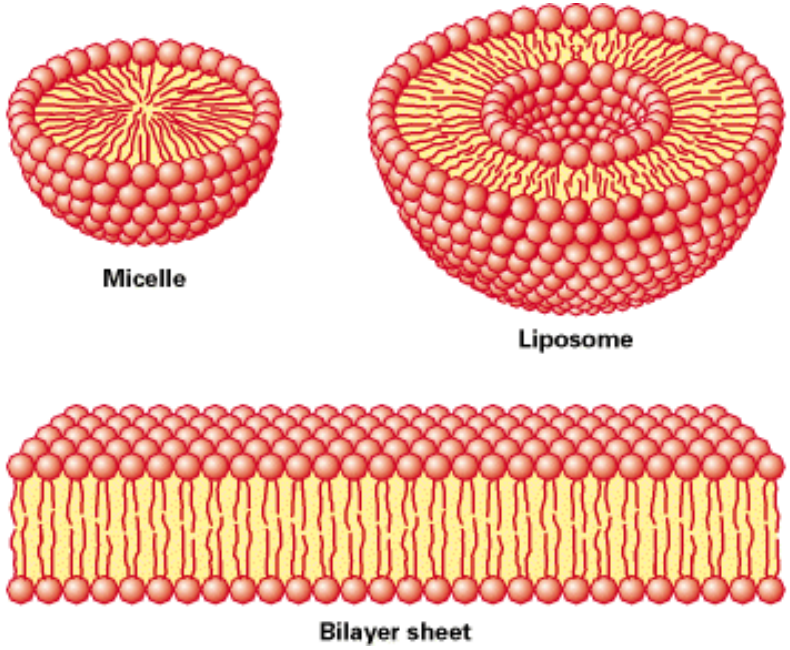


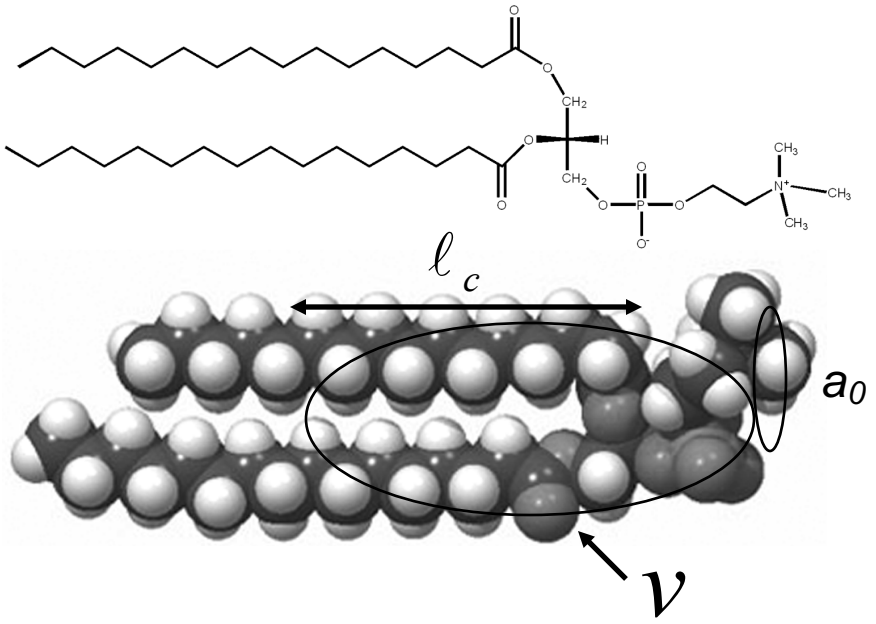
Polar head

Hydrophobic tail

Shape of aggregates

Packing effects depend on geometry





l_c = critical length of the hydrocarbon chain (maximum effective length)
v = volume occupied by the hydrocarbon chain
$\mathbf{a_0}$ = optimal area of the head group

Packing factor $\dfrac{v}{a_0 \ell_c}$

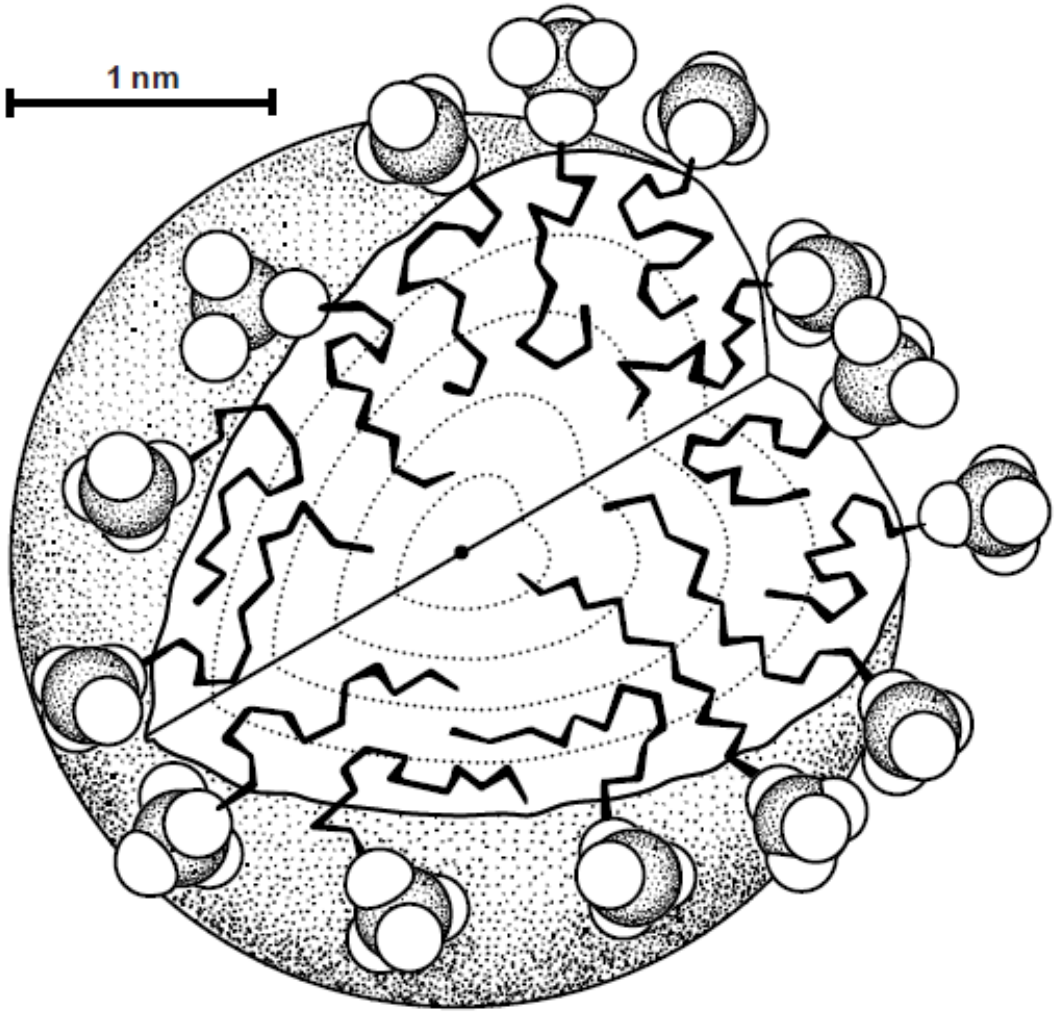
A dimensionless shape factor determining the aggregate geometry.

$$\frac{v}{a_0 \ell_c} < \frac{1}{3}$$ ***Spherical micelles***

$$\frac{1}{3} < \frac{v}{a_0 \ell_c} < \frac{1}{2}$$ ***Non-spherical micelles***

$$\frac{1}{2} < \frac{v}{a_0 \ell_c} < 1$$ ***Vesicles or bilayers***

$$\frac{v}{a_0 \ell_c} > 1$$ ***Inverted cones***

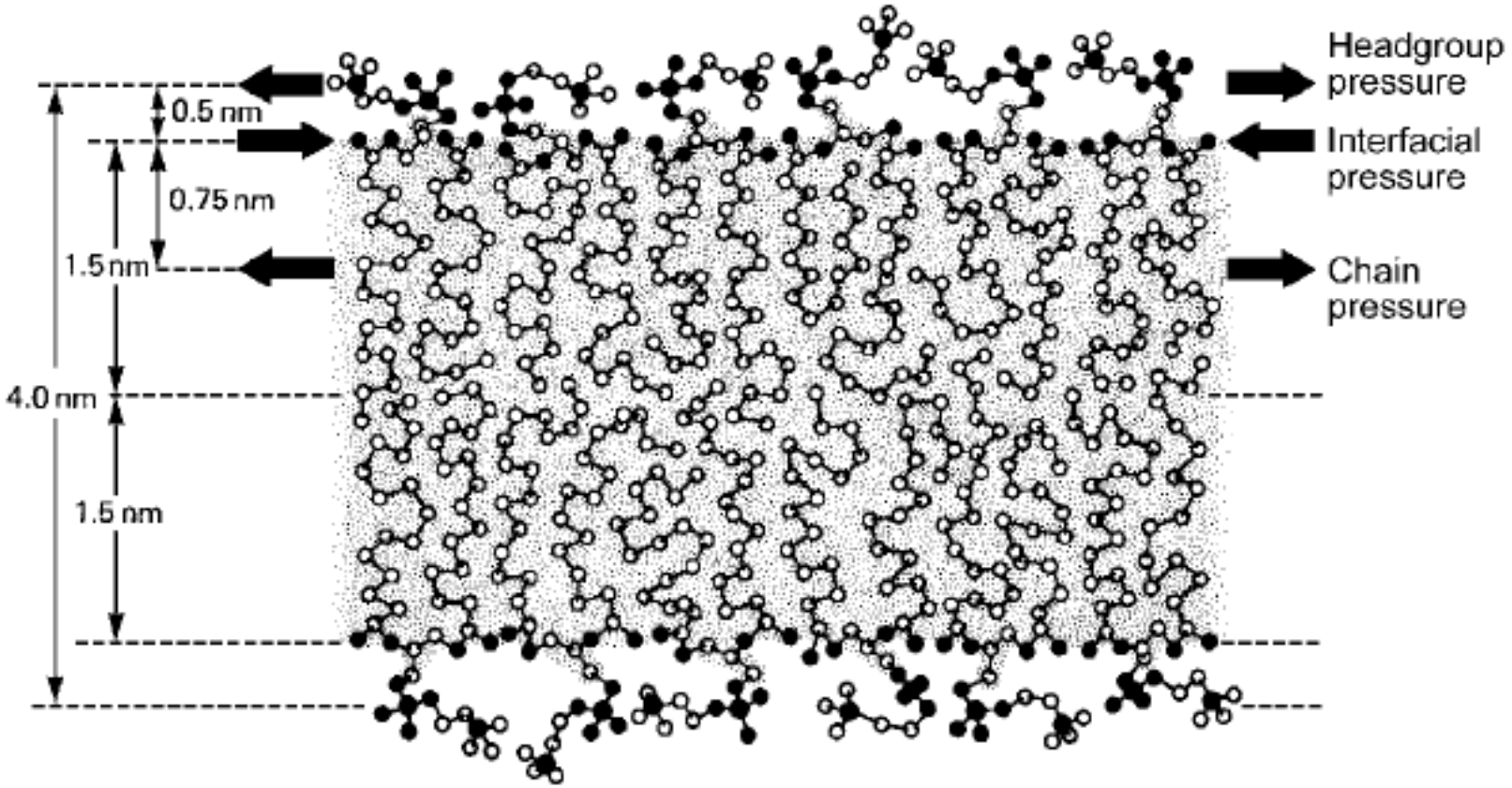


SDS micelles (N=60).

Note that all segments of the chain spend an appreciable proportion of time near the micelle surface.

