Peptide Amphiphilic-Based Supramolecular Structures Interaction with Liposomes

Ramon Pons, Maria José Gómara, Isabel Haro

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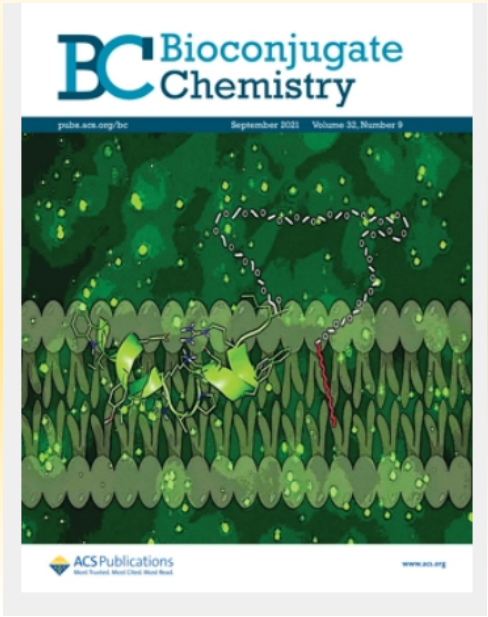

Peptide Amphiphilic-Based Supramolecular Structures with Anti-HIV-1 Activity
Maria J. Gómara, Ramon Pons, Carolina Herrera, Paul Ziprin, and Isabel Haro*
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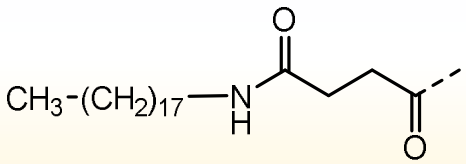
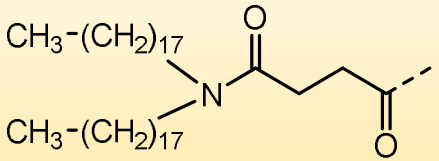
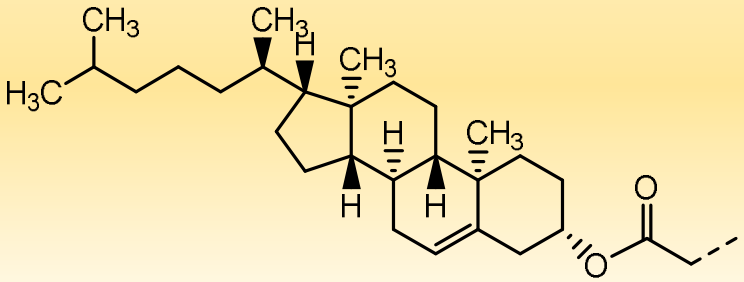
iQAC Institute for Advanced Chemistry of Catalonia "Where Chemistry Helps"

CSIC Consejo Superior de Investigaciones Científicas

Background

- Use of short peptides to inhibit virus entry into cells.
- Chemical modification of short peptides to improve effects.
- Study of the interaction of modified short peptides with membranes.

Hydrophobic moiety — PEG_x — WILEYLWKVPFDFWRGVI

Hydrophobic moiety	PEG_3	PEG_{27}
	**$PA1_{PEG3}$**	**$PA1_{PEG27}$**
	**$PA2_{PEG3}$**	**$PA2_{PEG27}$**
	**$PA3_{PEG3}$**	**$PA3_{PEG27}$**

N-peptide amphiphiles

Hydrophobic moiety — PEG_{27} — WILEYLWKVPFDFWRGVI

N-$PA_{mono\text{-}alkyl}$ *N*-$PA_{di\text{-}alkyl}$ *N*-PA_{chol}

C-peptide amphiphiles

WILEYLWKVPFDFWRGVIK — PEG_{27} — Hydrophobic moiety

C-$PA_{mono\text{-}alkyl}$ *C*-$PA_{di\text{-}alkyl}$ *C*-PA_{chol}

K-peptide amphiphiles

WILEYLWKVPFDFWRGVI

PEG_{27} — Hydrophobic moiety

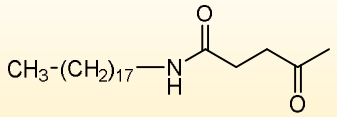
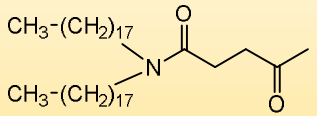
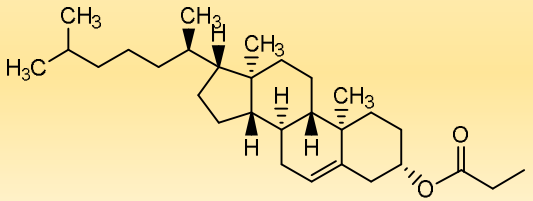
K-$PA_{mono\text{-}alkyl}$ *K*-$PA_{di\text{-}alkyl}$ *K*-PA_{chol}

