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Insight into the self-assembling properties of a peptergent: a molecular dynamics study

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Abstract: By manipulating the various physico-chemical properties of amino acids, design of peptides with specific self-assembling properties has been emerging since more than a decade. In this context, short peptides possessing detergent properties (so-called "peptergents") have been developed to self-assemble into well-ordered nanostructures that can stabilize membrane proteins for crystallization. In this study, the peptide with "peptergency" properties, called ADA8 extensively described by Zhang *et al.*, is studied by molecular dynamics for its self-assembling properties in different conditions. In water, it spontaneously forms beta sheets with a β barrel-like structure. We next simulated the interaction of this peptide with a membrane protein, the bacteriorhodopsin, in the presence or absence of a micelle of dodecylphosphocholine. According to the literature, the peptergent ADA8 is thought to generate a belt of β structures around the hydrophobic helical domain that could help stabilize purified membrane proteins. Molecular dynamics is here used to challenge this view and to provide further molecular details for the replacement of detergent molecules around the protein. To our best knowledge, this is the first molecular mechanism proposed for "peptergency". In addition, our calculation approach should serve as a predicting tool for the design of beta peptergent with diverse amphipathic properties.

Keywords: peptide; self-assembly; molecular dynamics; peptergency; beta structure

1. Introduction

By manipulating the various physico-chemical properties of amino acids, the design of peptides with specific self-assembling properties has been emerging for some years [1]. Due to their biocompatibility and chemical diversity, peptides are an attractive platform for the design of various nanostructures, such as nanotubes, vesicles, fibers, micelles or rod-coil structures, that have potential applications in drug delivery, tissue engineering or surfactants [2,3]. Depending on the sequence and environment, peptides can self-assemble into ordered structures constrained by non-covalent interactions, such as electrostatic interactions, hydrophobic interactions, van der Waals interactions, hydrogen bonds and π-stacking. Particularly, amphiphilic peptides have shown their ability to self-assemble into a range of nanostructures [3] and behave in some respects like conventional amphiphilic molecules such as surfactants, detergents and lipids. Amphipathicity can arise either from peptides containing polar and nonpolar residues distributed regularly along the peptide [4] or from alkyl chains linked to a hydrophilic peptide.

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In that way, short peptides possessing detergent properties, so-called "peptergents", have been developed in the last decade to self-assemble into well-ordered nanostructures that can stabilize membrane proteins for crystallization [5]. Three main classes are described in the literature: amphipathic helical peptides [6], lipopeptides [7–9] and short lipid-like peptides [10–12]. From a conformational point of view, some of these peptides can adopt α helical or extended β sheet structures during their self-assembly. Recently, the Zhang's group engineered a β-sheet peptide able to self-assemble and to sequester integral membrane proteins (IMPs) [13]. The peptide is amphipathic, alternating hydrophobic and hydrophilic residues. It is also methylated at some amino groups and is grafted with two alkyl chains. It is proposed that the peptide is able to associate with IMPs in a β barrel-like configuration.

There are many detergents available for the solubilization and crystallization of membrane proteins [14]. However, these detergents need to stabilize the native structure of the protein to maintain its function and avoid aggregation. Finding the optimal detergents for the protein studied requires wide screening and depends on the application [12]. New ones are required, and some peptergents have shown better stabilizing properties than commonly used alkyl chain surfactants [15]. Even though experimental evidence is available concerning the relative efficacy of peptergents in solubilizing and stabilizing IMPs [10,11,13,16], little is known about the molecular mechanisms involved in their interactions with proteins.

In this work, we studied the self-assembling properties of a known peptide called ADA8 [3] (Fig. 1a) using molecular dynamics (MD). In water, this peptide is able to self-assemble as a beta barrel-like structure. In the presence of an integral membrane protein, the peptide forms a beta belt around the protein with and without surfactant molecules. To the best of our knowledge, this is the first time that a molecular mechanism is proposed by MD for "peptergency". Our calculation approach should further serve as a predicting tool for the design of beta peptergent with diverse amphipathic properties, as suggested for a *de novo* designed peptide, ABZ12.

