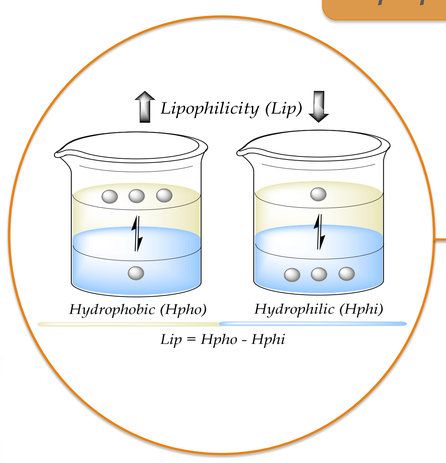
Alzheimer's Disease: What Can Lipophilicity Teach Us?

William J. Zamora R [1], Josep M. Campanera, Kasper P. Kepp[2] & F. Javier Luque [1]

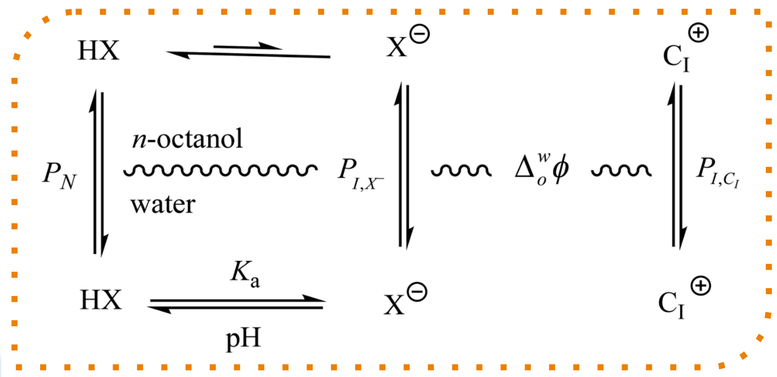
1. Department of Nutrition, Food Science and Gastronomy, Faculty of Pharmacy and Food Science, Institute of Biomedicine (IBUB) and Institute of Theoretical and Computational Chemistry (IQTCUB), Campus Torribera , University of Barcelona , 08921 Santa Coloma de Gramenet , Spain.
2. Department of Chemistry, Technical University of Denmark, DK-2800 Kongens Lyngby, Denmark.

willquim@gmail.com



Lipophilicity: A Cornerstone in Chemistry and Biology

Lipophilicity (*Lip*) is a key physicochemical descriptor used to understand the biological profile of (bio)organic compounds and a broad variety of biochemical, pharmacological, and toxicological processes. It "*represents the affinity of a molecule or a moiety for a lipophilic environment*" and is a more complete and general descriptor than hydrophobicity (*Hpho*), which in fact can be viewed as a part of lipophilicity



This property is estimated from the partition coefficient between aqueous and nonaqueous environments for neutral and/or ionic species (P_N, P_I) and corrected for the pH-dependence of ionizable compounds as the distribution coefficient (D).