Hydrophobic moiety — PEG_{27} — WILEYLWKVPFDFWRGVI *N-derivatized peptide*

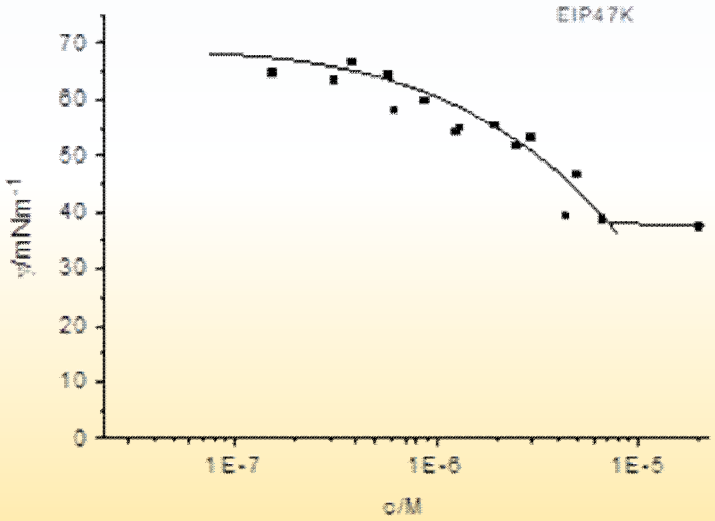
WILEYLWKVPFDFWRGVIK — PEG_{27} — Hydrophobic moiety *C-derivatized peptide*

WILEYLWKVPFDFWRGVI

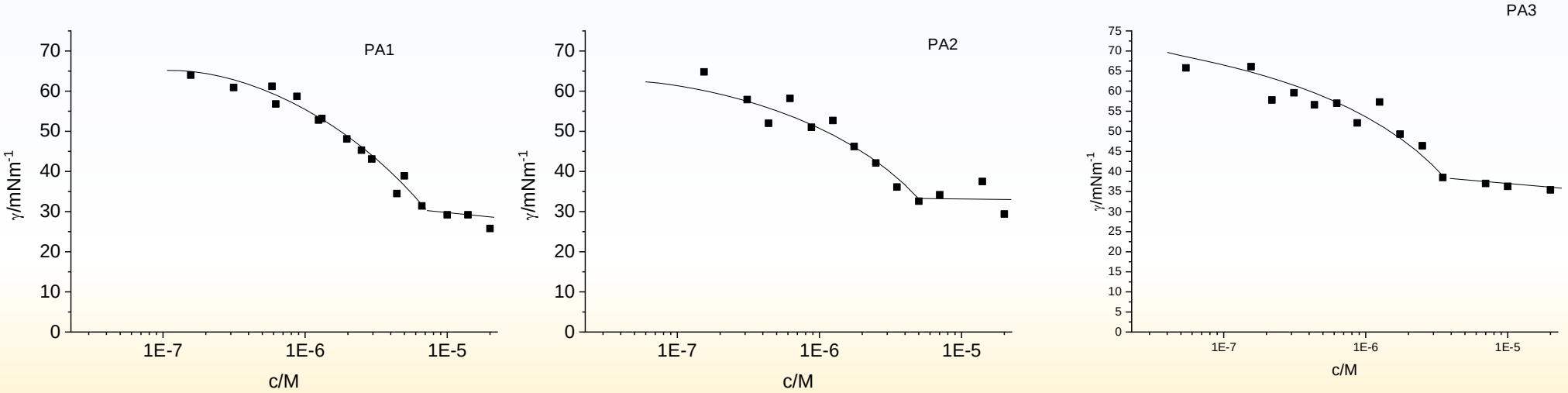
PEG_{27} — Hydrophobic moiety K^8*-derivatized peptide*

Hydrophobic moiety	*N*-	*C*-	K^8-
	**PA1** $_{PEG27}$	**PA4** $_{PEG27}$	**PA7** $_{PEG27}$
	**PA2** $_{PEG27}$	**PA5** $_{PEG27}$	**PA8** $_{PEG27}$
	**PA3** $_{PEG27}$	**PA6** $_{PEG27}$	**PA9** $_{PEG27}$