2. Results

2.1. Simulations in water

Ten ADA8 peptides (fig. 1a) were simulated in water in atomistic (AT) (1 μs) and coarse grained (CG) (10 μs) representations to follow their self-assembly (Fig. 1). The black curve of Fig. 1b shows a rapid increase in the beta structure during AT simulations in water and the beta sheets formed can be seen in Fig. 1c. These structures are similar to beta barrels with the peptides adopting amphiphilic beta strand conformations, their hydrophobic residues facing the inside of the barrel. The strands can be parallel or anti-parallel. The self-assembly has also been simulated in a CG representation since longer time scales can be achieved. At the end of the CG simulation, we observed two amphiphilic beta sheets facing each other, with the hydrophobic residues buried between the sheets (fig. 1d). Polar interactions between sidechains as well as backbone interactions between the strands are also noticed. To estimate the formation of beta structures, a parameter that is based on Cα or backbone beads positions has been used (see Methods). As observed in AT simulations, the peptides are able to adopt a beta conformation along the simulation, as assessed by the green curve in Fig. 1b and the molecular assembly in Fig. 1d. Though the beta sheet twist observed in atomistic simulations is not reproduced by the CG model and leads to the formation of two facing beta sheets instead of a beta barrel. It is worth noting that the MARTINI force field is, in principle, not designed to sample native conformations [17], especially for beta sheet structures, since there is no hydrogen bond representation. In the literature, several fibril-forming peptides have been studied using MARTINI [18,19], such as the aggregation of the Apo C-II amyloid peptide or the assembly of the protofibrils of amylin. However, beta sheet formation was not observed for the Apo C-II peptide, and the beta conformation of amylin protofibrils was restrained before elongation could occur. Nevertheless, Seo *et al*. have observed beta sheet formation with MARTINI, but they modified the backbone potentials to reproduce structural properties derived from atomistic simulations [20]. Here, we observed the appearance of beta sheets without any modification of the force field; this is mainly due to the beta amphipathic nature of the ADA8

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peptide. Some differences between CG and AT beta sheets were nevertheless observed. CG strands in beta sheets are shifted by one residue compared to atomistic beta sheets (Fig. 1d). In the latter, the relative positions of the beta strands are defined by hydrogen bonding and the side chains on both sheet sides align. In contrast, in CG, the attraction comes from the backbone (BB) beads, and the shifted position minimizes the overall BB bead distance between strands. The question of the backbone representation in MARTINI was discussed by Marrink *et al.* in 2013; a perspective evolution of the force field would be to add charged beads to the backbone in order to reproduce the structural preferences of proteins [21].

To assess the stability of the beta structure formed, the structure represented on Fig. 1d has been transformed to an atomistic resolution and further simulated for 25 ns. This simulation shows a small decrease in the beta sheet content with a reorganisation to form a beta barrel (see Supplementary Fig. S1). Globally, for all the simulations, the peptides are able to form beta structures, which agrees with the literature [13].