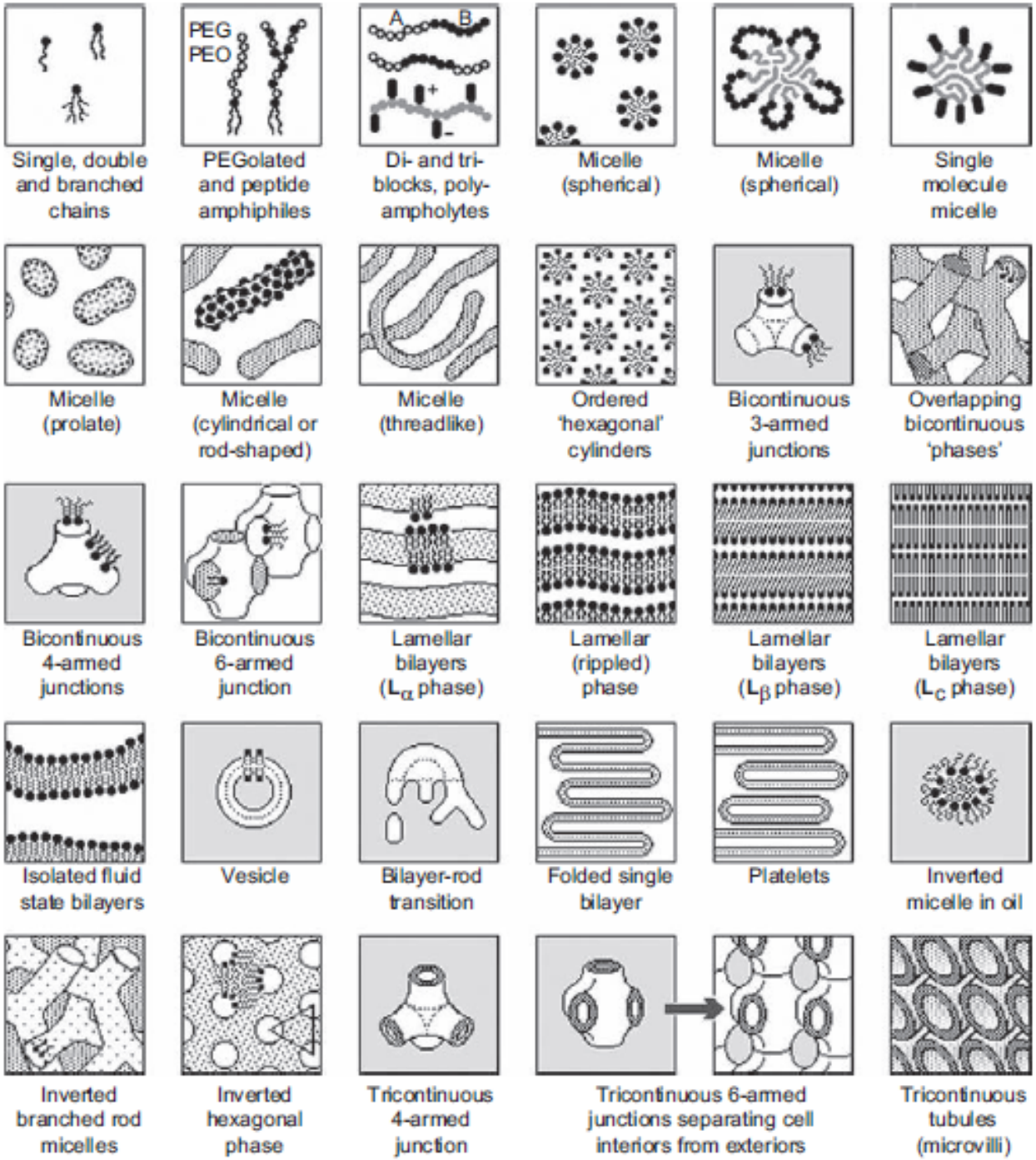
Bilayers

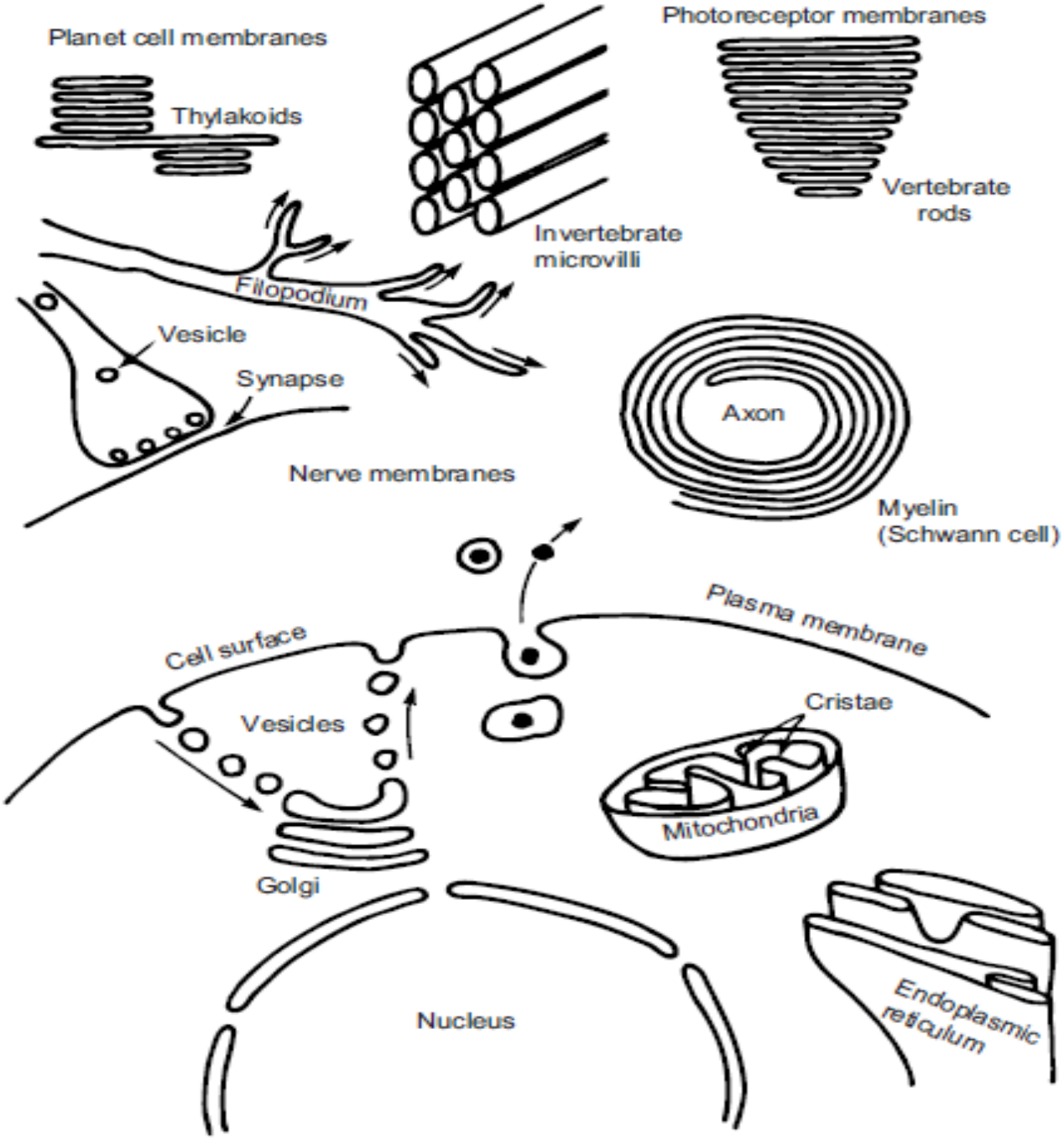
$$\frac{v}{a_0 \ell_c} \approx 1$$



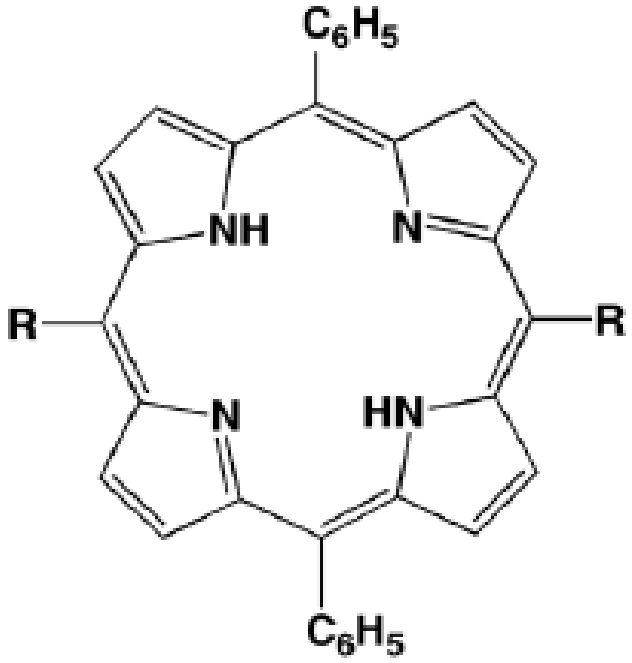
Phosphatidyl choline (PC)

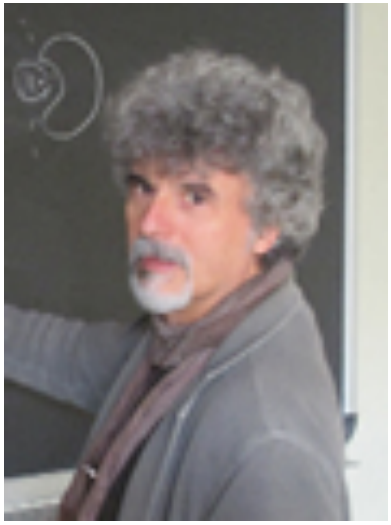
MESOPHASES


Single, double and branched chains
PEG
PEO
PEGolated and peptide amphiphiles
A
B
+
−
Di- and tri-blocks, poly-ampholytes
Micelle (spherical)
Micelle (spherical)
Single molecule micelle
Micelle (prolate)
Micelle (cylindrical or rod-shaped)
Micelle (threadlike)
Ordered 'hexagonal' cylinders
Bicontinuous 3-armed junctions
Overlapping bicontinuous 'phases'
Bicontinuous 4-armed junctions
Bicontinuous 6-armed junction
Lamellar bilayers (L_α phase)
Lamellar (rippled) phase
Lamellar bilayers (L_β phase)
Lamellar bilayers (L_c phase)
Isolated fluid state bilayers
Vesicle
Bilayer-rod transition
Folded single bilayer
Platelets
Inverted micelle in oil
Inverted branched rod micelles
Inverted hexagonal phase
Tricontinuous 4-armed junction
Tricontinuous 6-armed junctions separating cell interiors from exteriors
Tricontinuous tubules (microvilli)

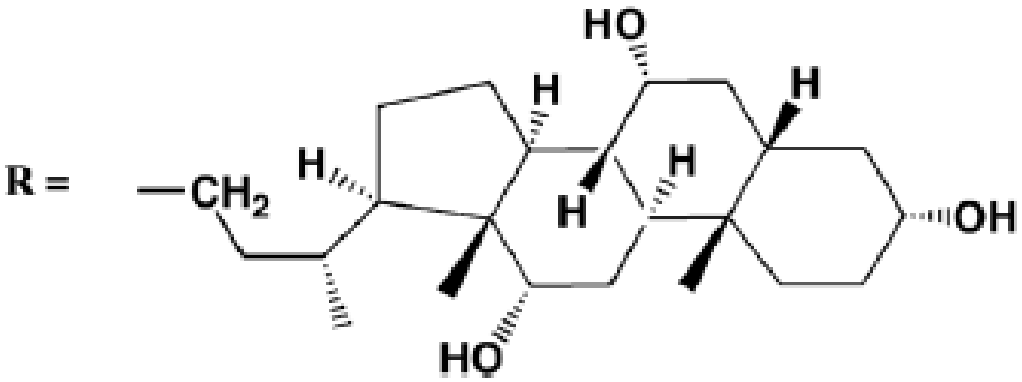

Planet cell membranes
Thylakoids
Photoreceptor membranes
Vertebrate rods
Invertebrate microvilli
Filopodium
Vesicle
Synapse
Nerve membranes
Axon
Myelin (Schwann cell)
Plasma membrane
Cell surface
Vesicles
Cristae
Mitochondria
Golgi
Nucleus
Endoplasmic reticulum

Chiral self-assembly





Donato Monti

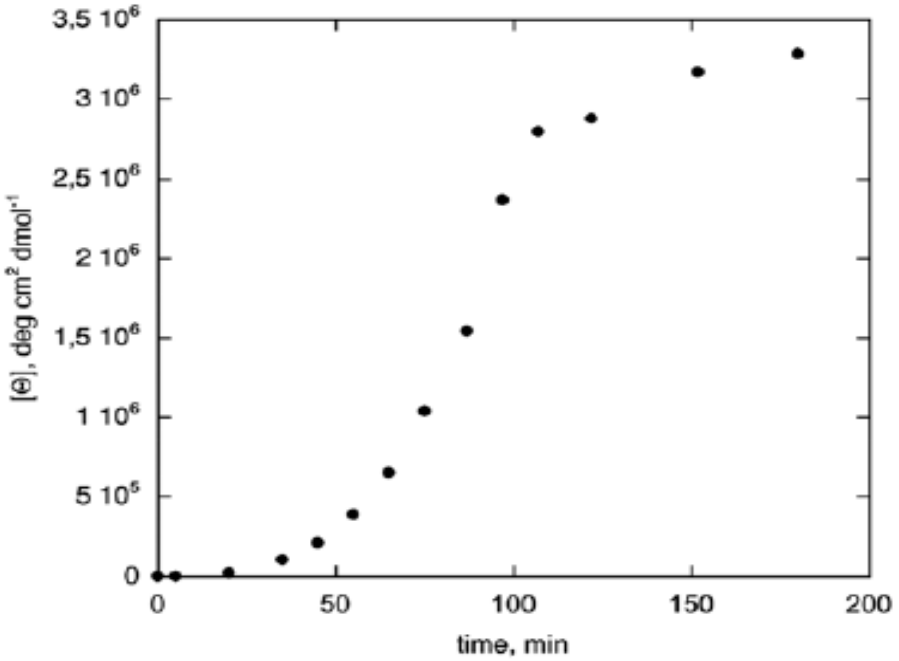


Cholic acid

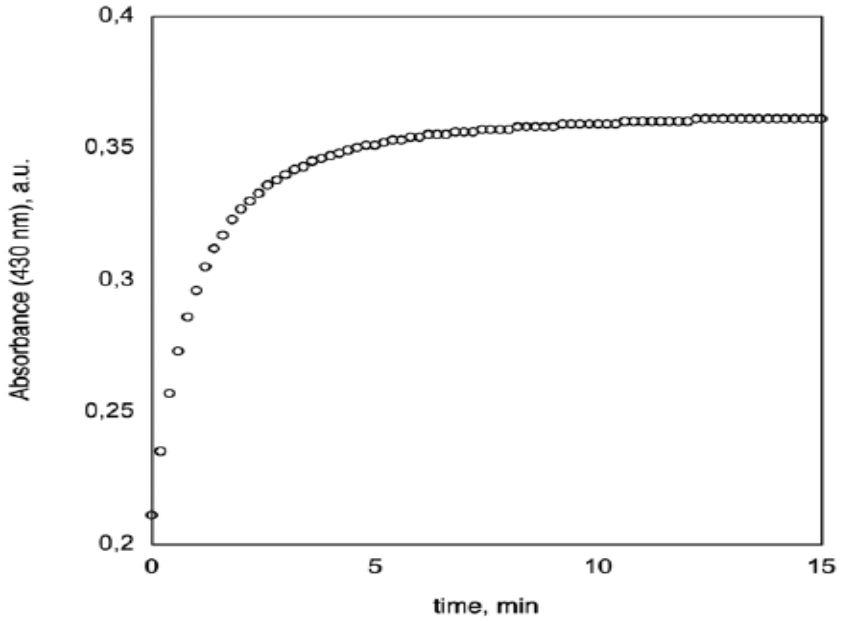
Org. Biomol. Chem. 2014, 12, 3956-3963

Concentration-dependent aggregation

3 µM

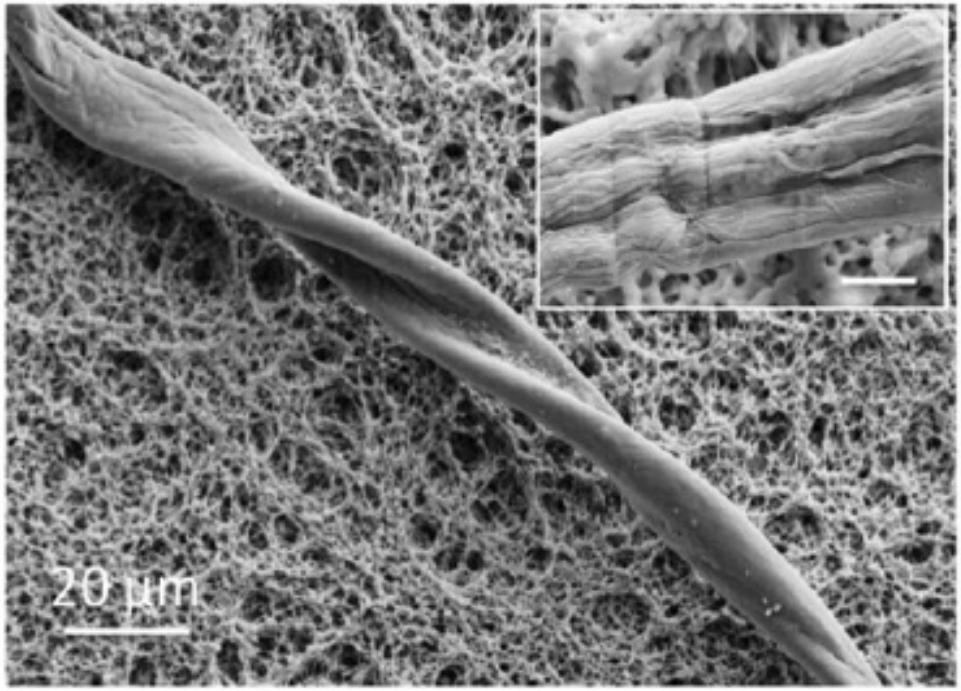


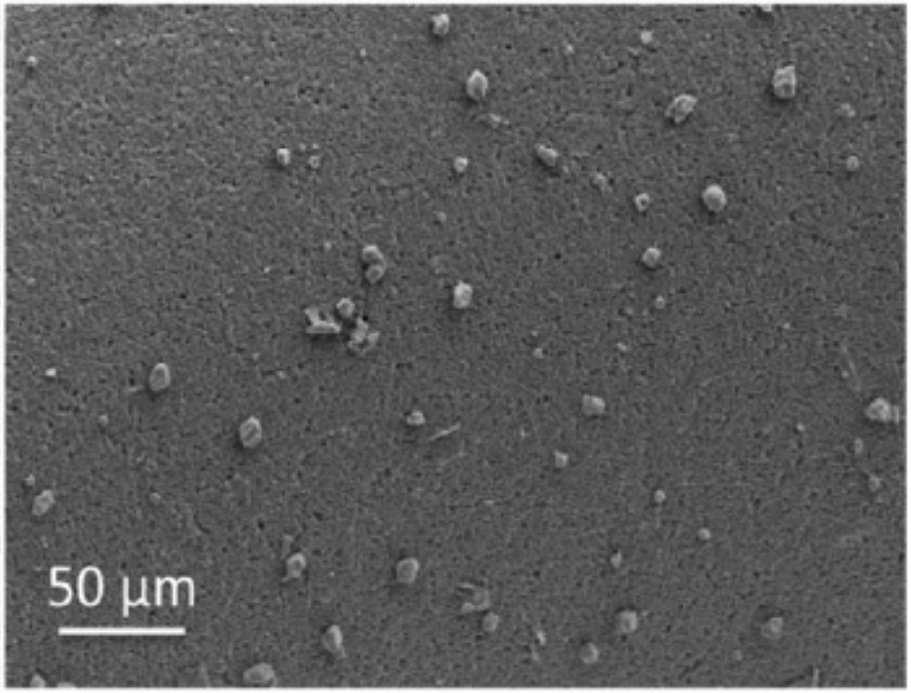
10 µM



in DMA/H_2O 58/42 (v/v)