Surface tension in water



Surface tension in water

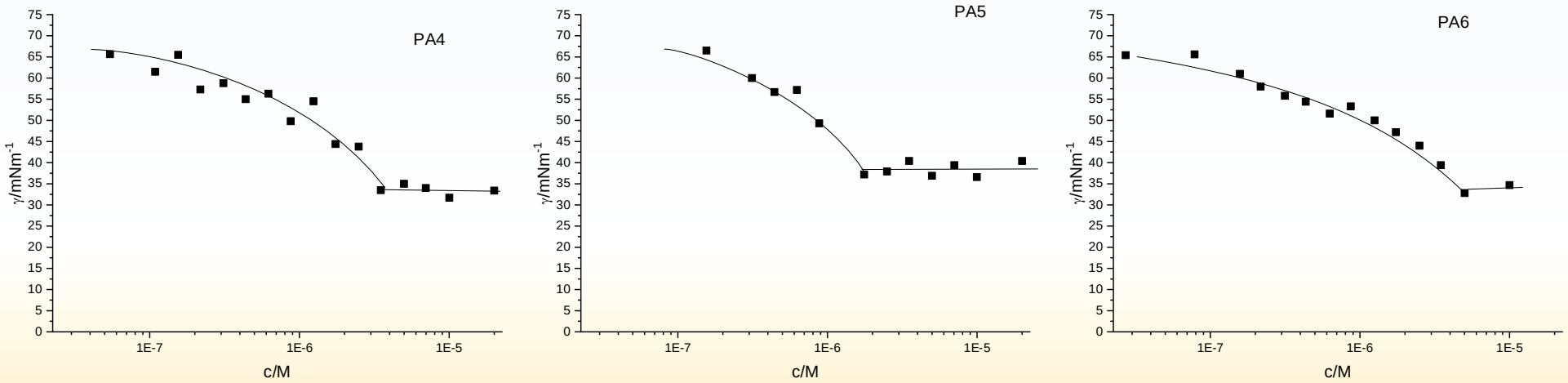


***N*-peptide amphiphiles**

Hydrophobic moiety — PEG_{27} — WILEYLWKVPFDFWRGVI

N-$PA_{mono\text{-}alkyl}$ *N*-$PA_{di\text{-}alkyl}$ *N*-PA_{chol}

Surface tension in water

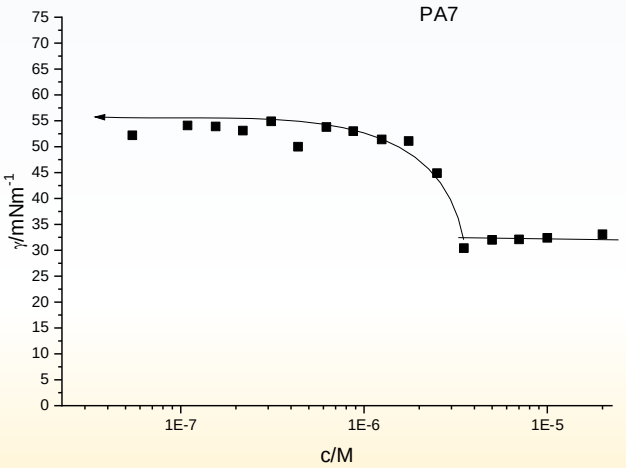


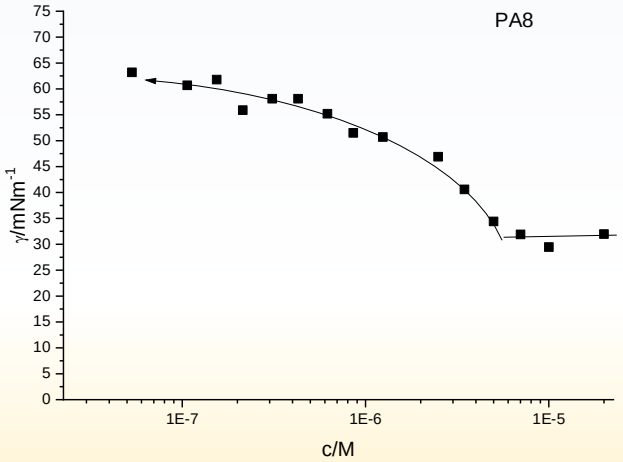
C-peptide amphiphiles

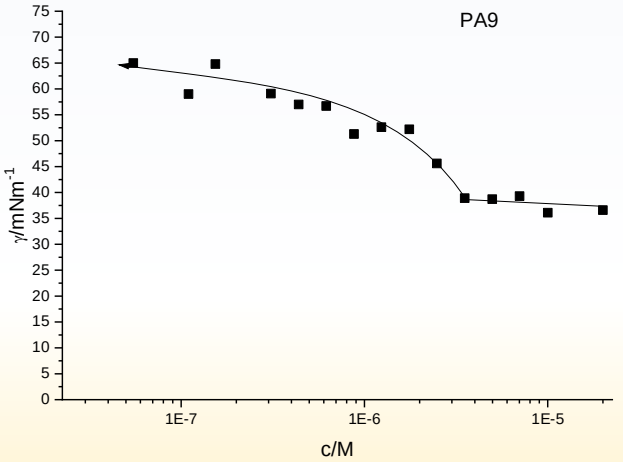
WILEYLWKVPFDFWRGVIK — PEG_{27} — Hydrophobic moiety

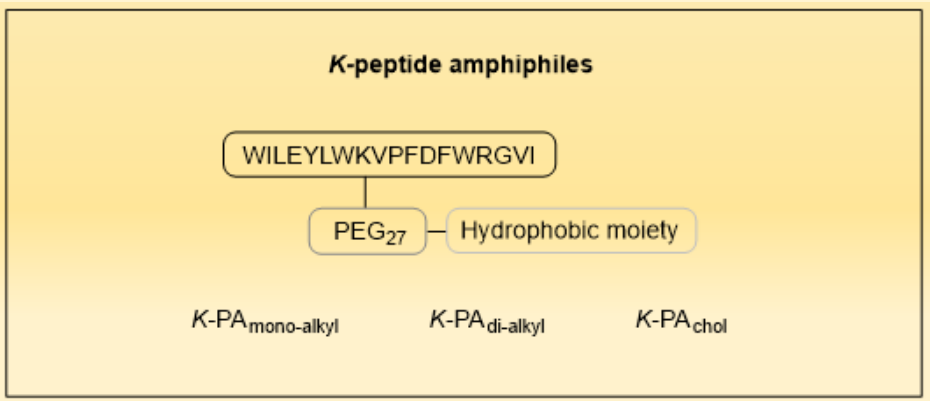
$C\text{-}PA_{mono\text{-}alkyl}$ $C\text{-}PA_{di\text{-}alkyl}$ $C\text{-}PA_{chol}$