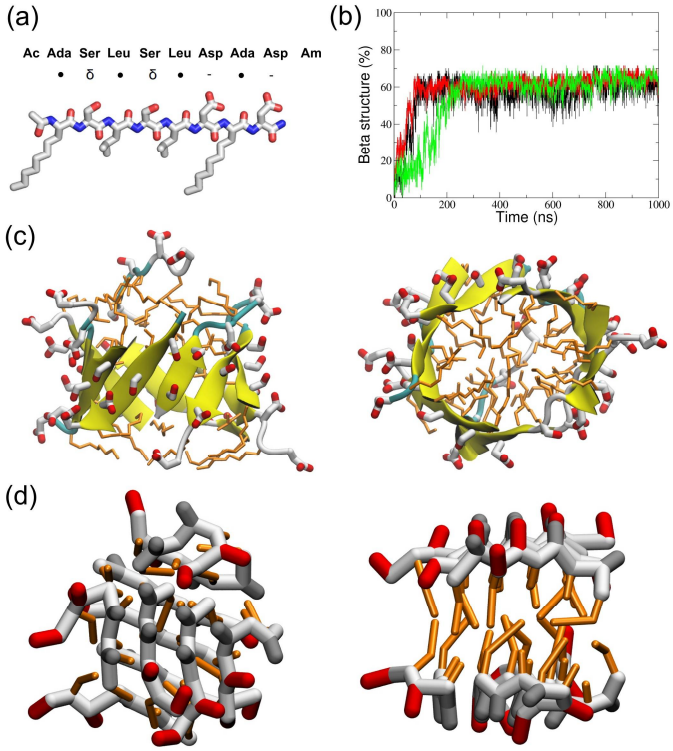

Figure 1. ADA8 peptide structures in water. (**a**) Representation of the ADA8 peptide. •, δ and - represent hydrophobic, polar and negatively charged residues, respectively. (**b**) Percentage of beta conformation. The structure is assigned by Stride in AT (black curve) and by using the following parameter in CG : a dihedral angle greater than 100° for four following CA atoms and two other following CA atoms within 6 Å. The red and green curves correspond to this parameter for AT and CG simulations respectively. Conformations at the end of simulations in atomistic and coarse grained representations are in panels (c) and (d), respectively; the right panels are an upper view of the left panels. AT beta sheets are in yellow in the AT representations. Polar, negatively charged and hydrophobic CG residues are represented in gray, red and orange, respectively.

2.2. Coarse grained simulation of the peptide in the presence of a membrane protein

ADA8 was shown by Tao *et al.* to be a very efficient peptergent and to solubilize membrane proteins such as rhodopsin [13]. Thus, we chose an IMP with a known and well-characterized 3D structure, bacteriorhodopsin (BRD). Twenty peptides were simulated in water in the presence of one BRD protein over 10 μs in CG representation. Figure 2 represents the peptides interacting with BRD at the end of the simulations and shows that the peptides form amphipathic beta sheets at the hydrophobic domain of the IMP and present their hydrophilic residues to water. This process can

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be followed in Fig. 3a, which shows an increase in the beta sheet content during the simulations, and Fig. 3b, where an increase in the area of the interacting surfaces between the peptides and the protein is observed. The peptides are rapidly attracted by the protein surface, and through interactions with BRD, they bury their hydrophobic residues. They form hydrophobic, polar and backbone interactions between the antiparallel or parallel beta strands (Fig. 2). Once at the protein surface, the reorganization of the peptides slowly occurs. The protein surface is 115 nm^2 and the portion covered by the peptides represents about 50 nm^2. The peptides are also positioned mainly on the hydrophobic part of the protein. They are not always oriented parallel to the helices axis as expected for a beta barrel-like organization.

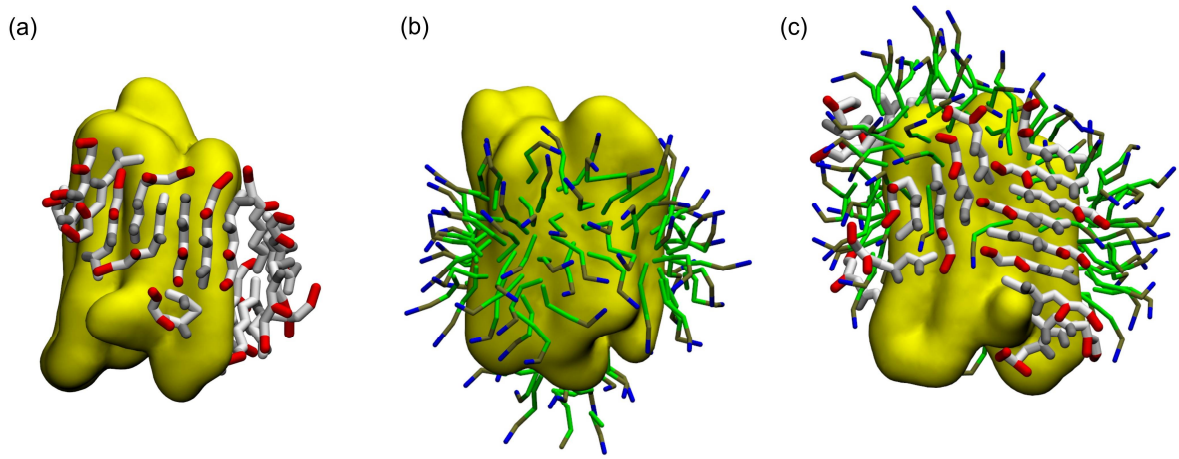

Figure 2. ADA8 peptide organization on the surface of the membrane protein. The structures show 20 peptides at the end of the CG simulations when the protein (in yellow) is alone (**a**) or covered by DPC (**c**). The protein surrounded by DPC is shown (**b**), and this structure was used as a starting point before the addition of the peptides (**c**).