Imaging Steroid Porphyrins superstructures





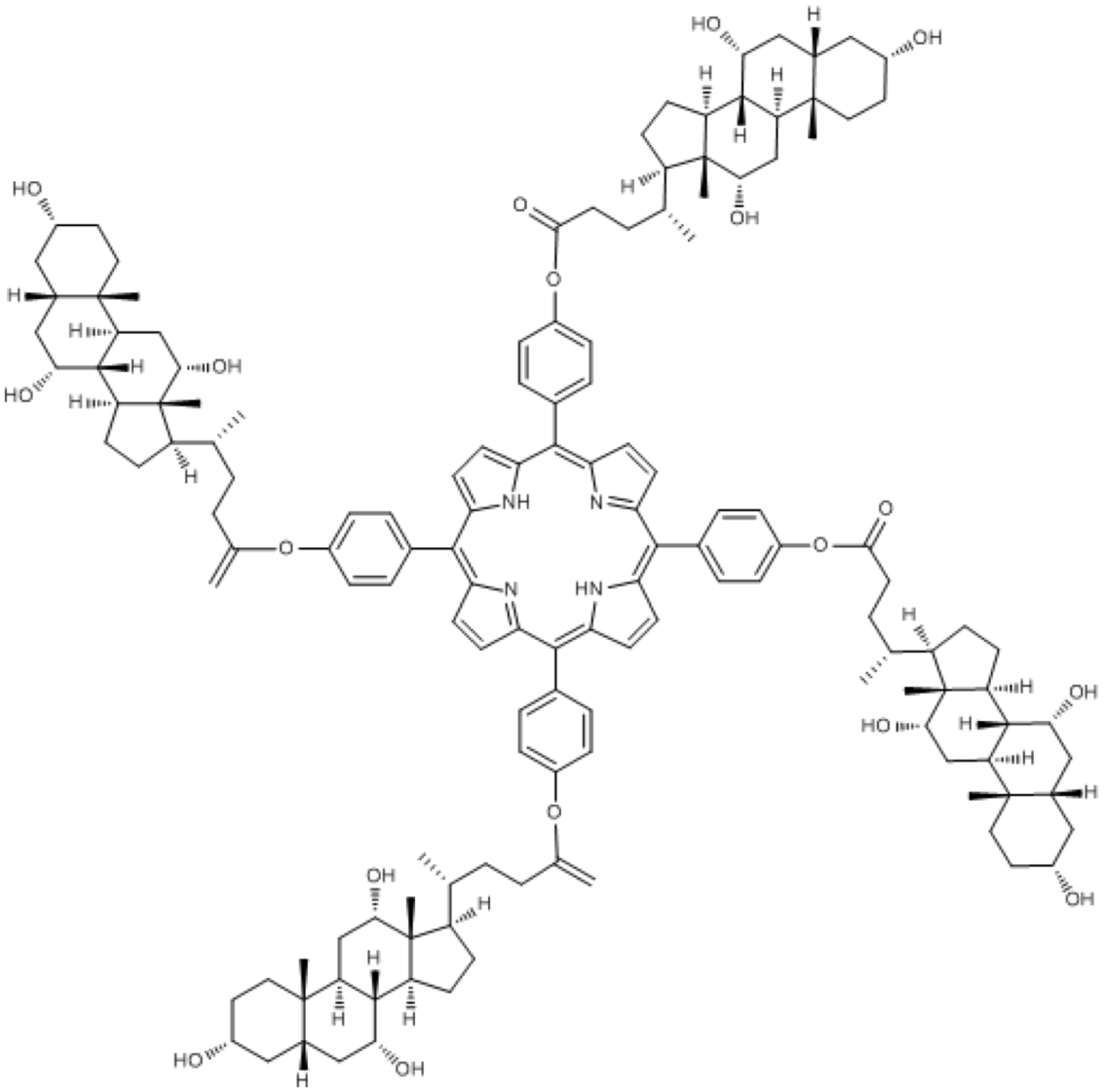
3µM in DMA/H_2O 58/42 (v/v)

10µM in DMA/H_2O 58/42 (v/v)

Entangled fibrils!

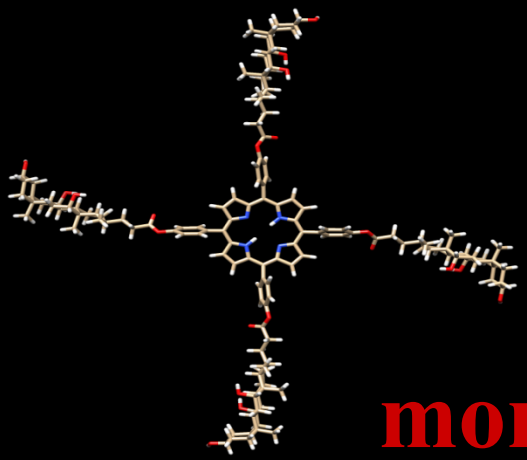
Globules!