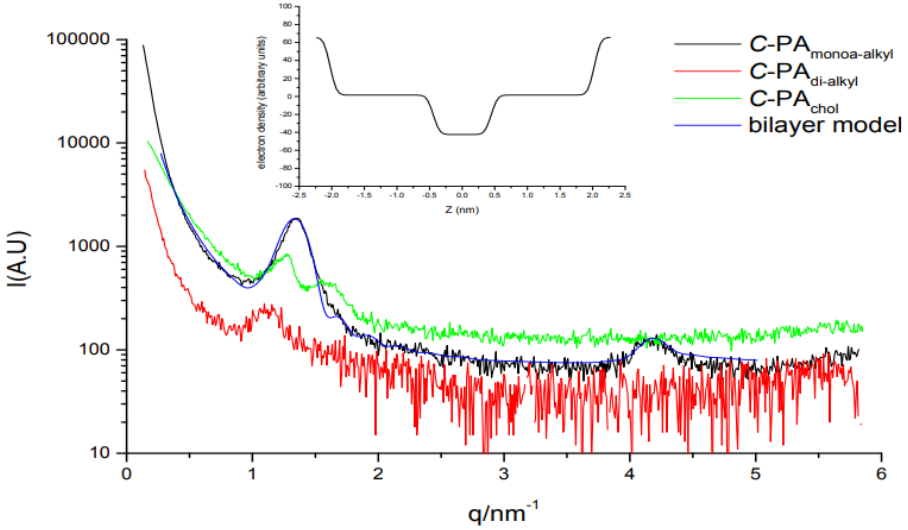
Surface tension in water

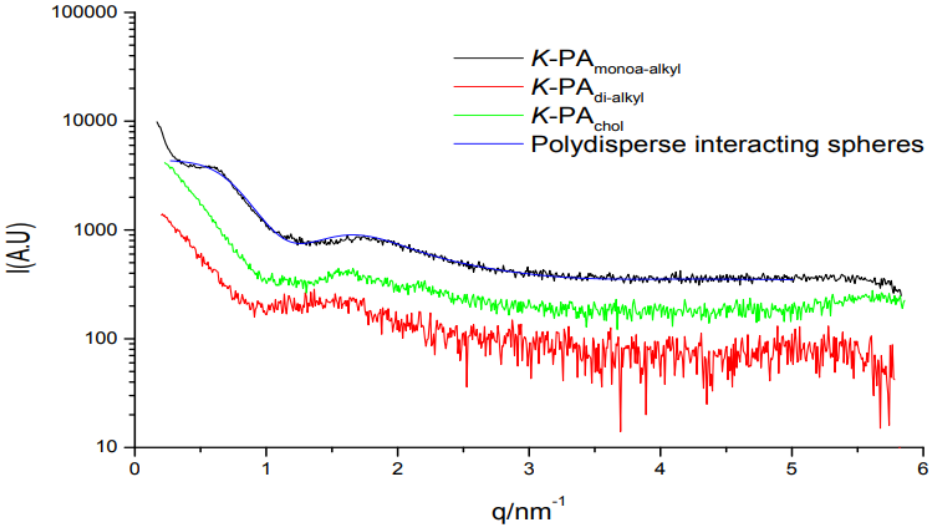


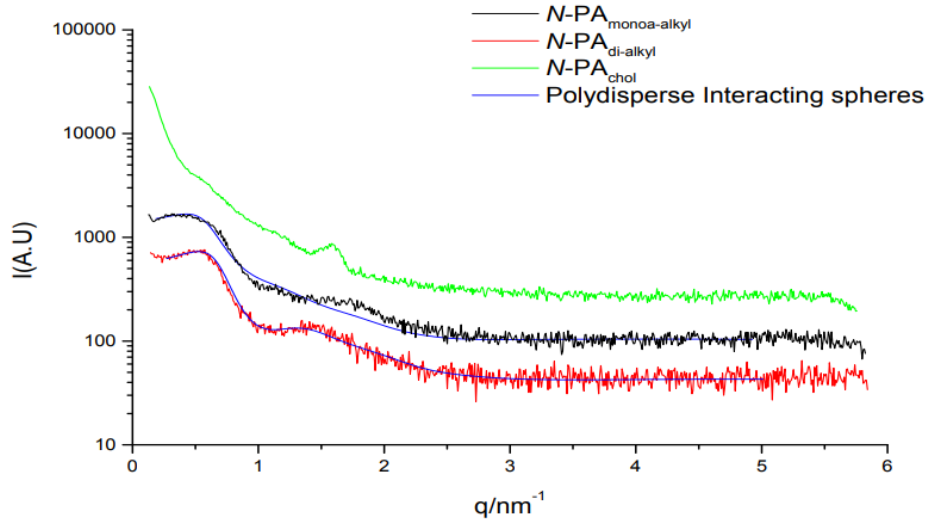


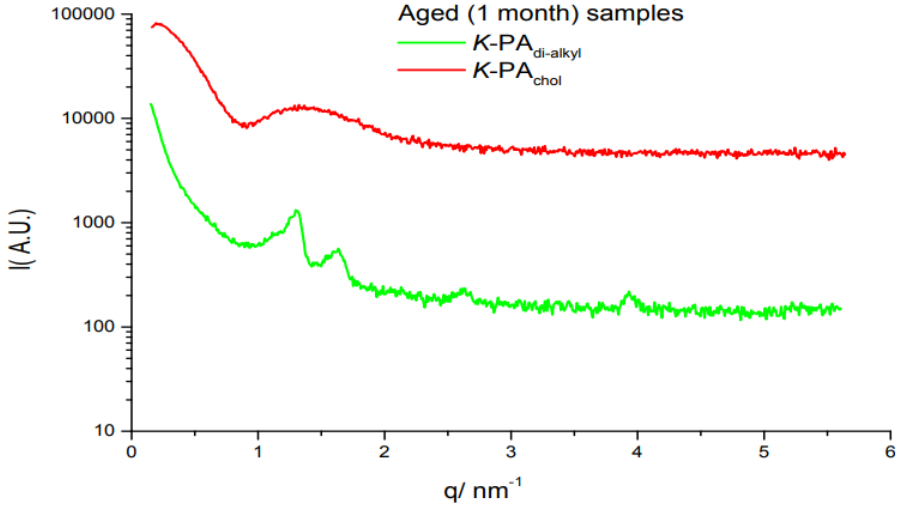





C-PA monoa-alkyl
C-PA di-alkyl
C-PA chol
bilayer model
I(A.U)
q/nm-1
electron density (arbitrary units)