Figure 2c shows that when DPC is present at the surface of the protein, the peptide is able to go to the protein surface and form beta sheet structures similar to the situation without DPC. Furthermore, as the peptide is located on the transmembrane domain of BRD, it displaces DPC molecules around the hydrophobic core of the protein (Fig. 2c). Figure 3 depicts the beta structure (Fig.3a) and the surface of the interaction between the peptides (with or without DPC) and the protein (fig.3b) that are relatively stable along the simulations.

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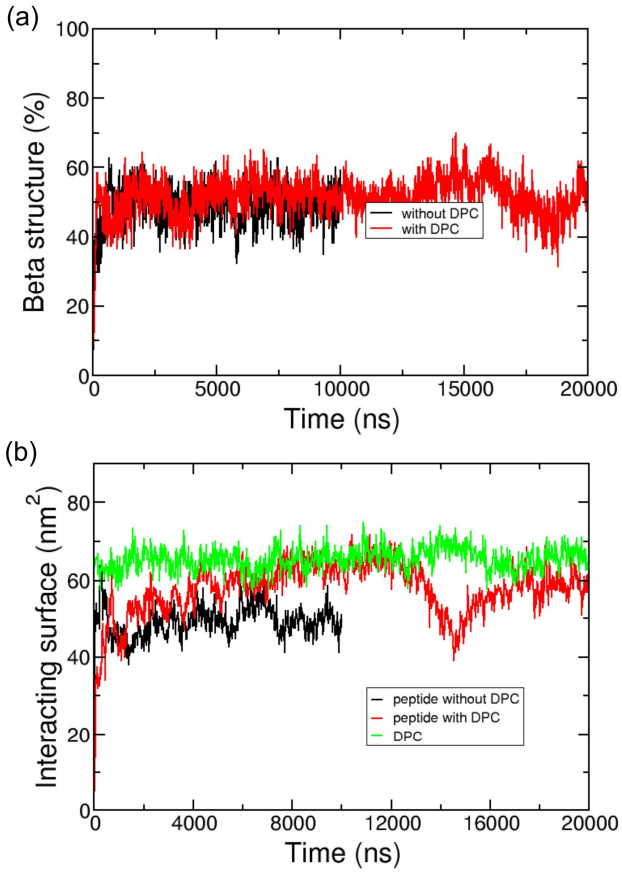

Figure 3. Secondary structure evolution (a) and surface of the interaction (b) of the peptide ADA8 in the presence of a membrane protein with (red lines) and without (black lines) DPC. The surface of the interaction between DPC and the membrane protein in the presence of the ADA8 peptide is represented in green.

3. Discussion

In this study, we have analyzed the molecular behavior of ADA8, a well described peptergent, for its solubilizing and stabilizing propensity of IMPs by molecular dynamics. The peptide self-assembles into beta structures in water and is able to interact with a membrane protein, in agreement with the experimental data previously published [3]. In water, the peptide forms amphipathic beta sheets that look like β-barrel for the AT representation or as 'sandwich' like β-sheets in CG. It is worth noting that the peptides were successfully simulated in atomistic and coarse grained representations, validating the CG approach for such amphipathic beta peptides. The validation of the CG approach was notably assessed by using reverse transformations: hence, AT simulations carried out after reverse transformation showed that the beta sheets formed in CG were still stable.