Tetrasteroid porphyrins

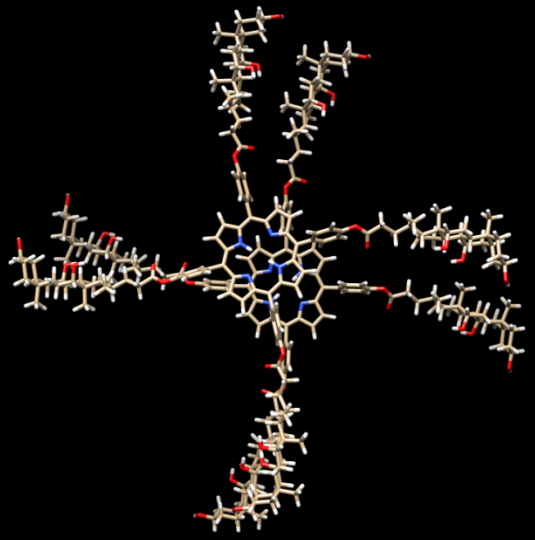


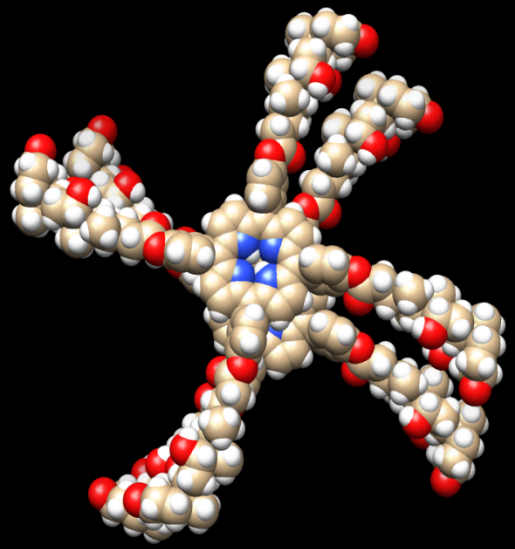
TSPc

TSPc

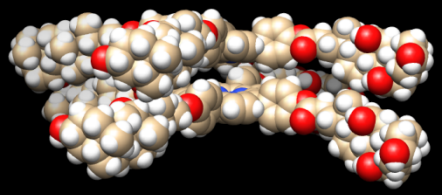


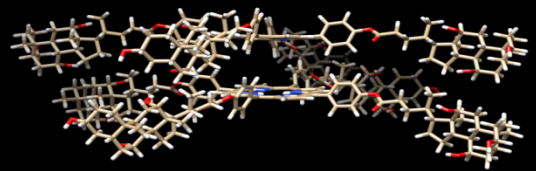
monomer



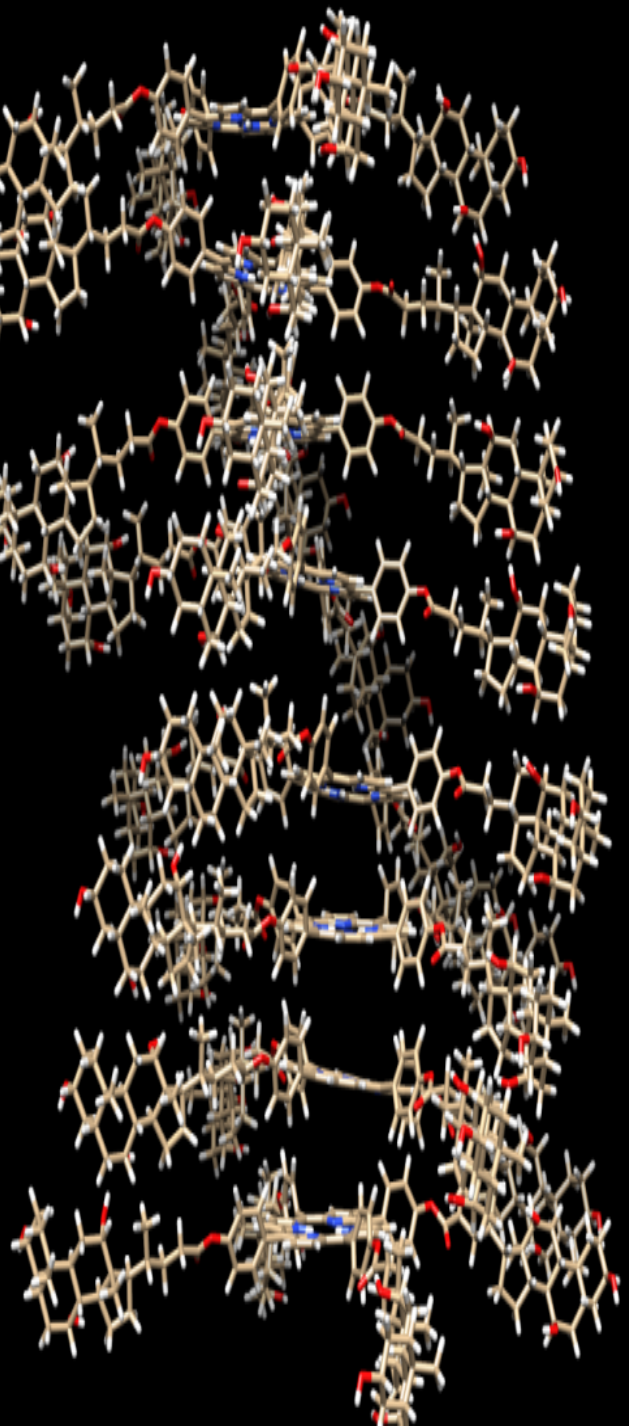


dimer

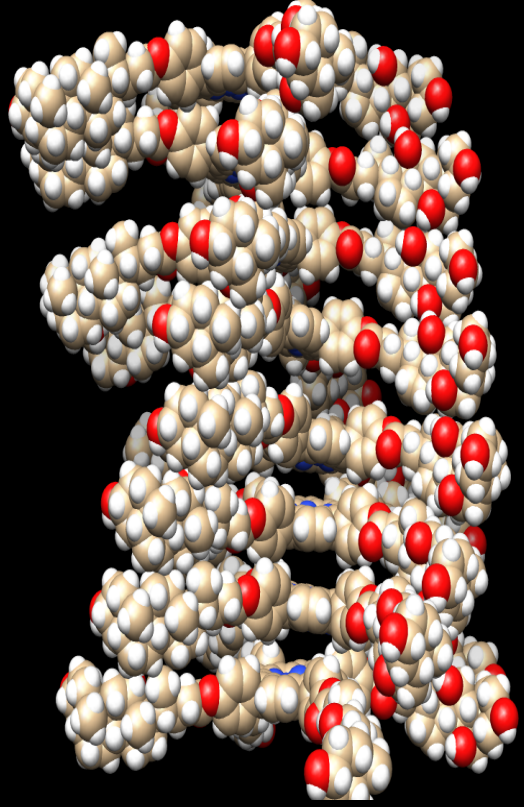


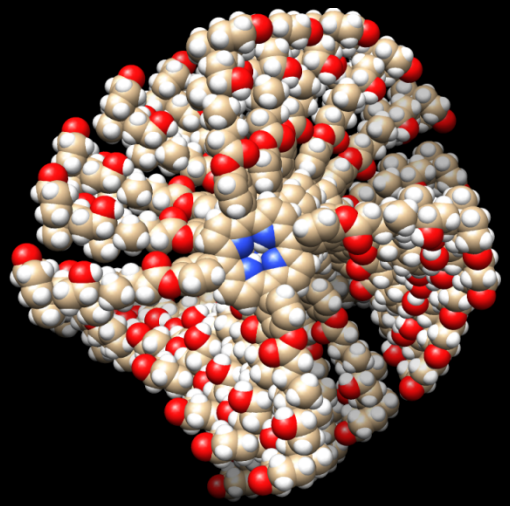


TSPc



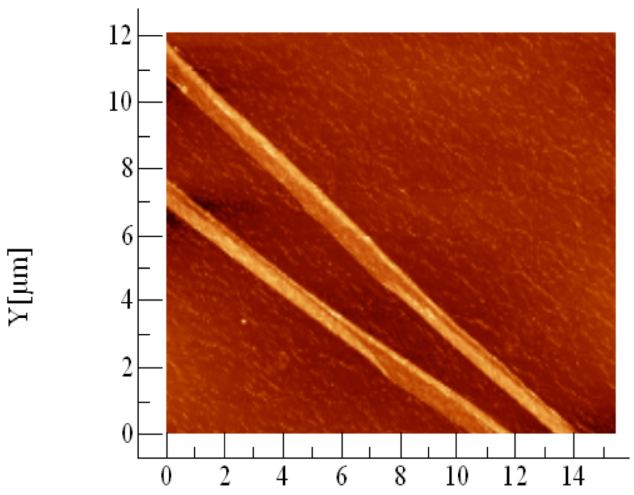
octamer

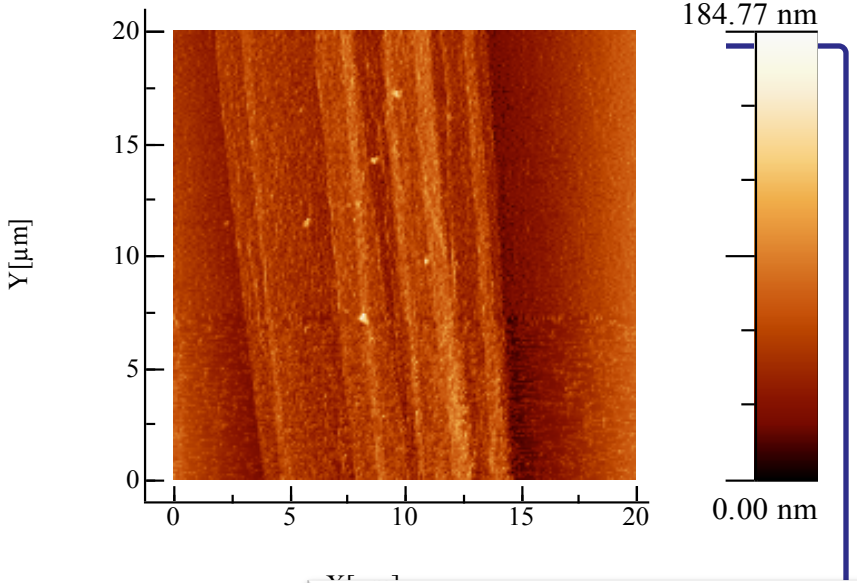


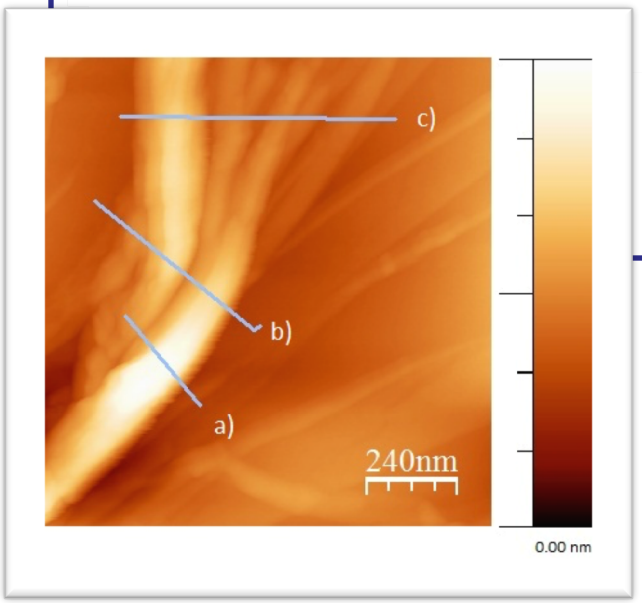


Atomic Force Microscopy

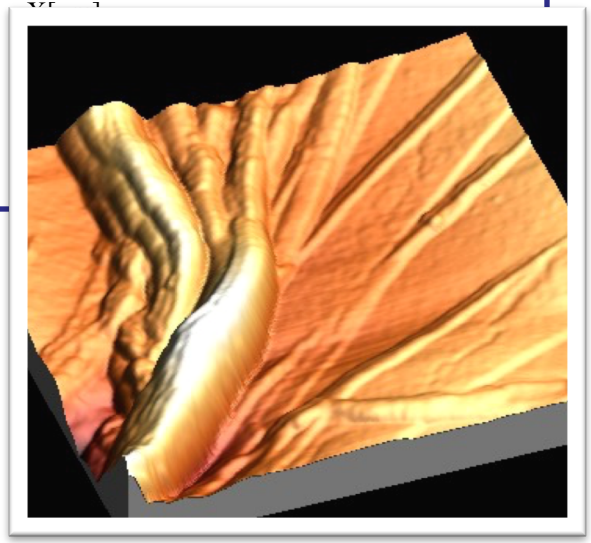
TSP: LB deposition on silicon wafer





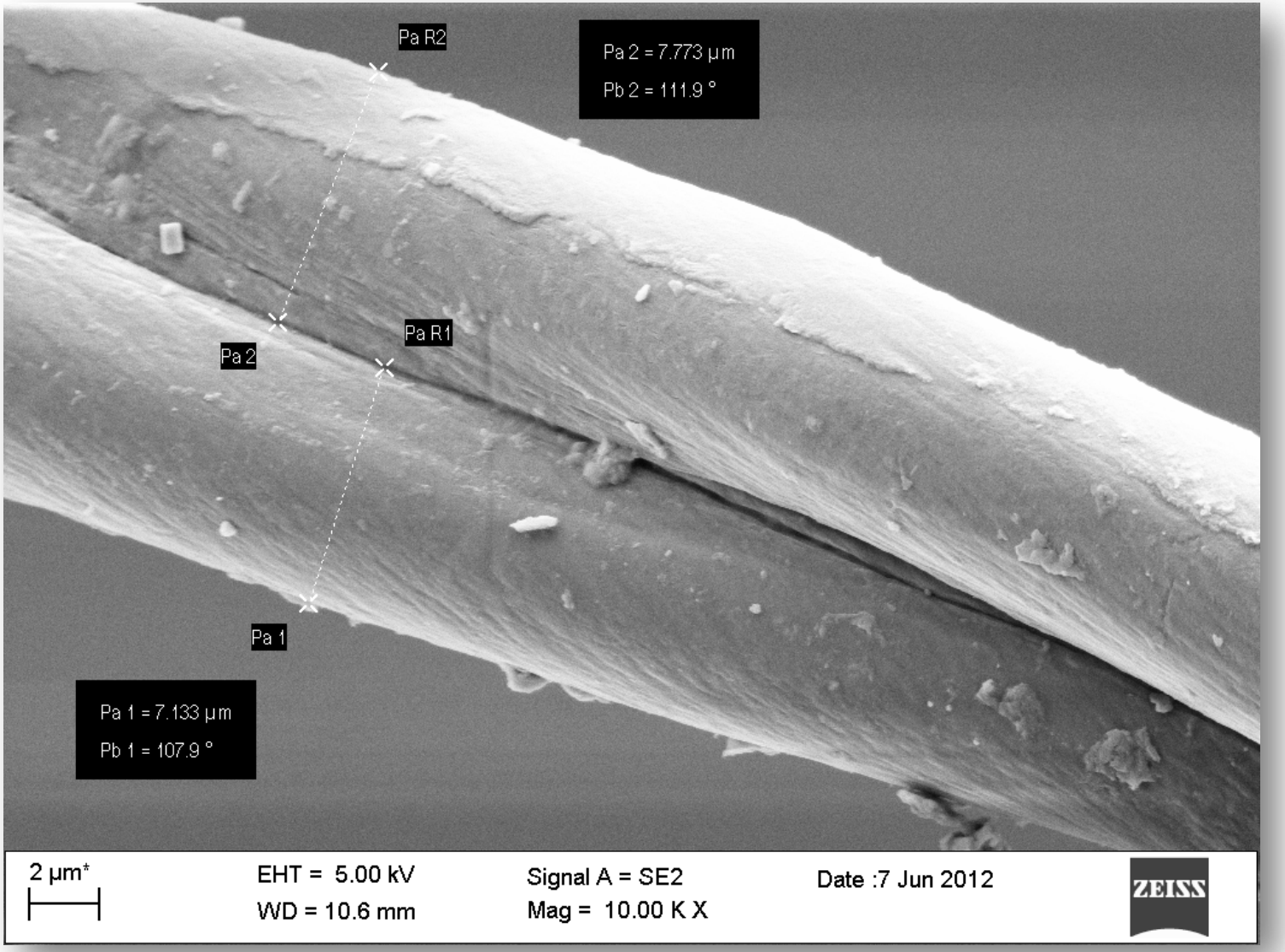


Diameter: 130 ± 30 nm
Thickness: 80 ± 20 nm



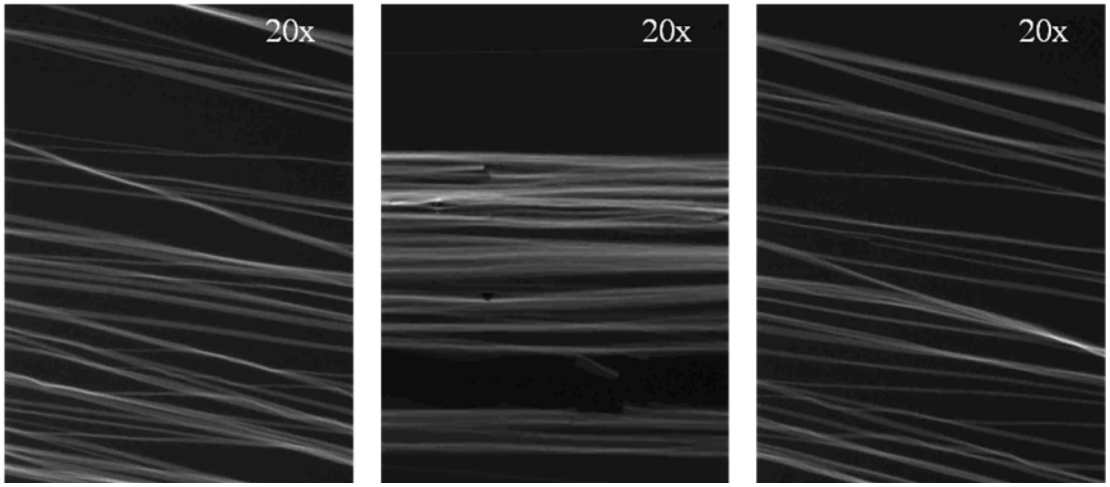
Scanning Electron Microscopy

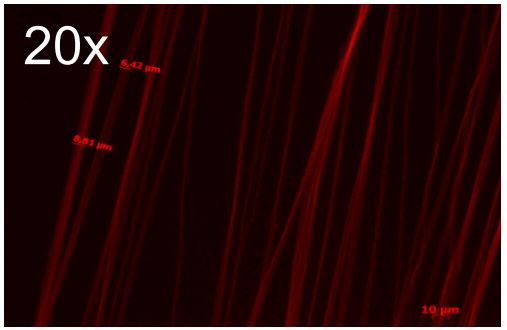
TSPc multilayer on glass

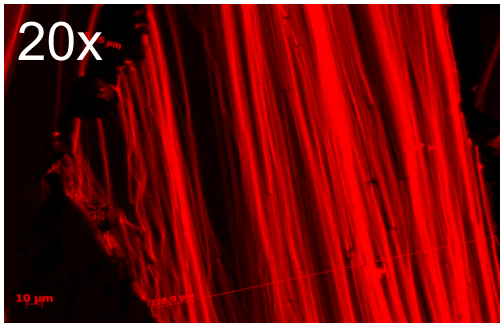


Fluorescence Microscopy of LB films

TSP (multilayer)

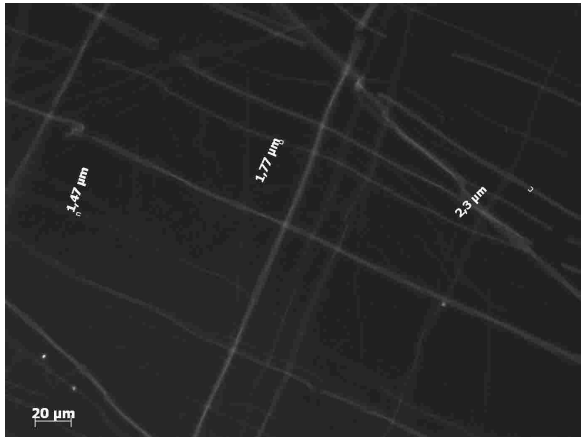


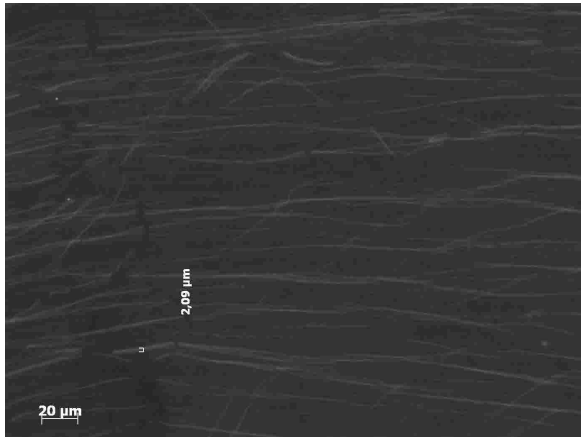




Fibrils of millimetric length

TSPc (multilayer)



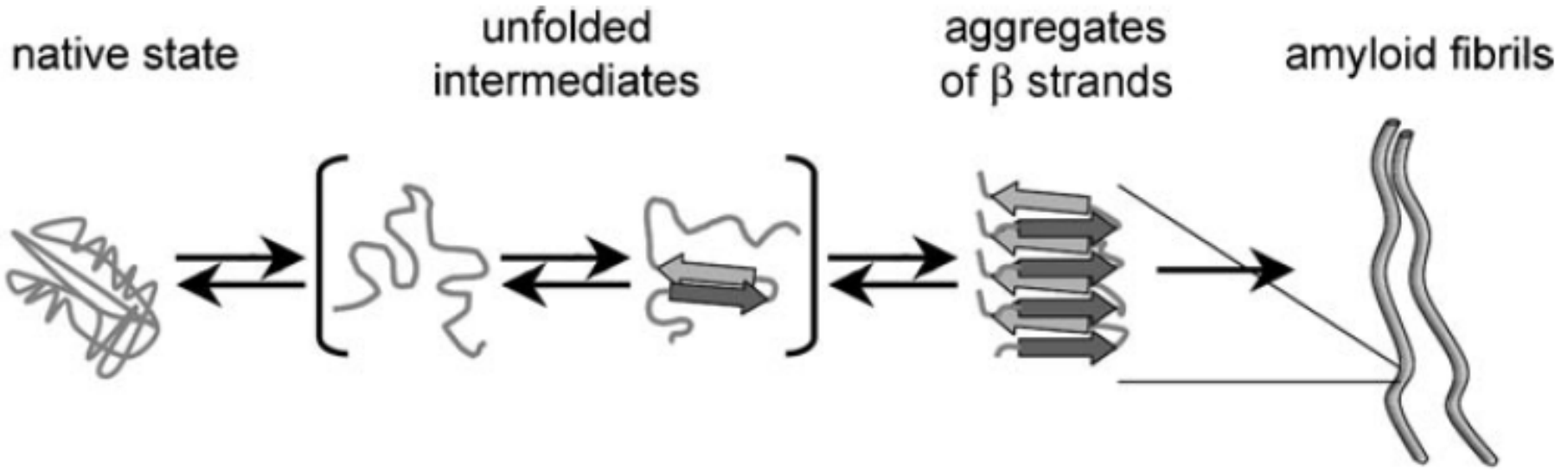


Thickness:

2.4 ± 0.6 µm

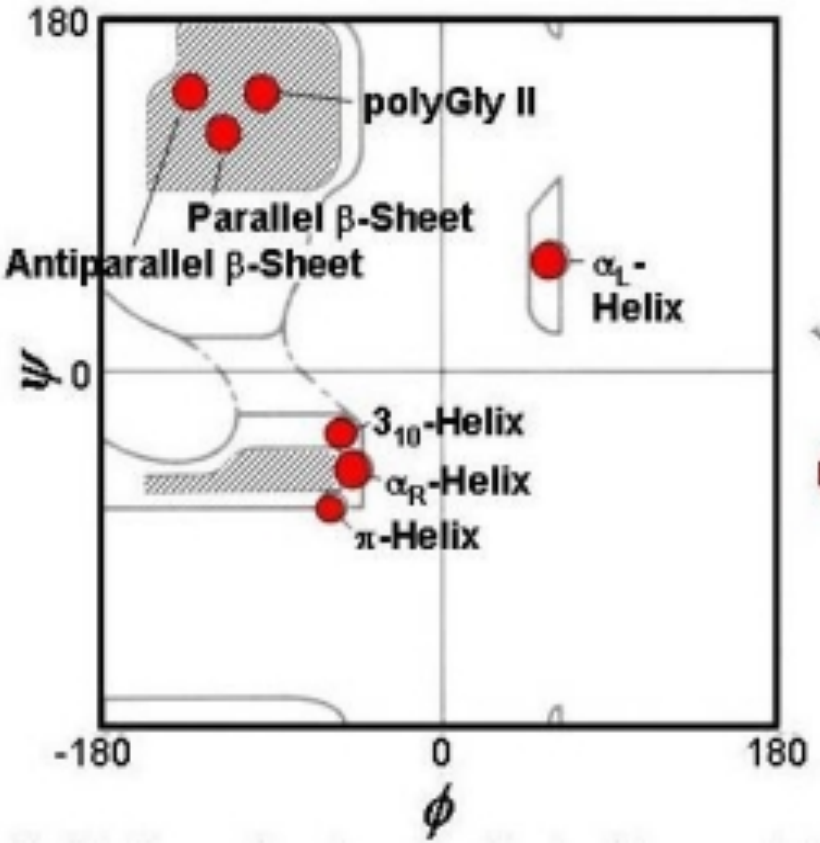
Hierarchical self-assembly

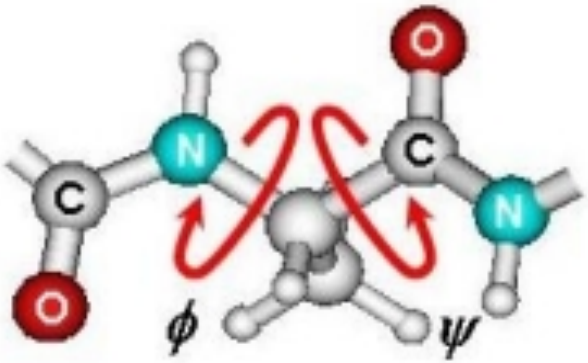
A self-assembly process that can be broken down into distinct steps that can not proceed until the preceeding step is complete.



Peptide Foldamers

'Foldamers are molecules that have well-defined and predictable folding properties in solution.'

