Modeling of the cyclic lipodepsipeptide Pseudodesmin A self-assembly through molecular dynamic simulations

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The self-assembly of short peptides into supramolecular structures represents an active field of research with potential applications, ranging from material sciences to medicine. Pseudodesmine A is a cyclic lipodepsipeptide of nine residues which presents a moderate antibacterial activity and whose structure has been resolved by X-ray and NMR. In acetonitrile, Pseudodesmine A is monomeric while in chloroform, it has the same structure but assembles in a supramolecular complex. This structure could associate with membranes and be responsible for the biological activity of the peptide. Comparison of NMR data in the two solvents has given indications on the intermolecular contacts that arise in chloroform and a model for the self-association was proposed. To study in more details this assembly, molecular dynamics simulations have been carried on. The resultswere compared with detailed information given by NMR, regarding the dimensions of the assembly and the orientation of the individual peptide building blocks inside the supramolecular assembly. In acetonitrile, the simulations show that the peptide has transient interactions while in chloroform, interactions between monomers are always observed. In agreement with NMR, these interactions arise mainly between the backbone protons of the LEU1 and the GLN2, the GLN2 sidechain and the loop located on the opposite end of the monomer structure. From 10 simulations of dimerization, hydrogen bonds were followed and specific interaction patterns were identified regarding the hydrogen bonds formed. Peptide interactions are mainly described by 13 interaction patterns characterized by 2 to 4 hydrogen bonds. In dimers, the peptides can have a linear, a perpendicular or a side by side configuration. From the linear dimer, it is possible to reconstruct filaments and, by combining a linear and a lateral dimer, it is possible to build fibrils with multifilaments, as found in the NMR-derived model. Two self-consistent supramolecular models can be built from dimers and they present a very good correlation with NMR data regarding the supramolecular organization. Besides, the perpendicular dimer can gives peptide rings that can also explain the potential ability of this peptide to form ion pores in membranes.