When a membrane protein is present, the peptide steadily forms a beta sheet structure at the protein surface and is able to displace DPC surfactants. Tao *et al*. proposed a model for the organization of the peptides around an IMP [9]. The peptides are thought to generate a beta-barrel belt around the hydrophobic helical domain that could help stabilize purified membrane proteins [13]. The MD approaches developed in our study challenge this view and provide further molecular details for the replacement of detergent molecules around the protein. Although a complete belt was not obtained during the course of the simulations, the system tended to move toward this configuration.

In their work, Tao *et al*. also asked how IMPs are stabilized by beta strand peptides that can assemble into beta structures in solution [13]. Our calculations suggest that beta sheet formation is favored in water, suggesting a strong peptide/peptide interaction. In the presence of membrane proteins, even those solubilized with surfactants, the ADA8 peptide could also form beta sheets at

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the protein surface. As the peptide/peptide interaction is stronger than that of surfactants, the former appears to steadily displace surfactants from the protein hydrophobic surface. Since Tao *et al*. showed that their model membrane protein retains its activity, we assumed that the IMP structure is not restrained by the beta sheet structure. Compared to the assumption of Tao *et al*., our calculations suggest that the belt formed around the membrane protein is not 'perfect'. The beta strands can be parallel or antiparallel and beta sheets perpendicular to the protein α helices are observed.

Our MD approach could be used to select peptides with 'peptergency' properties, i.e. amphiphilic peptides with a β sheet structure propensity and the ability to form a β belt-like structure around an IMP in the presence or absence of detergent molecules. As an example, we designed a peptide called ABZ12 to be in a β conformation, being composed of residues most frequently found in β conformation, such as Arg, Val, Ile or Thr [22,23]. A size of 12 amino acids is also compatible with the width of membrane bilayers and is usually observed for membrane proteins with a beta barrel fold [24,25]. Hydrophobic amino acids (Val and Ile) alternate with hydrophilic residues (Arg, Thr, and Ser) to generate amphipathy and promote the formation of beta strands [4]. Positive charges in the N-terminal part combined with negative charges at the C-terminal part should allow an antiparallel arrangement while keeping global neutrality. A fluorescent N-terminal cap is added in the form of an aminobenzoyl group for experimental purposes. ATR-infrared spectroscopy assays on the peptide (see Supplementary Fig. S3) shows a peak at approximately 1630 cm^{-1}, characteristic of β-sheet conformations. According to what was carried out for ADA8, CG simulations of the system IMP/ABZ12 in the presence or absence of DPC molecules were calculated. As shown on Fig. S4, the same molecular picture is obtained; ABZ12 forms a beta belt around the membrane protein and displaces detergent molecules when they are present, suggesting a peptergent-like behavior. Actually, the detergents moved to more apical regions of the protein in the presence of the peptides. The contact surface between DPC and the protein decreased by at least 10 nm^2 (Fig. S5). Preliminary experimental results of FRET assays with ABZ12 show fluorescence energy transfer between the IMP and the aminobenzoic acid group of ABZ12 (data not shown), suggesting a direct interaction between ABZ12 and the protein. Future experimental investigations on the ability of ABZ12 to solubilize membrane proteins should help to assess its 'peptergency' potential.

In conclusion, our MD approach using atomistic and coarse grained representations suggest that one possible mechanism for membrane proteins to be solubilized by β amphipathic self-assembling peptides is the formation of a belt-like structure around the IMP. This belt is not a perfect β barrel, contrary to what was suggested previously. To our best knowledge, this is the first molecular insight proposed for "peptergency".

4. Materials and Methods

4.1. Peptide synthesis

The ABZ12 peptide was synthesized by conventional solid phase peptide synthesis using Fmoc for transient NH2-terminal protection and was characterized using mass spectrometry. The peptide was lyophilized and resolubilized in DMSO at a final concentration of 10 % (w/v) peptide as a stock solution. Before mixing with water, the peptide solution in DMSO was first diluted to 0.5% to avoid insolubility.