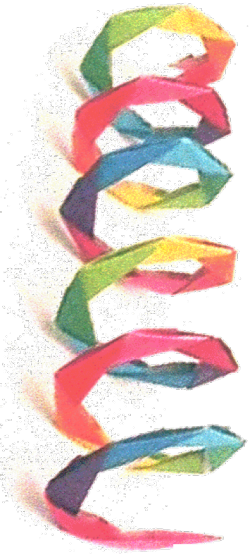


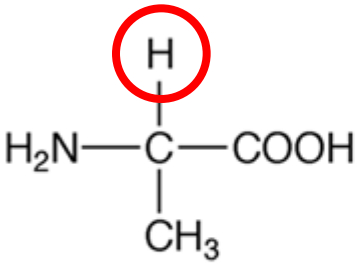


Claudio Toniolo

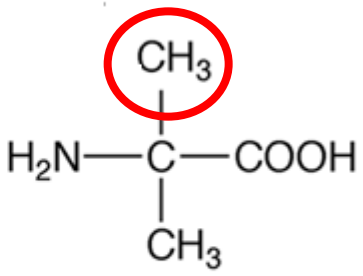
Fernando Formaggio

$C^{\alpha,\alpha}$-disubstituted aminoacids

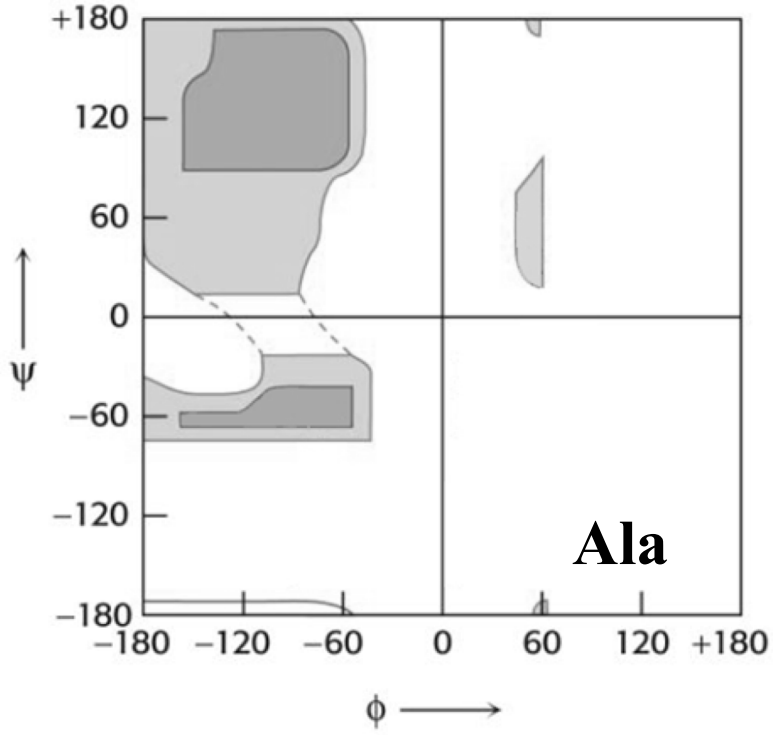


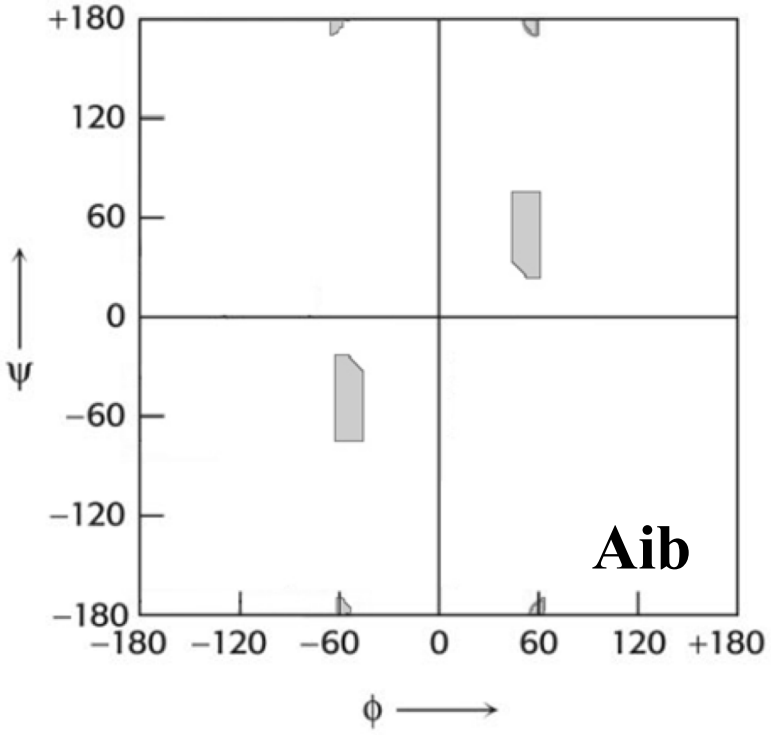


Ala

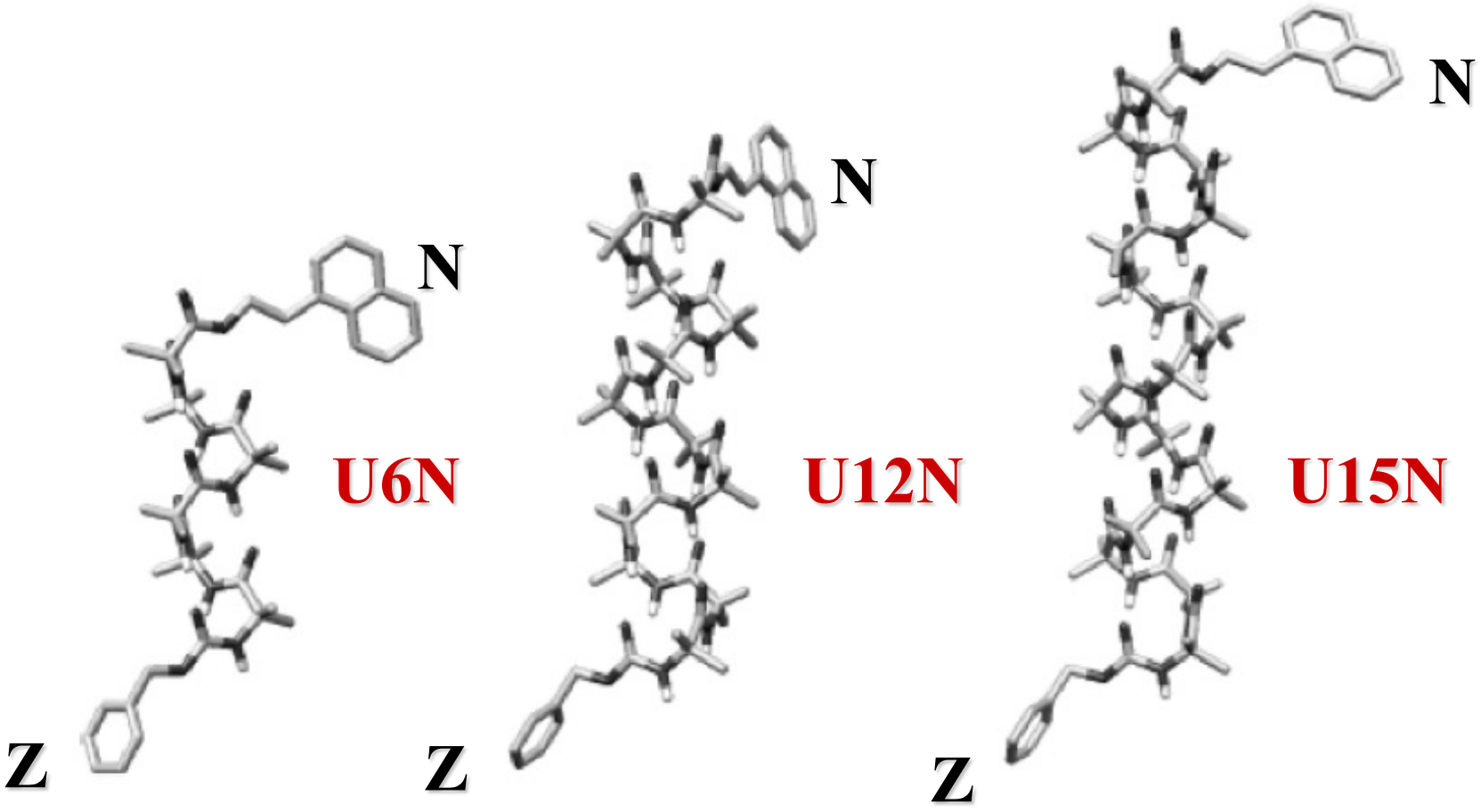


Aib





Aggregation of conformationally constrained model peptides

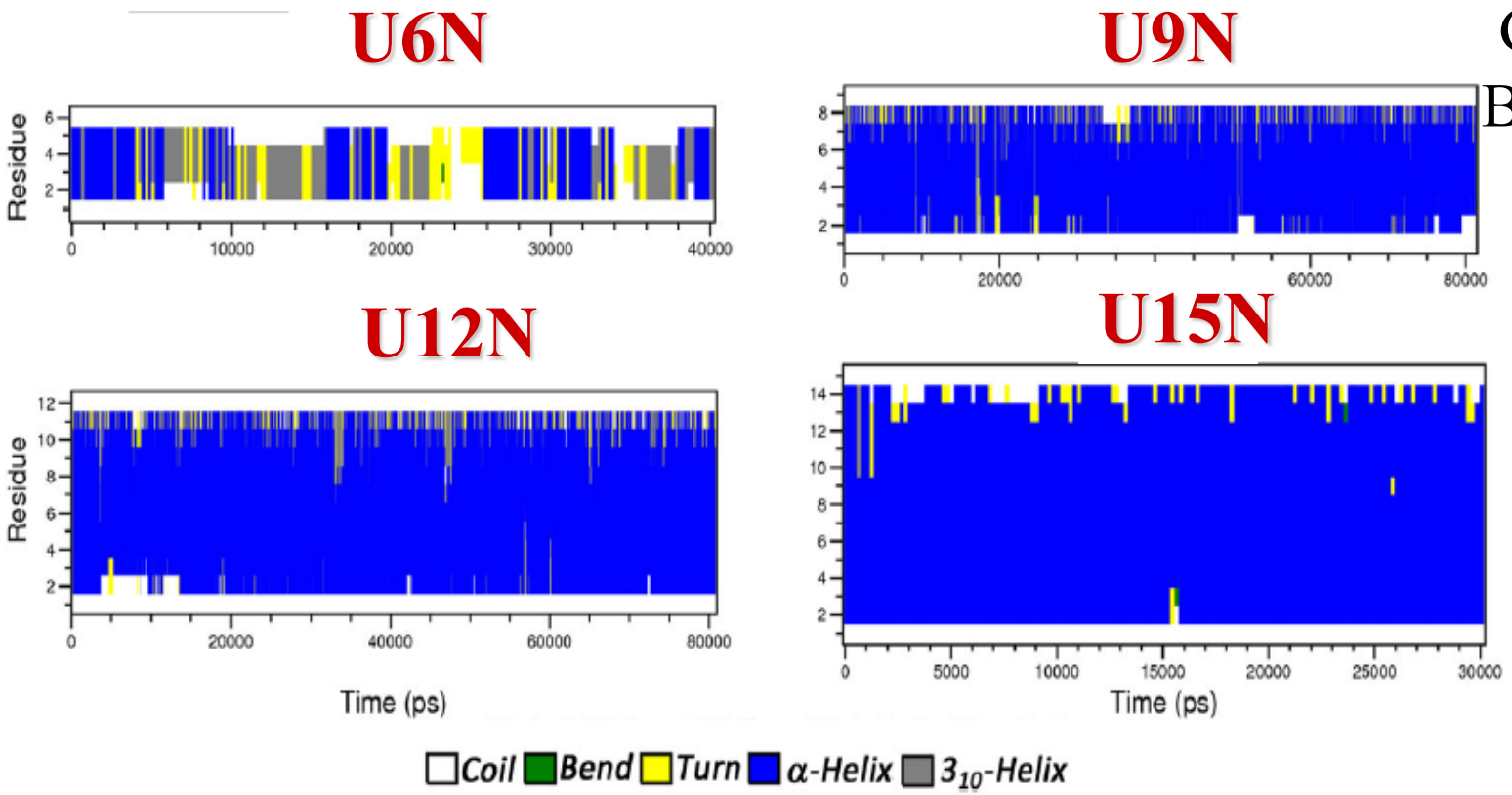


U = Aib; N = Naphthyl; Z = Benzyloxycarbonyl

***J. Phys. Chem. B* 2013, 117, 5448-5459**

Molecular Dynamics

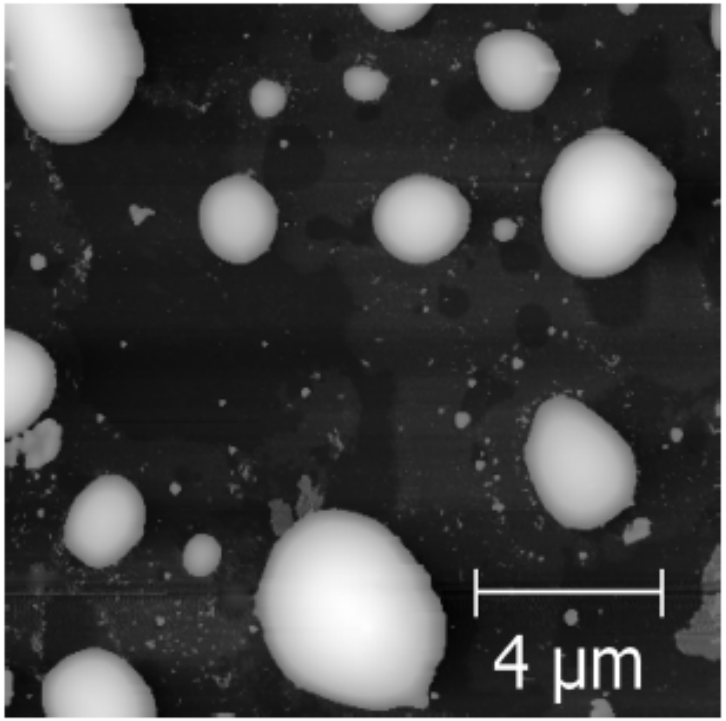
Gianfranco Bocchinfuso



For the longer homologues of the series (n ≥ 9), unfolding events during the simulation time were not detected.