Z (nm)

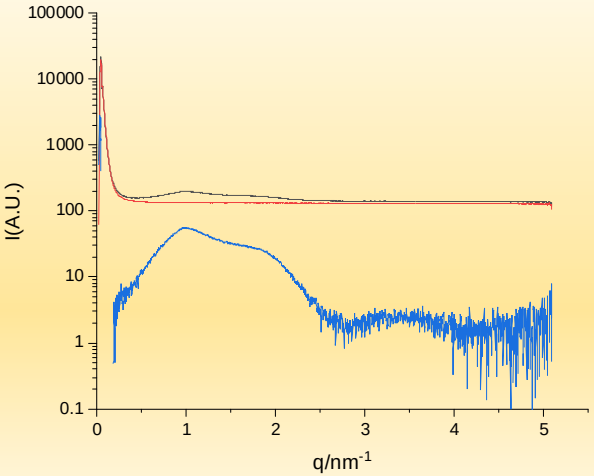

K-PA monoa-alkyl
K-PA di-alkyl
K-PA chol
Polydisperse interacting spheres
I(A.U)
q/nm-1

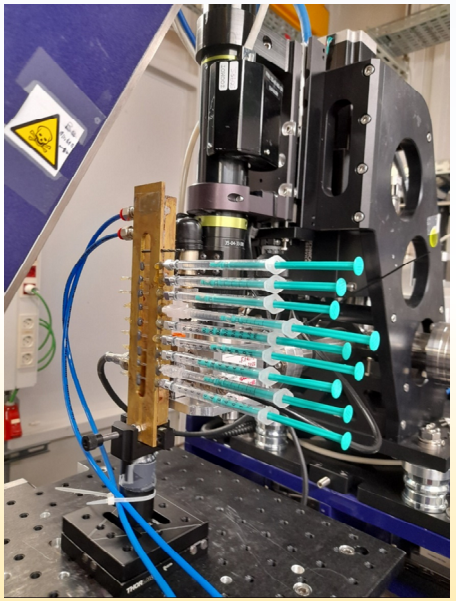

N-PA monoa-alkyl
N-PA di-alkyl
N-PA chol
Polydisperse Interacting spheres
I(A.U)
q/nm-1