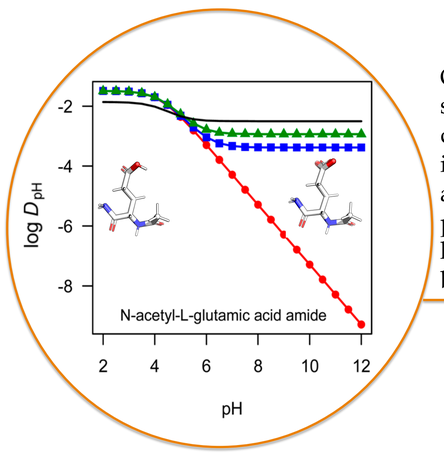
Lipophilicity Descriptors

$$\log D = \log P_N - \log (1+10^{\delta}) \quad [1]$$

$$\log D = \log (P_N + P_I \cdot 10^{\delta}) - \log (1+10^{\delta}) \quad [2]$$

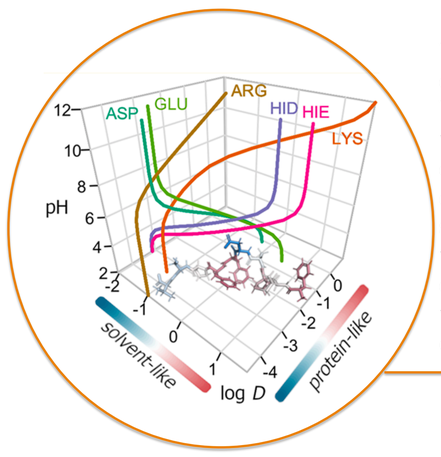
$$\log D = \log \left(P_N + \sqrt{P^{o}_{I,X^-} \cdot P^{o}_{I,C_I^+}} \cdot 10^{\delta} \right) - \log (1+10^{\delta}) \quad [3]$$

pH-Dependent Lipophilicity Profiles

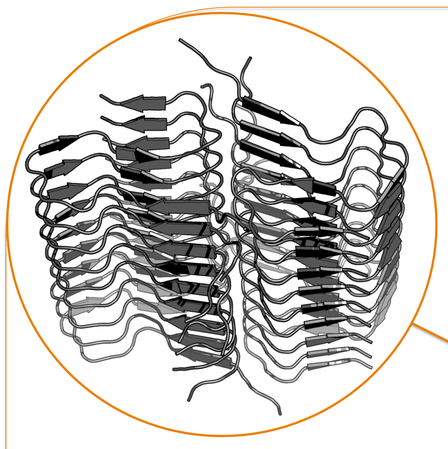


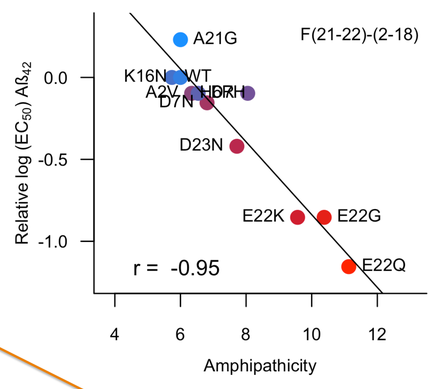
Our results suggest that eq 2 is the minimal scheme required to rationalize the pH-dependent distribution profile of ionizable compounds, including acidic and basic compounds as well as amino acid analogues. The role of the Galvani potential difference between the two phases (eq 3), however, may vary at higher concentrations of the background salt.

Lipophilicity Scale of Amino Acids



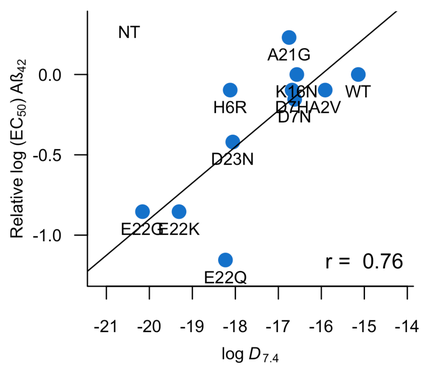
The scale relies on theoretical estimates of distribution coefficients from conformational ensembles of amino acids. This is accomplished by using an accurately parametrized version of the IEFPCM/MST continuum solvation model, in conjunction with eq 2. Two weighting schemes are considered to derive solvent-like (*SolvL*) and protein-like scales (*ProtL*), which have been calibrated by comparison with other experimental scales developed in different chemical/biological environments and pH conditions as well as by examining properties such as the retention time of small peptides and the recognition of antigenic peptides.





Segment lipophilicity rather than global features of the $A\beta_{42}$ mutants monomers could shed some light in the understanding of the toxicity. Classical segments gave a significant correlation (r = 0.76) with the NT fragment and some correlation with the Loop (r = -0.44). These results pointed out two divergent tendencies that led us to the hypothesis that the amphipathicity, expressed as the difference in lipophilicity between the two segments, could explain better the toxicity of $A\beta_{42}$ peptides.