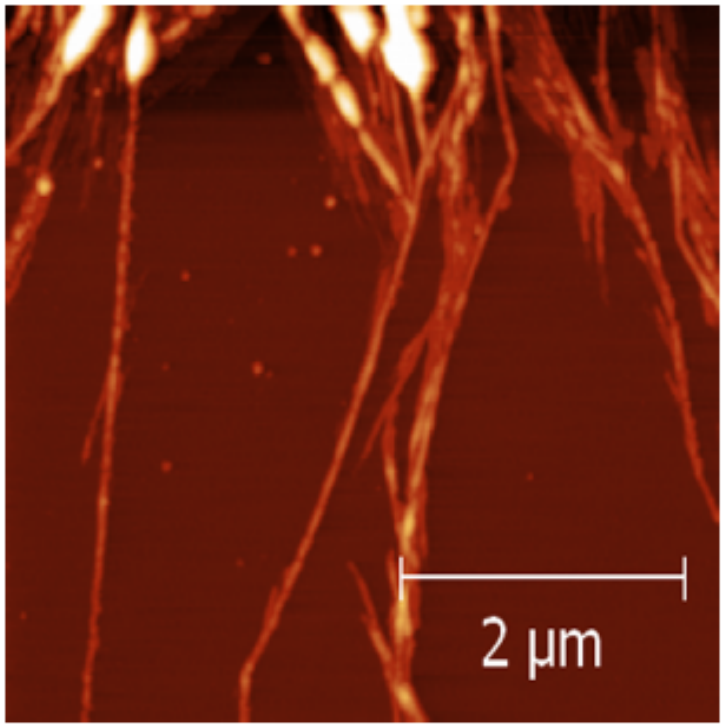
Atomic Force Microscopy

10μM 70/30 v/v MeOH/H_2O solutions on mica



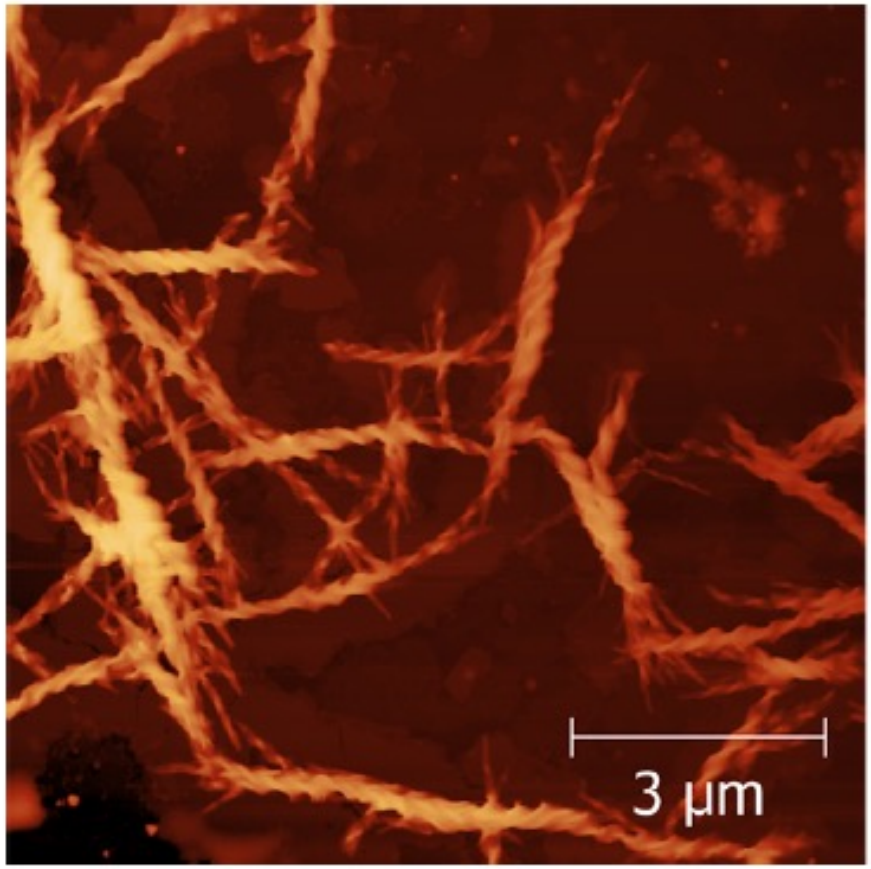
U6N

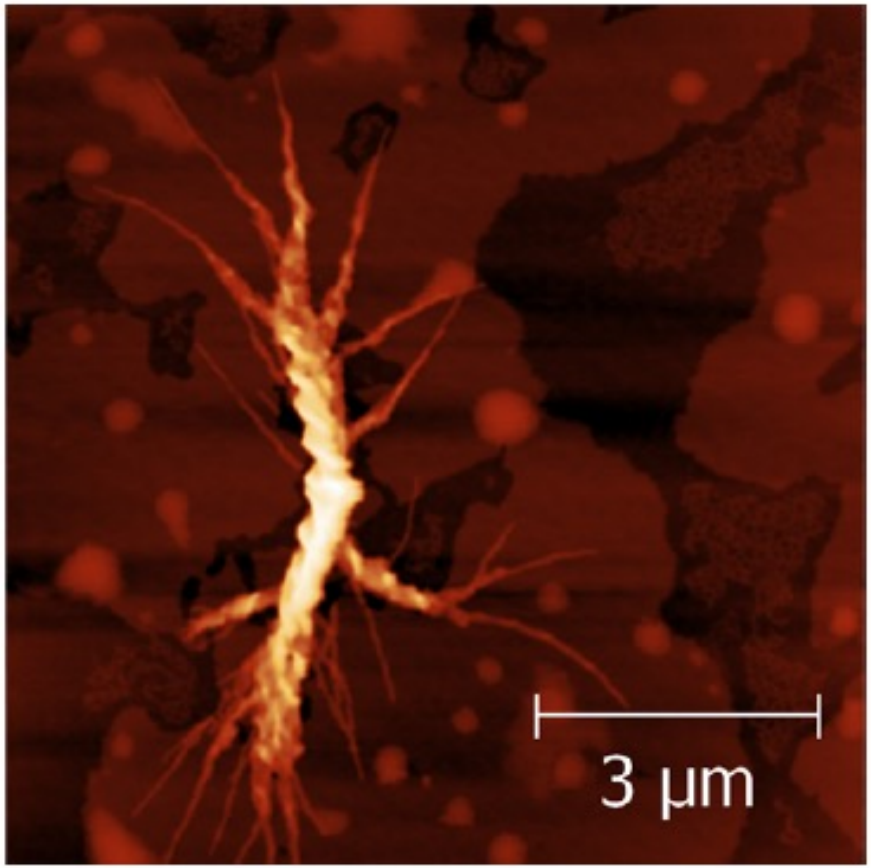
Hydrophobic effects predominate



U15N

Secondary structure drives hierarchical self-assembly





U12N

(from 125 µM 70/30 v/v MeOH/H_2O deposition solution)

Soft Matter

PAPER

View Article Online
View Journal | View Issue

A single-residue substitution inhibits fibrillization of Ala-based pentapeptides. A spectroscopic and molecular dynamics investigation†

Cite this: *Soft Matter*, 2014, 10, 2508

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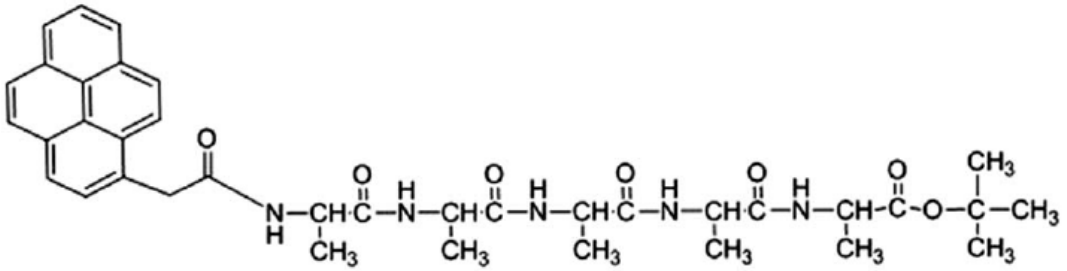
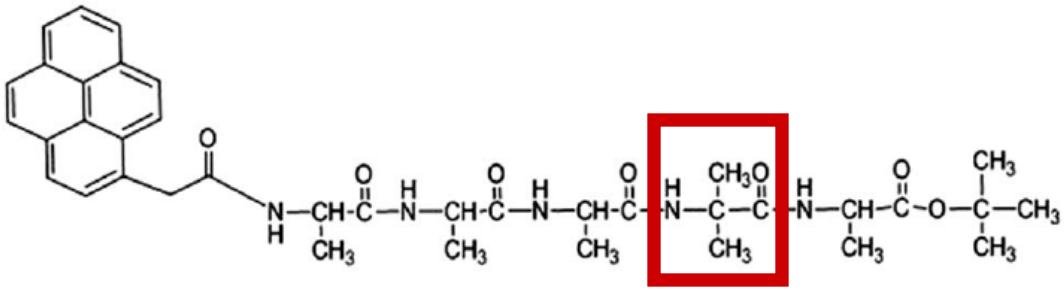


Py-CH_2-CO-(L-Ala)$_5$-OtBu (PyA5)

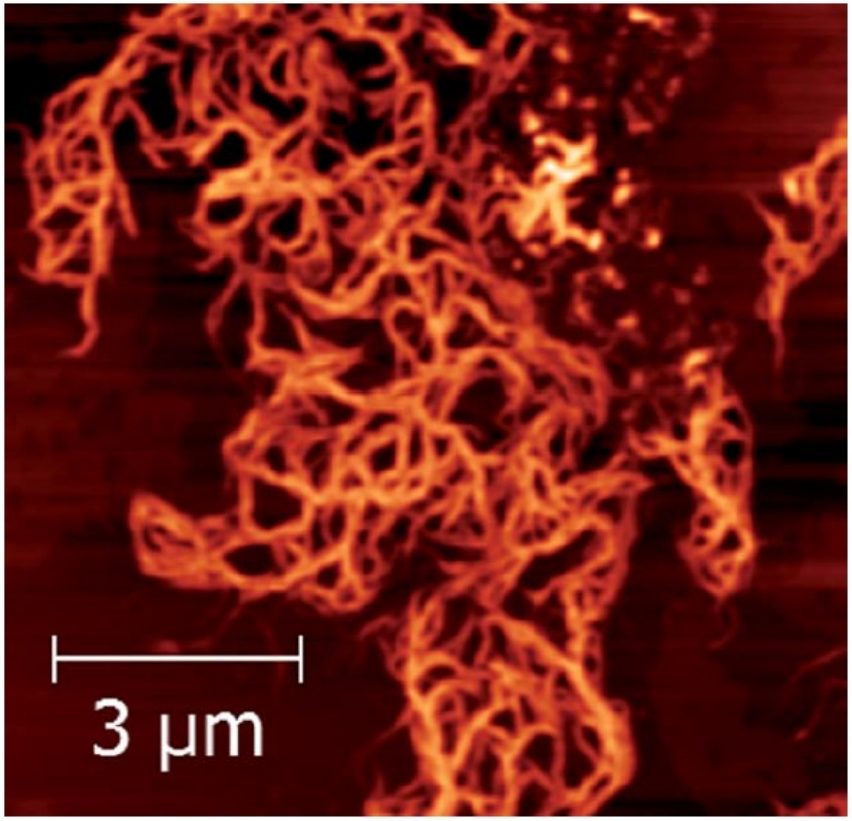


Py-CH_2-CO-(L-Ala)$_3$-Aib-L-Ala-OtBu (PyA3UA)