Aged (1 month) samples
K-PA di-alkyl
K-PA chol
I(A.U.)
q/ nm-1

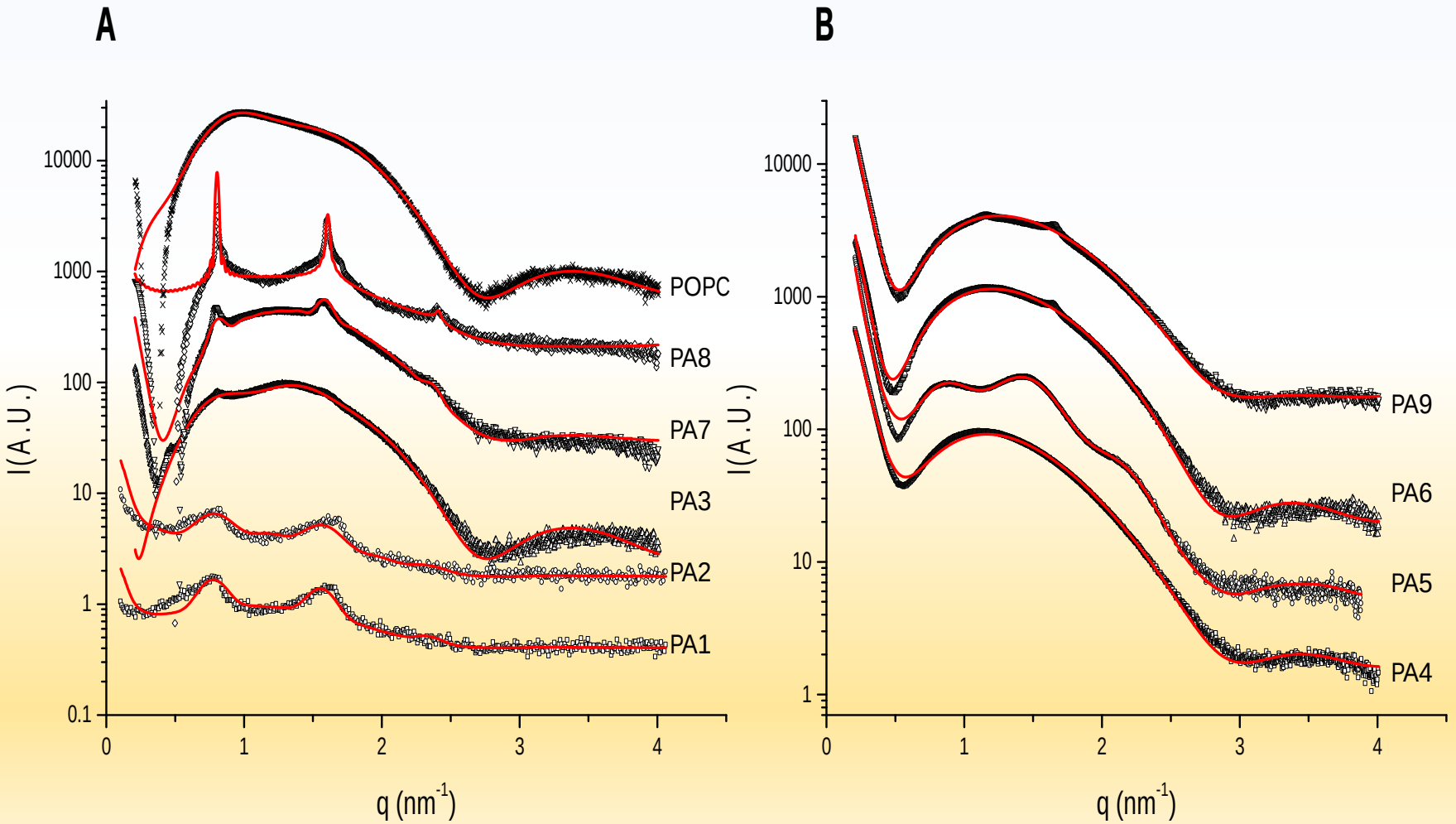
NCD-SWEET Beamline

Home made parallell capillary flow setup





20 mMPOPC+ 2mM PA+ 0.5% DMSO



1,2 precipitated 3 milky (N-terminal), 7,8, milky (K terminal)

4,5,6 (C-terminal), 9 (K-terminal) bluish

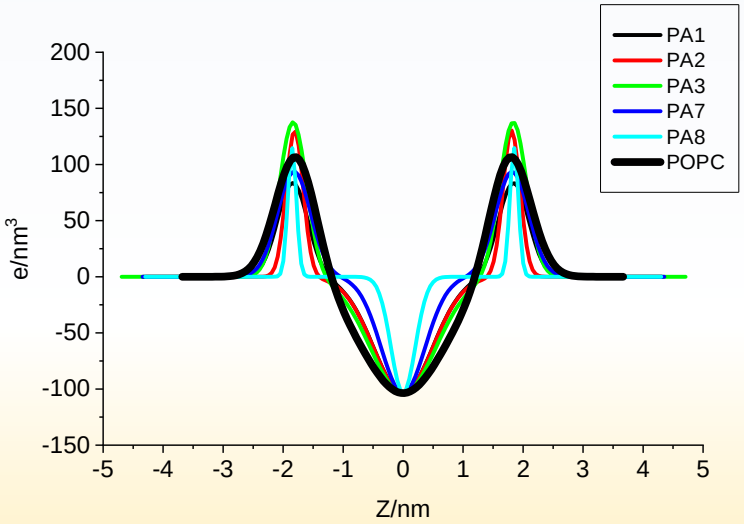
The model

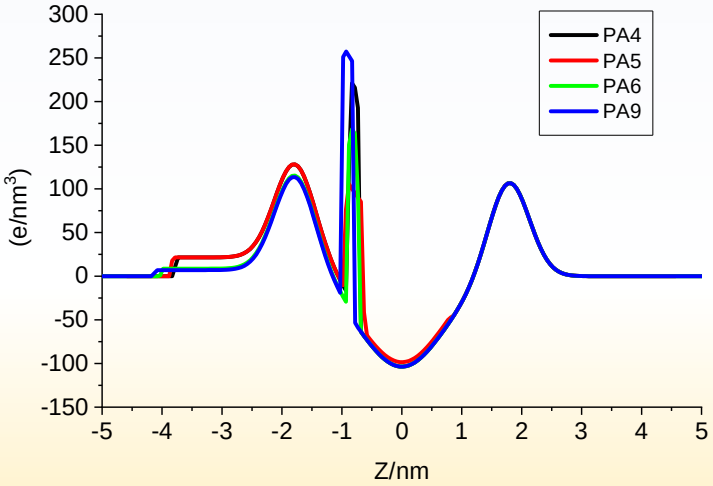
Hydrophobic layer $$G_m(z) = \frac{1}{\sqrt{2\pi}} \rho_m \exp\left(-\frac{z^2}{\sigma_m^2}\right)$$

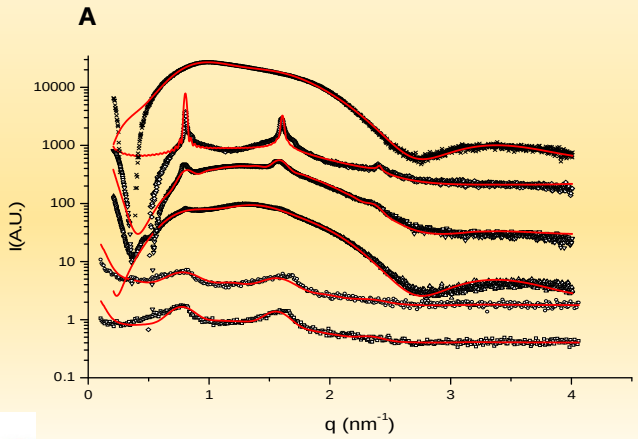
Symmetric polar headgroups $$G_{h1}(z) = \frac{1}{\sqrt{2\pi}} \rho_h \exp\left(-\frac{(z - z_h)^2}{\sigma_h^2}\right) \qquad G_{h2}(z) = \frac{1}{\sqrt{2\pi}} \rho_h \exp\left(-\frac{(z + z_h)^2}{\sigma_h^2}\right)$$