Toxicity in $A\beta_{42}$ Peptides

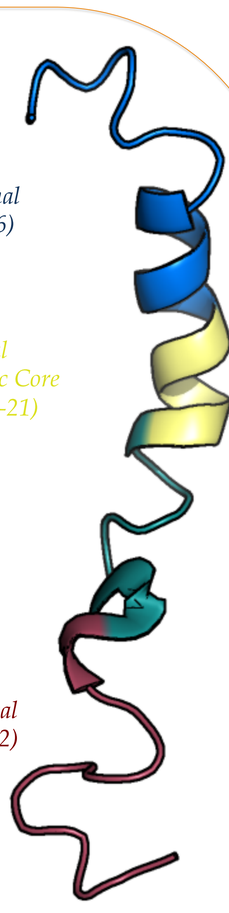


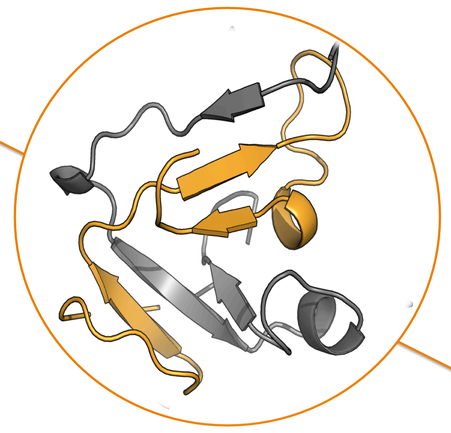
N-Terminal (NT; 1-16)

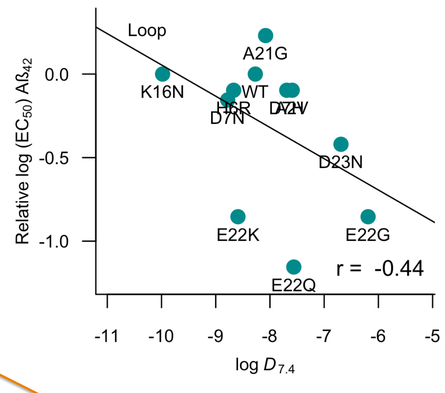
Central Hydrophobic Core (CHC; 17-21)

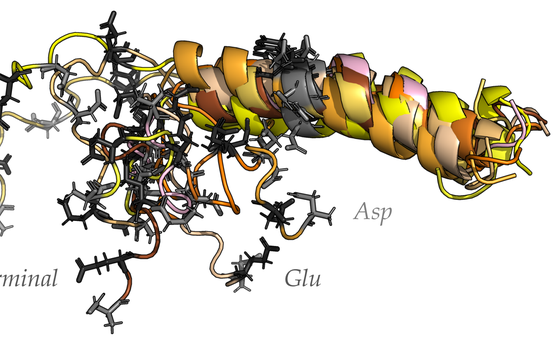
Loop (22-30)

C-Terminal (CT; 31-42)

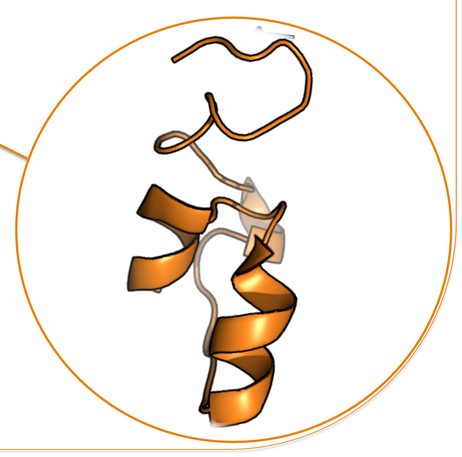








In vitro studies have demonstrated that acidic environments (pH = 5.8) promote the self-assembly of Aβ peptides more efficiently than to neutral pH. Therefore, low-pH environments, *e.g.*, endosome and lysosome, could potentiate the generation of toxic species by means of of Aβ self-aggregation which is driven by hydrophobic-hydrophobic interactions. Our ProtL scale predicts an increase of the peptide lipophilicity for $A\beta_{40}$ peptides as the pH decreases, in excellent correlation with experimental observations. Here, acidic residues, i.e., aspartic and glutamic acid, in the sequence are key because of they are the more sensible species to suffer lipophilic changes.



Aggregation in $A\beta_{40}$ Peptides

Selected References

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2. Somavarapu, A. K.; Kepp, K. P. Direct Correlation of Cell Toxicity to Conformational Ensembles of Genetic Aβ Variants. *ACS Chem. Neurosci.* **2015**, *6* (12), 1990–1996.
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