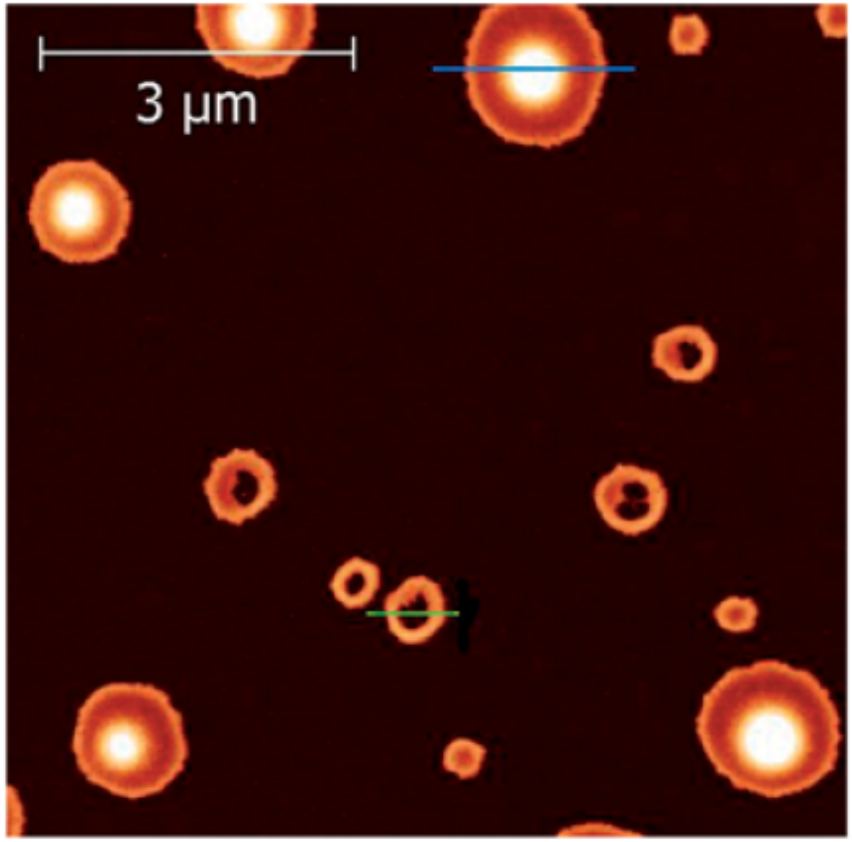
***Soft Matter* 2014, *10*, 2508-251**

Atomic Force Microscopy

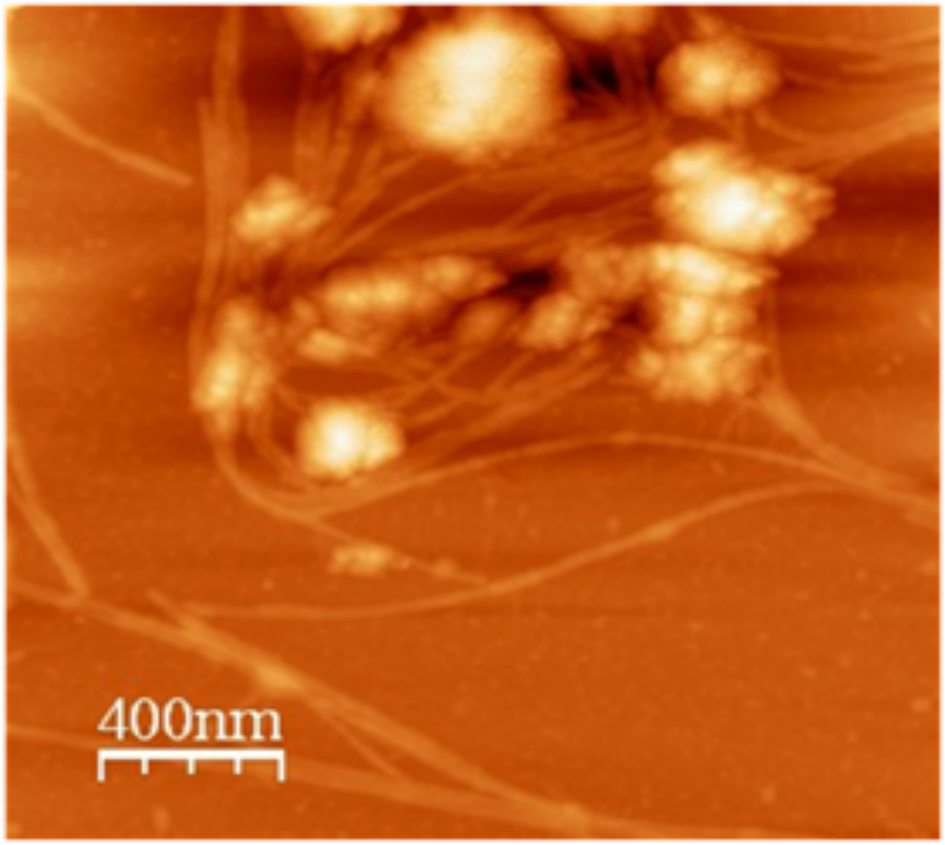
PyA5 on mica

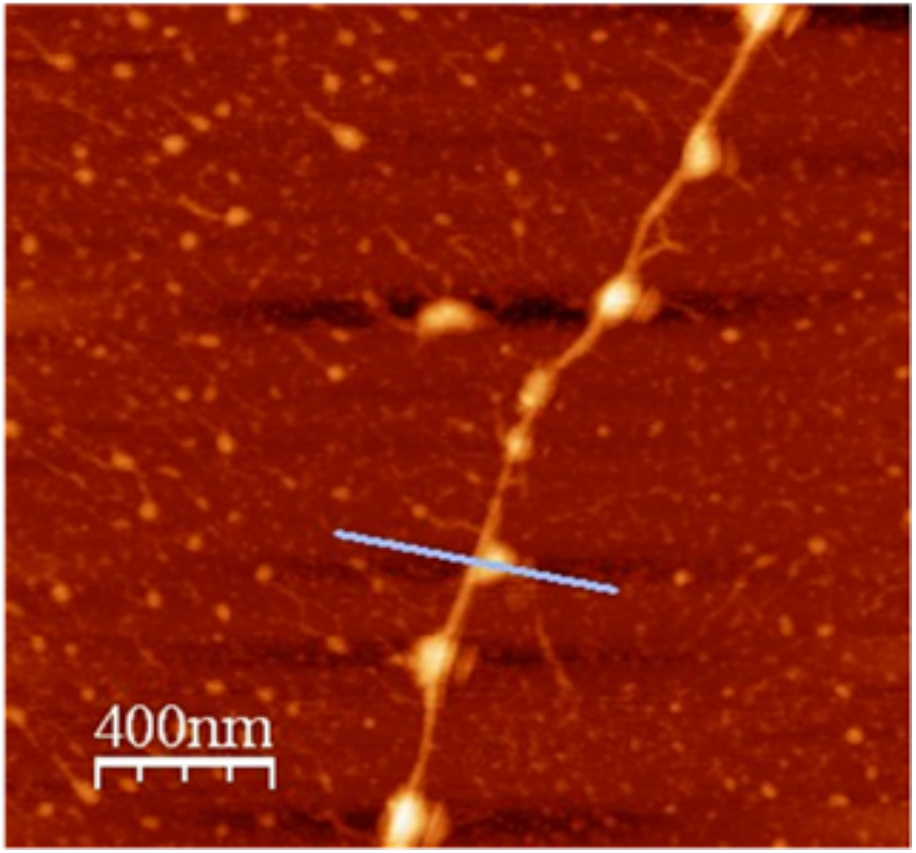


PyA3UA on mica

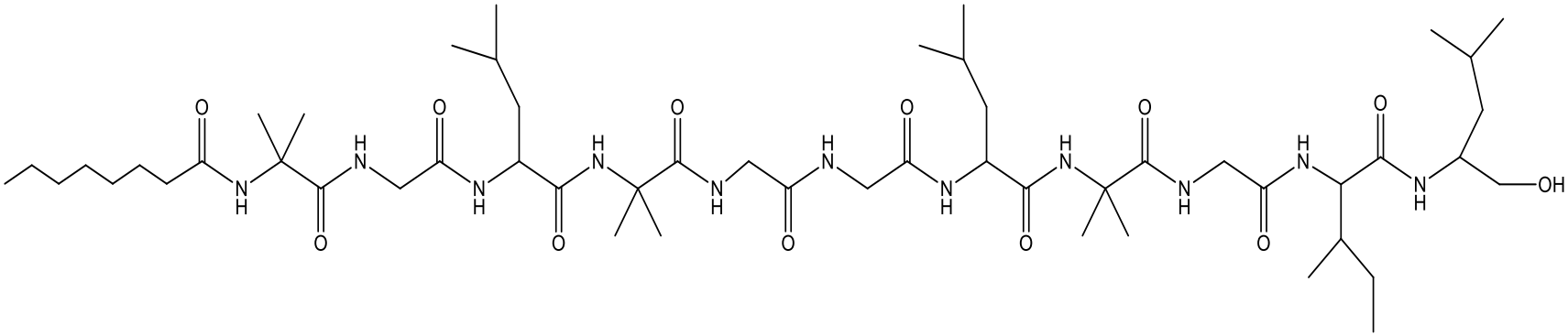


PyA5 LB films on mica

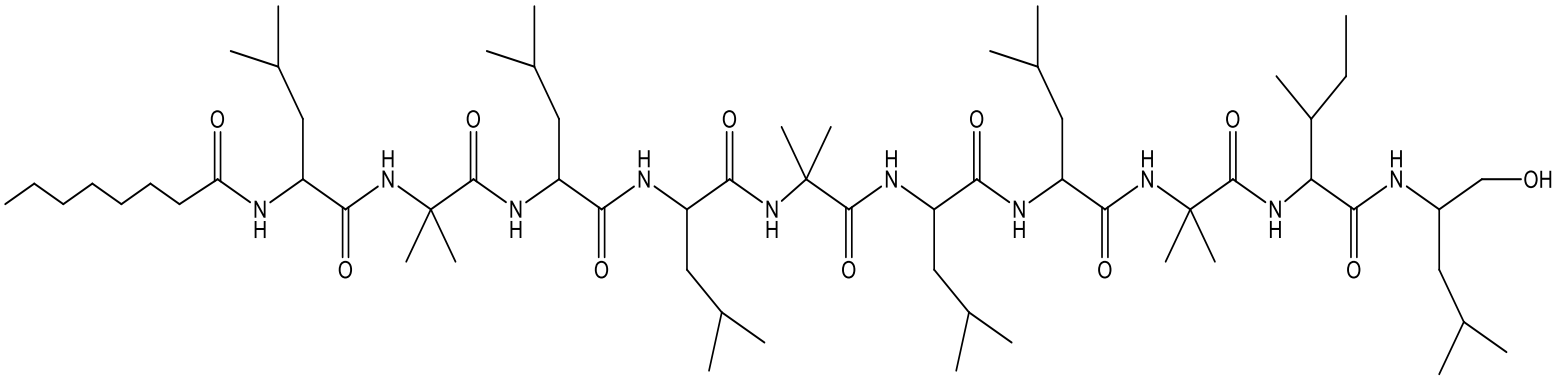




An antimicrobial peptide: Trichogin GA IV



Oct-Aib-Gly-Leu-Aib-Gly-Gly-Leu-Aib-Gly-Ile-Lol
(TrGA)

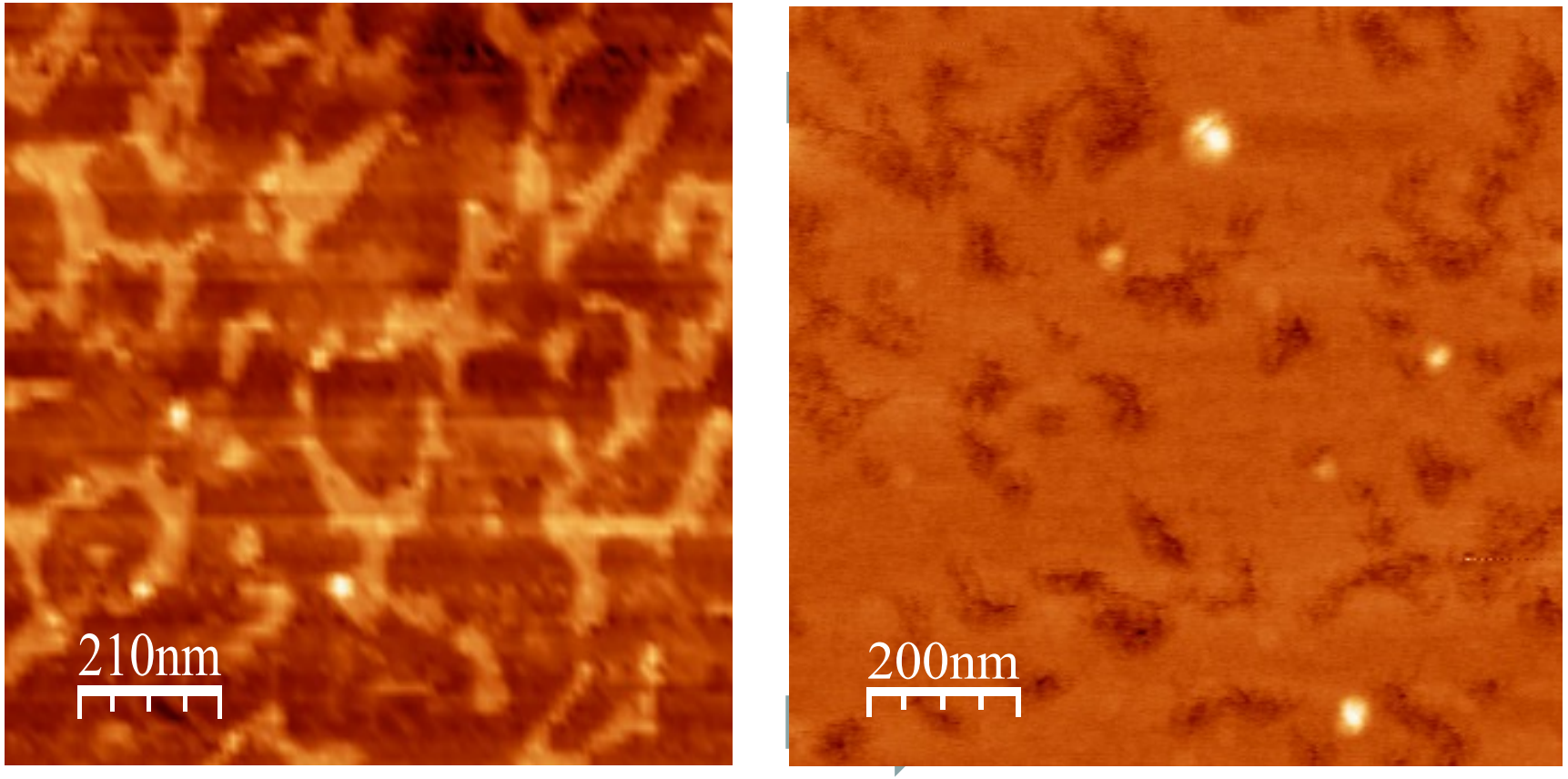


Oct-Leu-Aib-Leu-Leu-Aib-Leu-Leu-Aib-Ile-Lol
(TrGAr)

Marta De Zotti
(University of Padova)

TrGA *LB films*

Graphite (hydrophobic) **Mica (hydrophilic)**

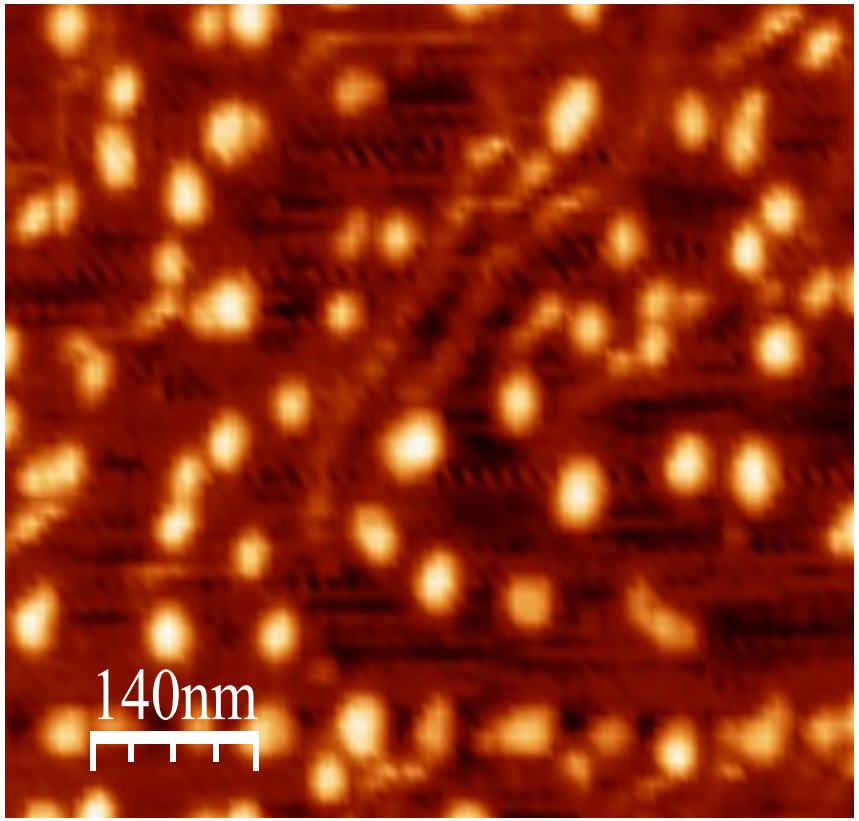


at 40 mN/m surface pressure

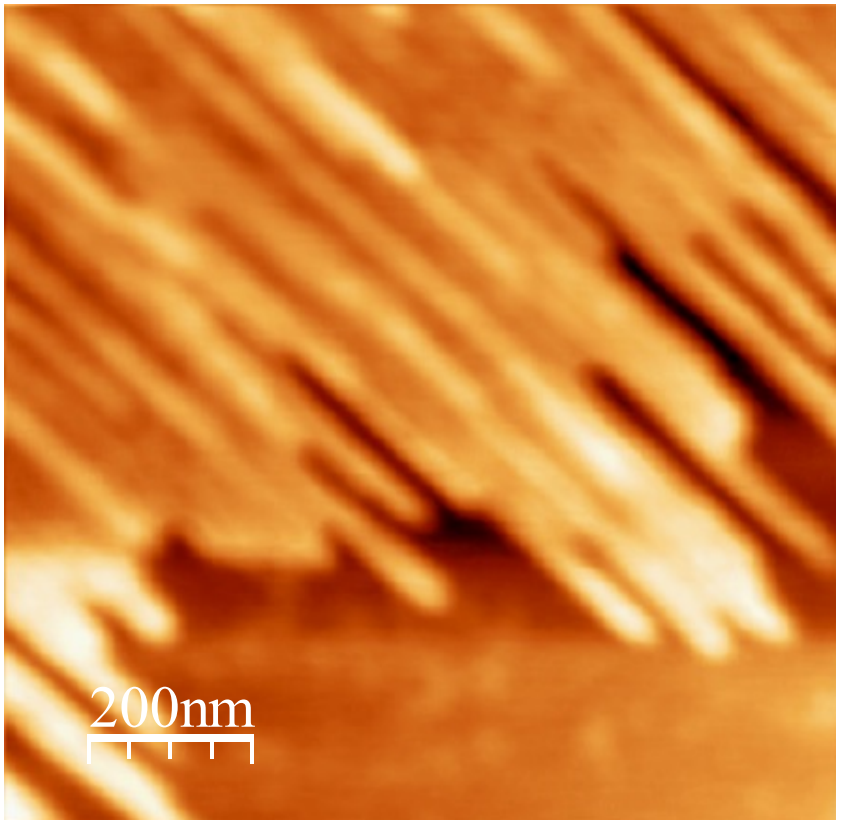
LB films

TrGAr

Graphite

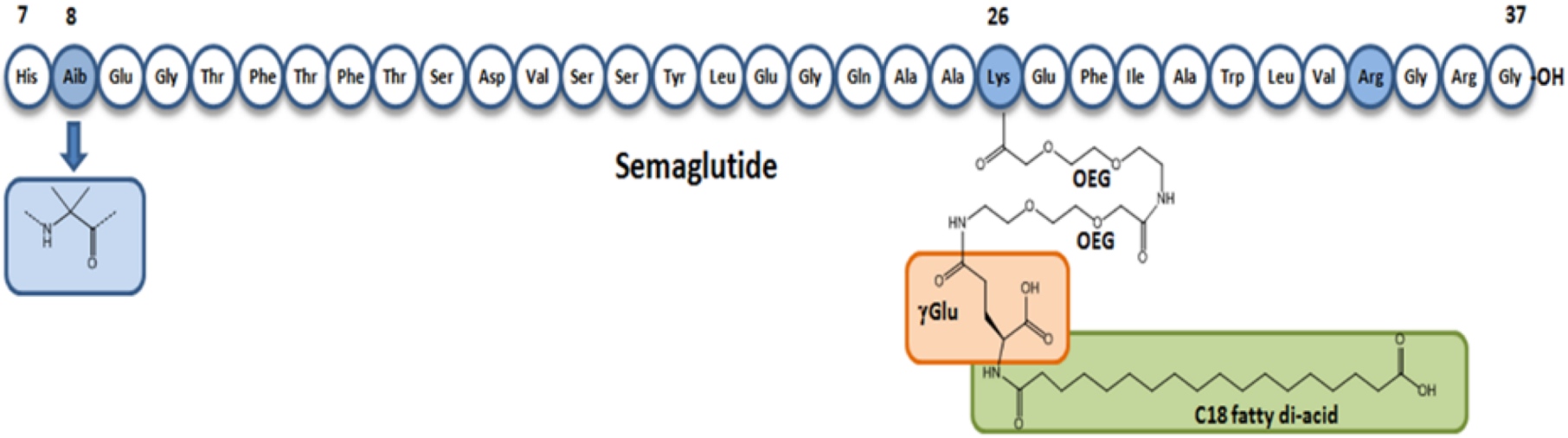


Mica



at 20 mN/m surface pressure

A therapeutic peptide
Semaglutide, a GLP-1 analog (IRBM)

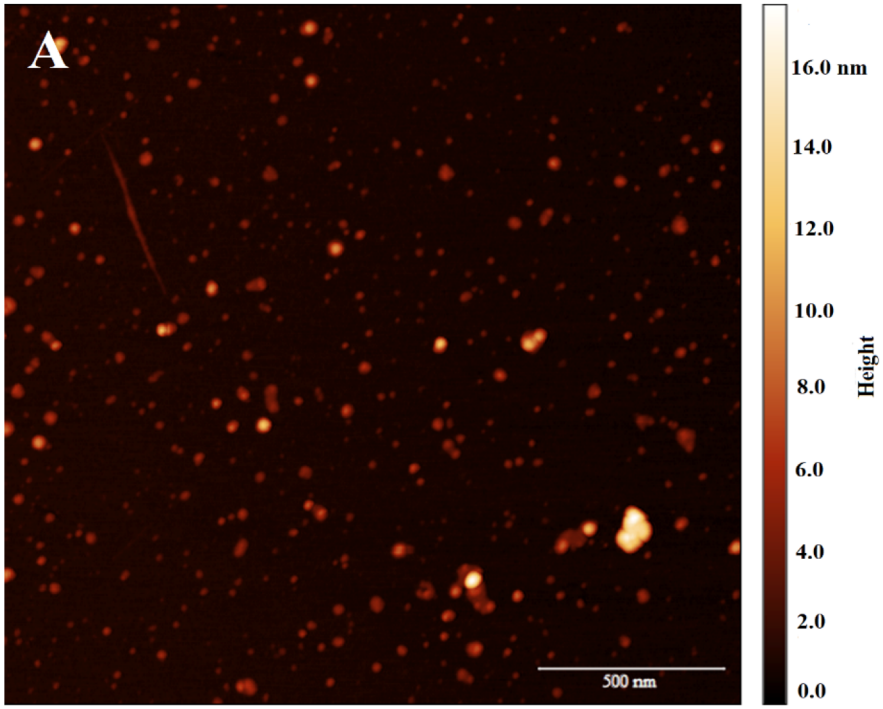


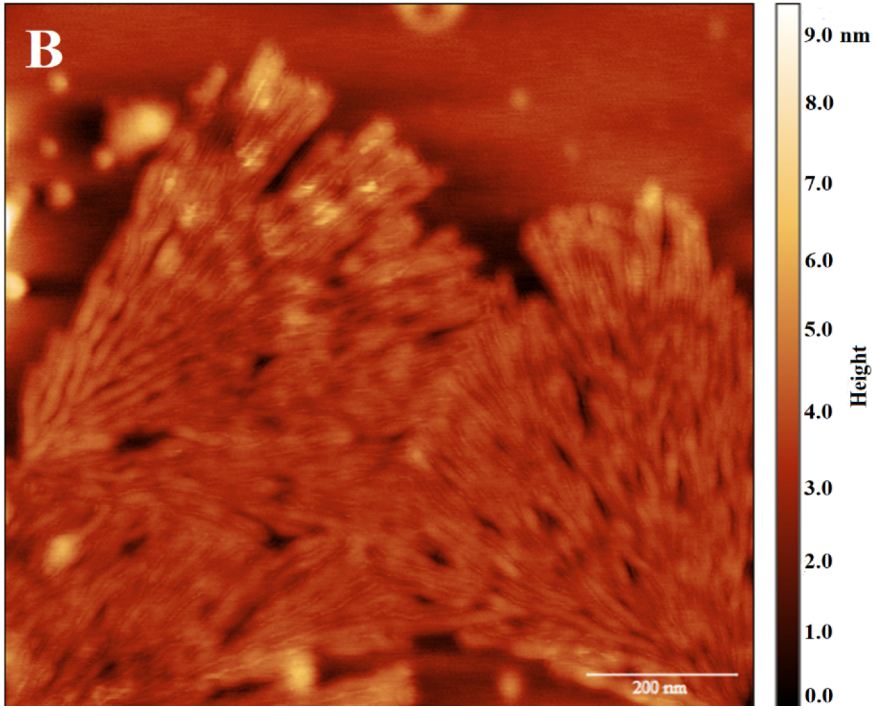
A spectroscopic and molecular dynamics study on the aggregation process of a long-acting lipidated therapeutic peptide: the case of semaglutide.