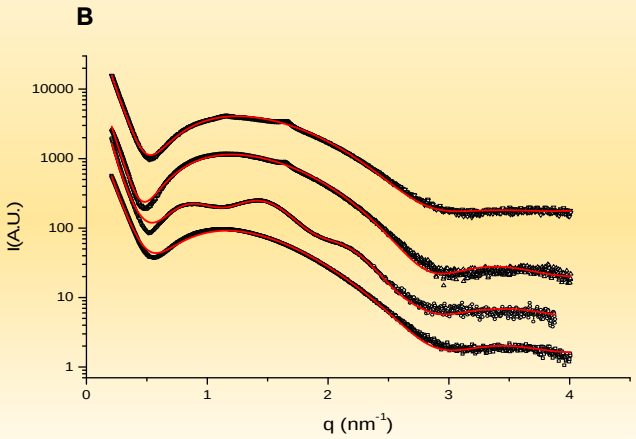
3 Slabs 4 distance parameters+ 3 electron densities

Numeric Fourier Transform

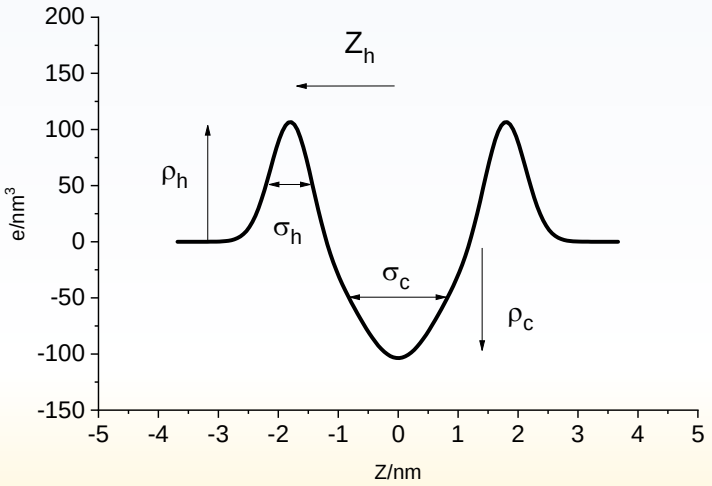

PA1
PA2
PA3
PA7
PA8
POPC
e/nm3
Z/nm


PA4
PA5
PA6
PA9
(e/nm3)
Z/nm


A
I(A.U.)
q (nm-1)


B
I(A.U.)
q (nm-1)

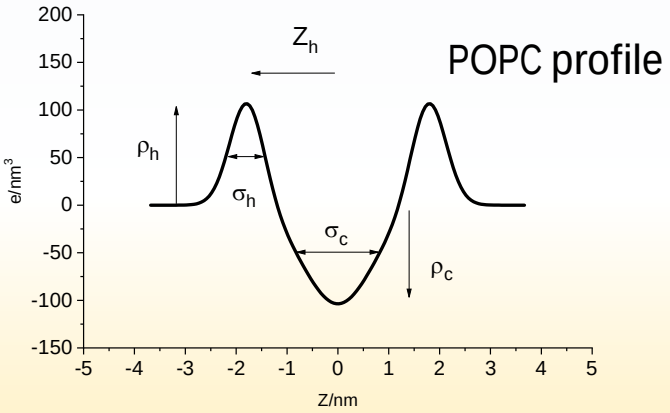
	N-PA$_{mono\text{-}alkyl}$	N-PA$_{di\text{-}alkyl}$	N-PA$_{chol}$	K-PA$_{mono\text{-}alkyl}$	K-PA$_{di\text{-}alkyl}$	POPC
χ^1	3.5	3.0	0.6	1.4	5.1	3.7
d[2] (nm)	7.89	7.79	8.53	7.90	7.81	6.70
η^3	2.8E-5	3.3E-5	0.19	0.0236	0.0923	0.502
N[4]	3.8	3.0	2.5	5.8	25.4	1.6
N_f[5]	6.9	7.4	12.2	54.1	35.1	1.0
σ_h (nm)	0.252	0.179	0.223	0.277	0.072	0.338
ρ_h (e/nm^3)	83	109	137	93	114	110
Z_h (nm)	1.84	1.79	1.83	1.82	1.85	1.79
σ_c (e/nm^3)	0.494	0.504	0.550	0.368	0.202	0.697



1 Reduced chi squared (pure statistical error corresponds to χ=1)
2 Bragg distance corresponding to multilamellar structures.
3 Caillé parameter (the smaller the more rigid the bilayer).
4 Number of correlated bilayers.
5 Number of uncorrelated bilayers.