4.2. Fourier Transform Infra Red (FTIR) experiments

The infrared spectra were measured using a Bruker Equinox 55 spectrometer (Karlsruhe, Germany) equipped with a liquid nitrogen-cooled DTGS detector. The spectra were recorded from 4,000 to 750 cm^{-1} in ATR mode after 1,024 scans at 4 cm-1 resolution and at a two-level zero filling. During the data acquisition, the spectrometer was continuously purged with filtered dried nitrogen. For sample measurement, the peptide solubilized in DMSO was deposited on a germanium plate, and DMSO was evaporated under the N2 flux for approximately 5 hours. Reference spectra of the

germanium plate were automatically recorded and subtracted from the sample spectrum. The resulting spectrum was then smoothed using the Savitzky-Golay algorithm available in the OPUS software.

4.3. Molecular systems studied by MD

Two peptides were studied by molecular dynamics (MD); their properties are depicted in Fig. 1 and S2. The ADA8 peptide is described in Tao *et al.* [13]; it contains two non-natural 2-aminodecanoic acids (ADA) and is acetylated at the N-terminus and amidated at the C-terminus (Fig. 1b) [13]. The ABZ12 peptide was designed as an example for this study; it is capped at the N-terminus by an aminobenzoic acid and is free at the C-terminus. The peptides have been modeled in an extended beta conformation based on experimental data (FTIR). The force field Gromos96 54a7 (G54a7) [26] was used during this study. The ABZ topology came from a study by Song *et al.* in 2010 [27], and the ADA topology was derived from the ILE amino acid. The SPC model [28] was used to simulate water. The MARTINI force field [17,29] has been used for coarse grained (CG) simulations. The ABZ residue was replaced by a PHE residue. The membrane protein used was bacteriorhodopsin (PDBID: 1PY6), and its tertiary structure has been maintained with the SAHBNET network [30].

4.4. Atomistic molecular dynamics

Simulations were performed with the G54a7 force field [26]. All the systems studied (see Supplementary Table S1) were first minimized by steepest descent for 5,000 steps. Then, a 1 ns simulation with the peptides under position restraints was run before the production simulations were performed. Periodic boundary conditions (PBC) were used with a 2 fs time step. All the systems were solvated with SPC water [28] and the dynamics were carried out under NPT conditions (298 K and 1 bar). The temperature was maintained using the v-rescale method [31] with $\tau T = 0.2$ ps, and an isotropic pressure was maintained using the Parrinello-Rahman barostat [32] with a compressibility of 4.5 × 105 (1/bar) and $\tau P = 1$ ps. Electrostatic interactions were treated using the particle mesh Ewald (PME) method [33]. Van der Waals and electrostatic interactions were treated with a 1.0 nm cut-off. Bond lengths were maintained with the LINCS algorithm [34]. Trajectories were performed and analyzed with GROMACS 4.5.4 tools as well as with homemade scripts and software. MDAnalysis was also used [35]. The 3D structures were analyzed with both the PyMOL [36] and VMD [37] softwares. The secondary structures were computed with STRIDE [38].

4.5. Coarse grained molecular dynamics

The peptide models were converted to a CG representation suitable for the MARTINI force field [17], and the coarse grained peptides were placed in a simulation box with water (see Supplementary Table S1). A total of 5,000 steps of steepest-descent energy minimization were performed to remove any steric clashes, and production simulations were run. Temperature and pressure were set at 298 K and 1 bar using the weak coupling Berendsen algorithm [39] with $\tau T = 1$ ps and $\tau P = 1$ ps. Pressure was coupled isotropically. Non-bonded interactions were computed up to 1.2 nm with the shift method. Electrostatic interactions were treated with $\varepsilon = 15$. The compressibility was 3 × 104 (1/bar). Coarse grained simulations were carried out using Gromacs 4.5.4. [40] To compare the structure evolution between AT and CG, we had to compute a parameter representing the beta structure in CG. Hence, as the backbone is only represented by one bead in CG, it is not possible to compute the phi/psi angles. A dihedral angle greater than 100° and the proximity of two other bonded backbone beads within 6 Å are used to consider a bead to be part of a beta sheet structure. These values have been taken from atomistic simulations and allow for the calculation of the beta structure content with enough precision (see Fig. 1b).

Supplementary Materials: Supplementary materials can be found at www.mdpi.com/link.

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Conflicts of Interest: "The authors declare no conflict of interest."

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