Venanzi M. et al. Soft Matter 2020, 16, 10122-10131

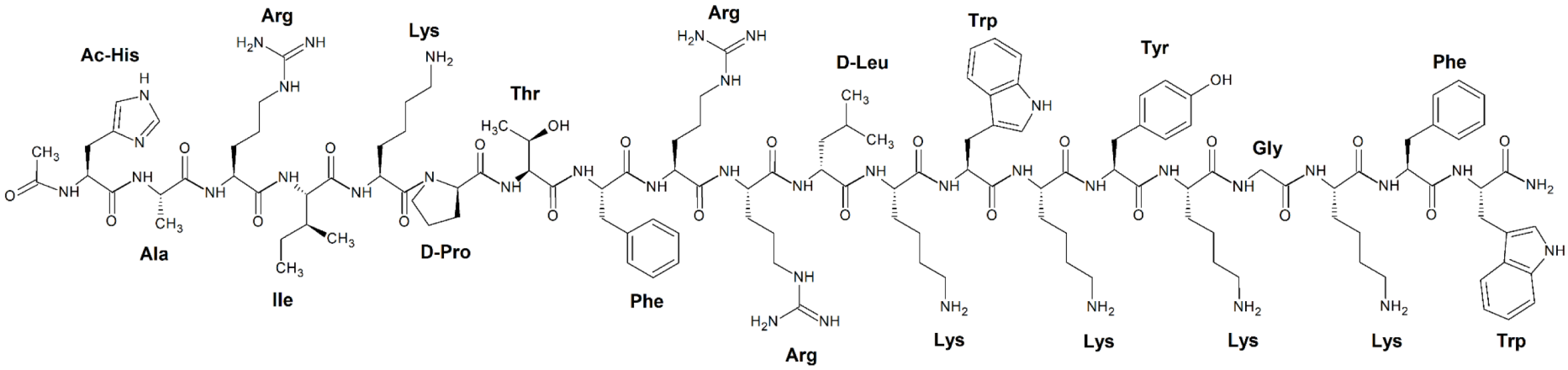
A: fresh solutions

B: aged solutions





A therapeutic peptide: CIGB552



Ac-HARIK(dP)TFRR(dL)KWKYKGKFW-NH_2

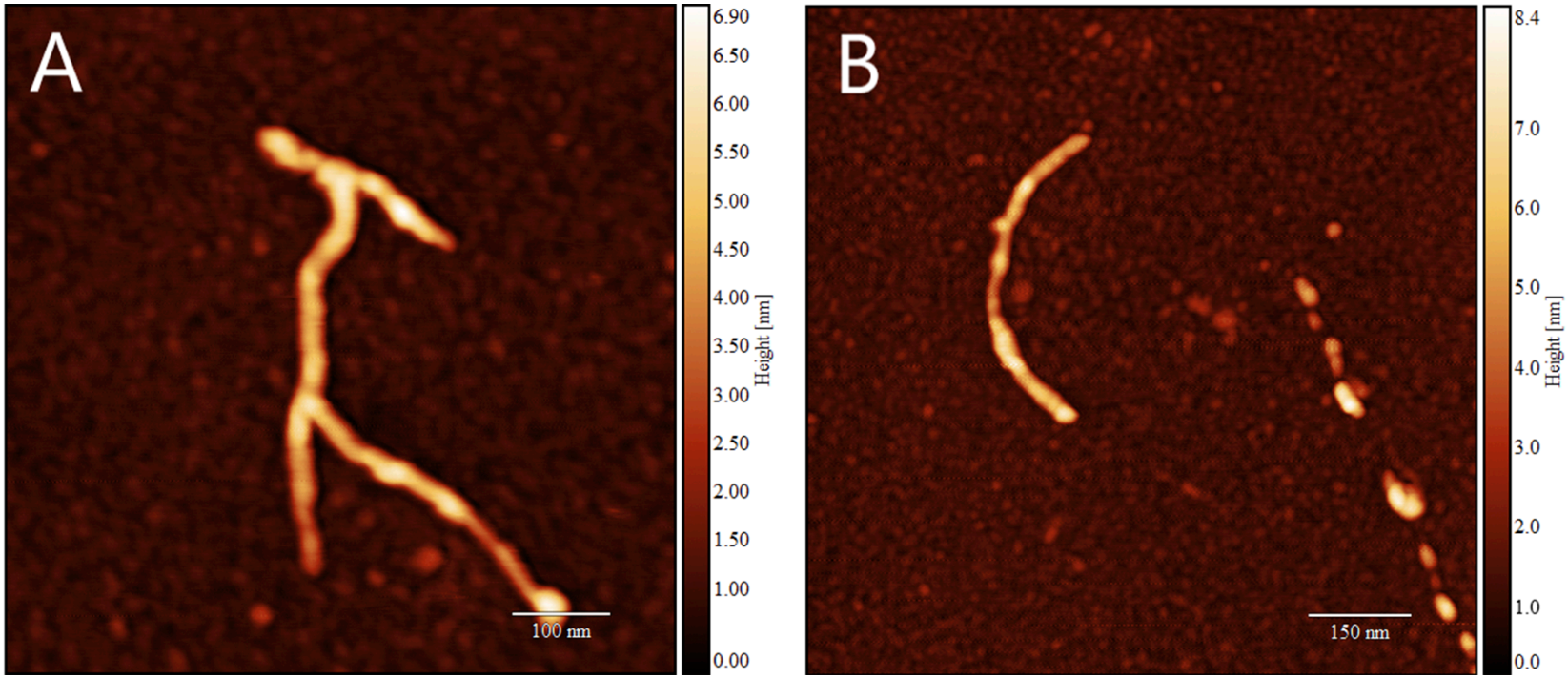
Antitumor activity was demonstrated in mouse cells.

Formulation matters! A spectroscopic and molecular dynamics investigation on the peptide CIGB552 as itself and in its therapeutical formulation

M. Savioli et al. J. Pept. Sci. 2021, https://doi.org/10.1002/psc.3356

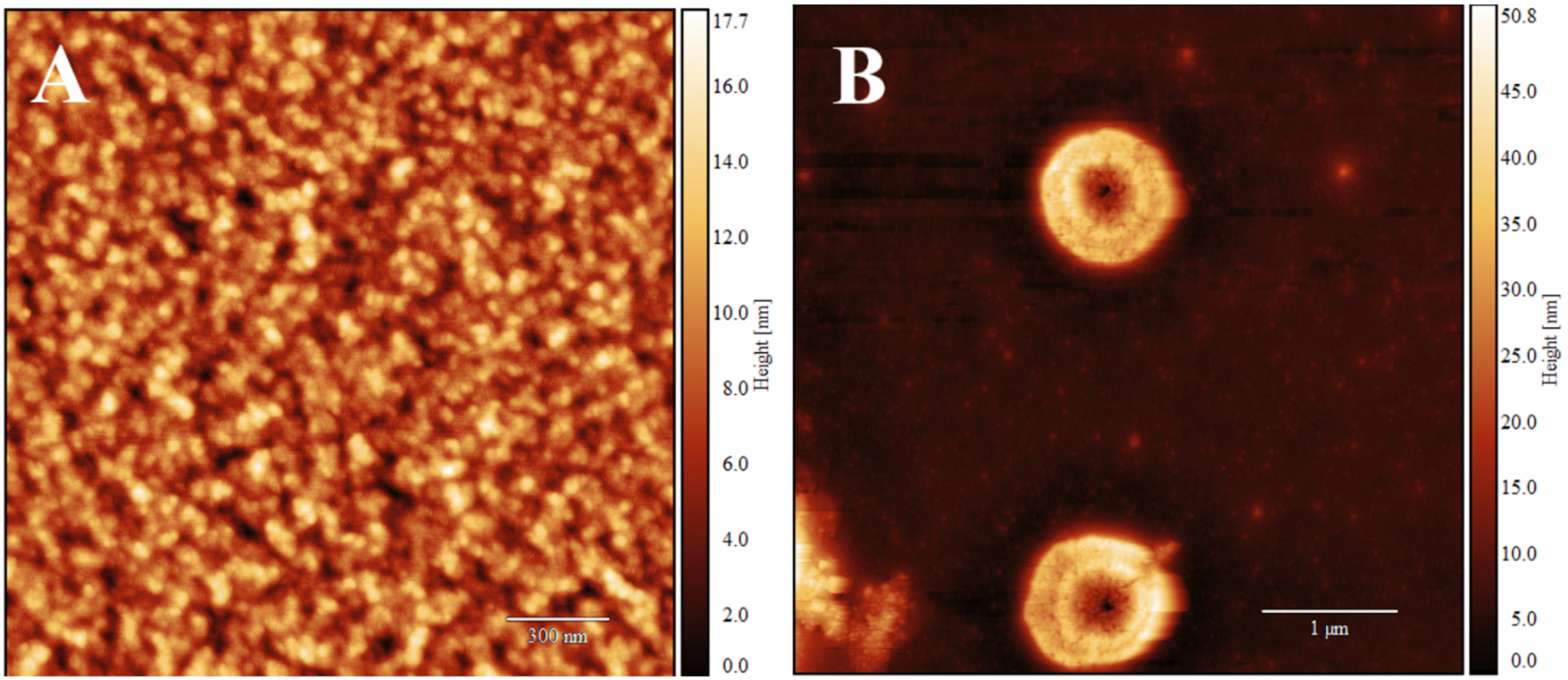
Atomic Force Microscopy

CIGB552



Filaments of lenghts comprised between 20 and 32 µm and width of 2 µm were observed. B: globular structures nucleating the growth of peptide fibrils.

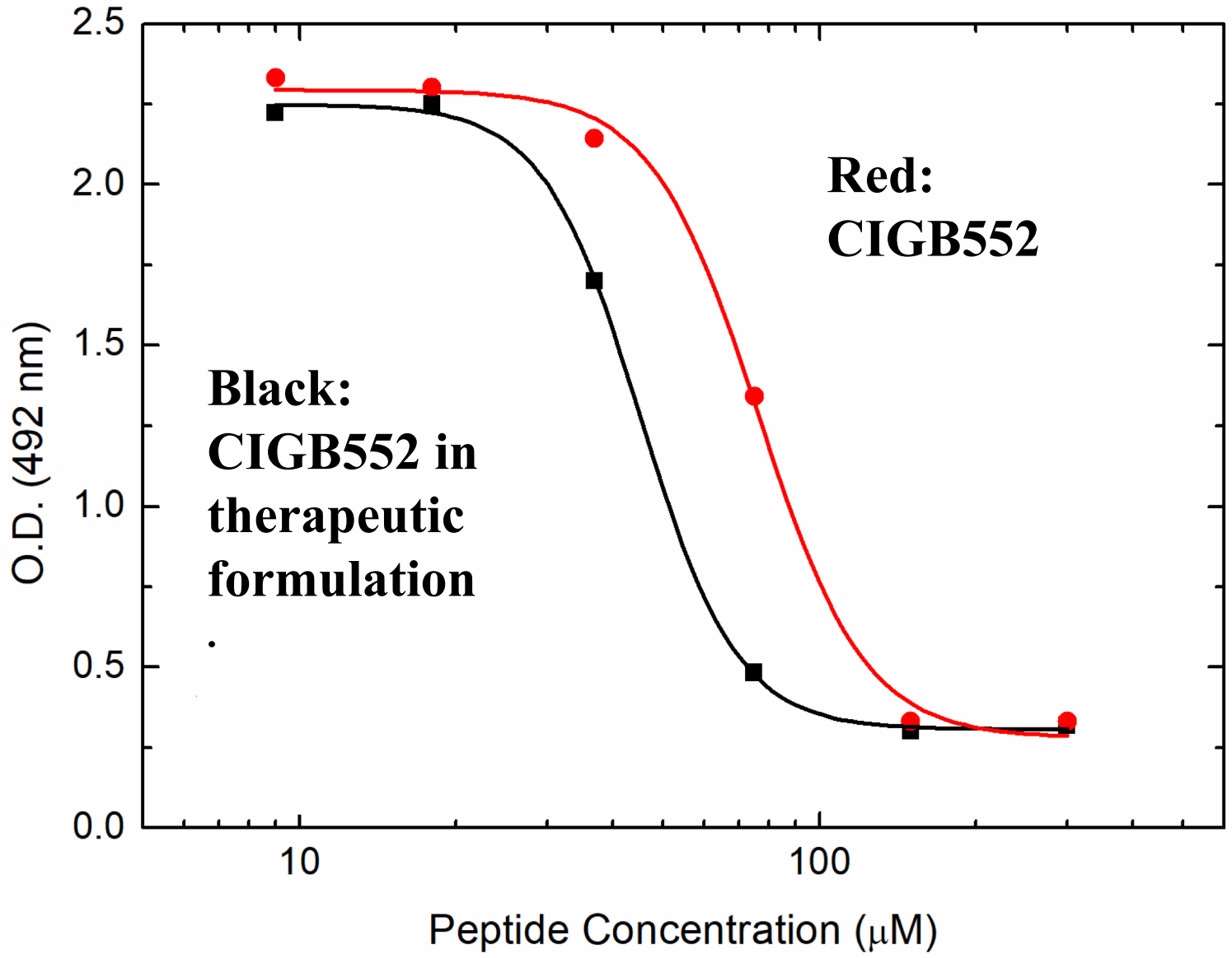
CIGB552 in therapeutic formulation



A: peptide nanoglobules (diameters between 10 - 50 nm)

B: micrometric annular structures (outer diameter: 1 µm; inner diameter: 60 nm).

Cell viability assay on H-460 tumour cells



The still open question is:

Do peptide nanostructures play a specific therapeutic role?

Take home messages

Controlling self-assembly	Response
Thermodynamic , kinetic and spatio-tempotal aspects should be considered (systems chemistry)	ϒ
Structure and dynamics properties of molecular building blocks matter!	ϒ
The morphology of nanostructures can be tuned by molecular engineering (hierarchical self-assembly)	ϒ
Nanostructures show emergent properties at each level	ϒ