	C-PA$_{mono\text{-}alkyl}$	C-PA$_{di\text{-}alkyl}$ *	C-PA$_{chol}$	K-PA$_{chol}$
χ	0.9	2.0	2.9	3.2
Z1 (nm)	-38.1	-38.8	-40.4	-41.5
Z2 (nm)	-9.1	-9.8	-9.3	-10.3
Z3 (nm)	-7.3	-6.8	-7.5	-8.3
Z4 (nm)	7.1	8.4	4.9	1.9
ρ_1 (e/nm^3)	22	22	9	7
ρ_2 (e/nm^3)	269	144	217	295
ρ_3 (e/nm^3)	6E-4	6	1.7E-11	2.6E-12

* ***C*-PA$_{di\text{-}alkyl}$** shows signs of multilamellarity with the following parameters d=8.33 nm, η=0.029, N=1.81, N_f=5.0



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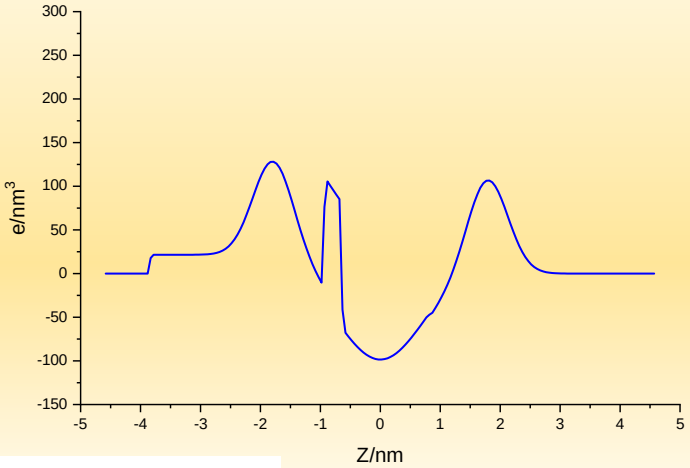

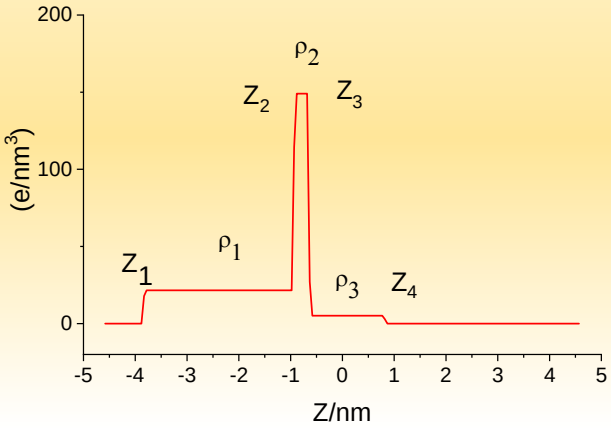

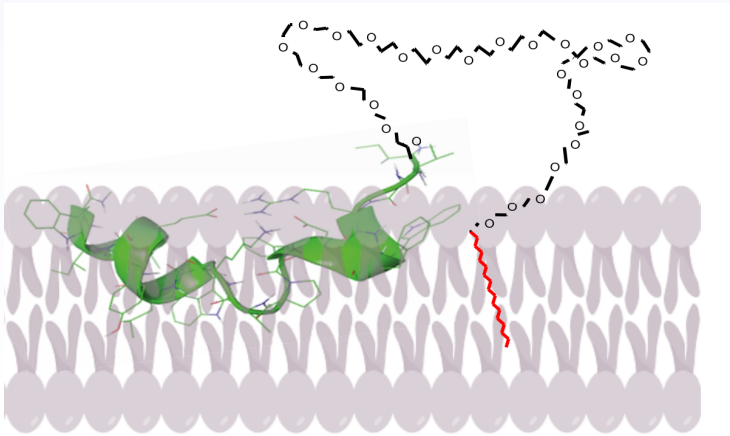

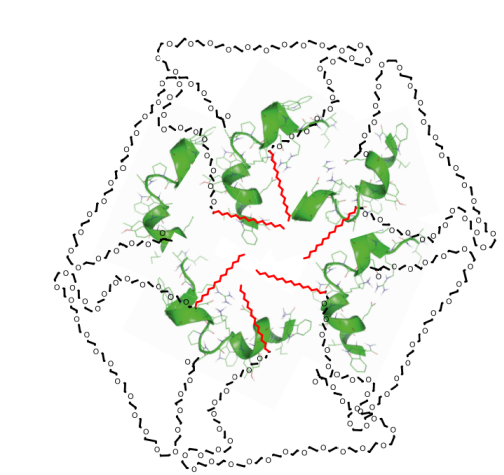

C-PA-monoalkyl

N-PA-monoalkyl K-PA-monoalkyl

Anti HIV activity

Conclusions

- The addition of hydrophobically modified amphiphilic peptides to POPC vesicles influence vesicles stability.
- SAXS allowed to locate the different moieties of the hydrophobically modified peptides.
- Different chemical structures lead to different incorporation to the bilayers.
- Those information could be correlated to the in vivo anti HIV activity.

Acknowledgements

- Ministry of Economy, Industry and Competitiveness, Spain (Grant CTQ2017-88948- P and Grant RTI2018- 094120-B-I00) and the European Regional Development Fund (FEDER).
- NCD-SWEET beamline at ALBA Synchrotron with the collaboration of ALBA staff (special thanks to Juan Carlos Martínez)
- Jaume Caelles, from the SAXS-WAXS service at IQAC.