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Self-assembling processes in minimalistic pseudopeptides

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Self-association and self-assembling (SA) are of the utmost importance in peptides and proteins. As a matter of fact, SA of specific proteins is involved in many neurological diseases associated to aging. In this regard, the design and study of pseudopeptidic models to rationalize the SA behaviour for peptidic and pseudopeptidic structures is an important target. In recent years, we have developed several families of pseudopeptidic compounds based on minimalistic structures such as 1. The high level of conformational or configurational preorganization that can be present in such compounds facilitates the easy assembly into [1+1] and [1+2] macrocyclic structures (2 and 3).[1] Besides, their high functional density allows achieving an induced preorganization based on anionic templates for efficient [2+2] cyclizations.[2] A third level of molecular diversity can be introduced through the funcionalization of the primary amino groups in 1, in particular with the preparation of anfifilic systems (4).[3]

SA processes for those pseudopeptides are dependent on the structural modifications (i.e. nature of the spacers or the side chain of the starting amino acid) but they are also responsive to external stimuli such as changes in the solvent or the pH of the medium. [1+1] macrocycles with an aliphatic chain ($(CH_2)_n$) and a meta-substituted aromatic as the spacers (2) can provide strong organogelating properties, transferring the intrinsic molecular configuration to the macroscopic chirality of the fibers in the organogel.[4] Additionally, the fibrilar network can be used as a template for the preparation of polymers with controlled porosity.[4d] For [2+2] macrocycles with a B spacer based on a m-substituted benzene, the change from the Phe to the Val derivatives is accompanied by a change from aggregation into vesicles to the formation of rods and fibers. Here, an acidic medium acts as a negative stimulus for SA and no ordered structures can be obtained. Interestingly, the opposite is found when the B spacer is derived from a p-substituted benzene: SA is only observed in acidic media, the Phe derivative assembling into fibers while the Val derivative is able to form a crystalline structure. The corresponding X-Ray structures reveal some interesting features, including the key role of the side chains for assembling columnar arrangements trough hydrophobic interactions (knobs into holes).[5] The importance of the side chains is also visible in the case of compounds 1 with the assembling into a crystalline structure containing chiral channels based on the aromatic ring of a Phe derivative.[6] SA properties of anfifilic derivatives 4 are of particular relevance as they clearly show the importance of the different structural parameters and external stimuli to direct their proper assembling to form strong organogels stable at high temperatures, nanotubular, fibrilar or spherical structures in the solid state or stable monolayers at interfaces.

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