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Conformational dynamics and aggregation behavior of piezoelectric diphenylalanine peptides in an external electric field

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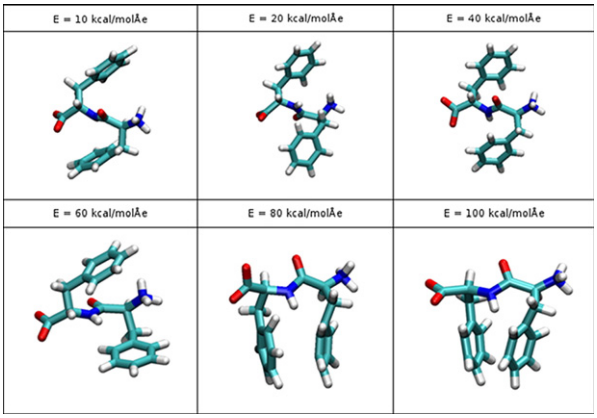
HIGHLIGHTS

- Molecular dynamics simulations of FF peptides in external electric fields.
- FF peptides with charged termini have a more complex conformational space.
- Electric fields induce extended FF conformations with larger dipole moments.
- Electric fields increase the self-assembly propensity of FF peptides in nanomaterials.

GRAPHICAL ABSTRACT



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ABSTRACT

Aromatic peptides including diphenylalanine (FF) have the capacity to self-assemble into ordered, biocompatible nanostructures with piezoelectric properties relevant to a variety of biomedical applications. Electric fields are commonly applied to align FF nanotubes, yet little is known about the effect of the electric field on the assembly process. Using all-atom molecular dynamics with explicit water molecules, we examine the response of FF monomers to the application of a constant external electric field over a range of intensities. We probe the aggregation mechanism of FF peptides, and find that the presence of even relatively weak fields can accelerate ordered aggregation, primarily by facilitating the alignment of individual molecular dipole moments. This is modulated by the conformational response of individual FF peptides (e.g., backbone stretching) and by the cooperative alignment of neighboring FF and water molecules. These observations may facilitate future studies on the controlled formation of nanostructured aggregates of piezoelectric peptides and the understanding of their electro-mechanical properties.

Abbreviations: FF, diphenylalanine; MD, molecular dynamics; RMSD, root mean square deviation; d_{EE}, end-to-end distance; SASA, solvent accessible surface area.

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1. Introduction

Aromatic peptides have the intrinsic ability to self-assemble into highly-ordered nanostructures such as nanospheres, nanotubes, nanofibrils, and nanoplates [1–3]. These structures form by conformational packing and linkage between the amino acid sequences, stabilized by non-covalent weak interactions (hydrogen bonds, van der Waals, electrostatic interactions), aromatic interactions and π–π stacking [4–6]. Such nanostructures possess high stiffness and excellent thermal and chemical stability [7,8]. Self-assembly facilitates opportunities for economical and environmentally propitious production of these nanomaterials. In addition, these materials are naturally biocompatible and easily chemically modified, resulting in their application to many areas including bio-sensing, drug delivery, tissue engineering, kinase activity measurements and pathogen detection [9–11].

Diphenylalanine (FF) is a common peptide occurring naturally as the core derivative of the amyloid beta (Aβ) protein. FF self-assembles, forming nanotubes through thermodynamic folding of the β-sheet [1,2]. FF nanotubes are intrinsically biocompatible, strong materials, with favorable thermal and chemical properties [7,9,11]. Furthermore, they are easily functionalized with receptor molecules and for this reason are the subjects of intense research [11,12]. Kholkin et al. have demonstrated that these nanotubes exhibit a strong piezoresponse using (piezoresponse force microscopy) PFM [13]. Piezoelectricity is a characteristic of non-centrosymmetric materials, whereby the material will undergo a mechanical stress/strain when placed under an electric field, or conversely, the material will generate an electric charge under a mechanical stress. FF nanotubes display a shear piezoelectric deformation due to the polarization orientation along the axis of the tubes and a piezoelectric coefficient $d_{15} \approx 60$ pm/V [13,14]. Therefore, FF peptide nanotubes could function as both the sensitive biological element and the transducer/detector element in an electromechanical biosensor, thus eliminating inorganic elements and complicated fabrication steps, and reducing costs. Materials exploiting electromechanical coupling could also potentially be used as energy generating devices in vivo, for example replacing batteries in medical devices such as pacemakers [13]. Lee et al. have shown that virus-based piezoelectric energy generation is possible [15], which is further motivation for exploiting electromechanical coupling using peptide nanostructures.

The source of this response is thought to be a result of the non-centrosymmetric nature of the beta sheet [13]. Piezoelectricity arises in a non-centrosymmetric material when it is placed under a mechanical stress, which distorts the atomic structure of the crystal, such that ions in the structure separate, and a dipole moment is formed. For a net polarization to develop, the dipole formed must not be canceled out by other dipoles in the unit cell. Therefore, to understand the source of this response in the nanotubes, it is important to understand the behavior of the dipole moments within the FF molecules during self-assembly.

Experimentally, Reches and Gazit were the first to report the spontaneous self-assembly of FF molecules into ordered semi-crystalline structures [5]. Since then Görbitz has shown using X-ray diffraction that the FF molecule has an unusual conformation, promoting the crystallographic hexagonal symmetry of hydrogen-bonded head-to-tail chains in the shape of helices with four to six peptide molecules per turn [1]. The side chains appear to emanate from the channel core and the resulting structures have chiral hydrophilic channels with a van der Waals diameter up to 10 Å [1]. Bystrov et al. have performed MD simulations investigating the piezoelectricity and related changes in the dipole moments and polarization of an isolated ring with six dipeptides, as well the parallel stacking of two rings [16]. Computational studies using coarse-grained models [17,18] have also illustrated both the role of solvation and of the specific side chain–side chain interactions in the self-assembly of FF peptides [19–22].

Directed self-assembly occurs when such a system is placed under the influence of an external stimulus, i.e., mechanical vibration and pH. This enables the tuning of desired interactions, structure and properties of the final assembly. The main challenge with directed self-assembly is the need for rigorous predictive models. An example of directed assembly is applying an electric field to the FF molecule and measuring the effect on the position of the dipole. Methods of self-assembly such as dielectrophoresis exert this kind of stimulus on the whole nanostructure and have been used to influence the alignment of FF nanotubes [23–29].

It remains unclear, however, how an electric field affects a single FF monomer dipole, and how it would affect the initial conditions for self-assembly. Therefore, the objective of this work is to provide a predictive model of the behavior of a single FF molecule when placed in an electric field and simulate the effect when the molecules begin to aggregate/self-assemble.

2. Methods

Two simple FF peptide models were constructed and studied using molecular dynamics (MD) simulations: one with neutral termini and one with charged termini. For neutral termini, NNEU (NH_2) and CNEU (COOH) caps were applied. For charged termini, NTER (NH_3^+) and CTER (COO^-) caps were applied. In the first stage, the FF monomer conformational dynamics was studied (Fig. 1A). In the second stage, using the model with charged termini, a 64-FF system was also created by randomly placing FF molecules with an overall concentration of approximately 16 FFs per 100,000 $Å^3$ (Fig. 1B). This relatively high concentration allows for faster aggregation and shorter simulation times.

MD simulations (see Table 1 for a summary) were performed with the NAMD 2.8 software [30] using the CHARMM27 force field [31,32]. All simulations were performed in the isothermal–isobaric ensemble (i.e., NPT, constant number of atoms, pressure and temperature), using periodic boundary conditions. We used the modified Nosé–Hoover Langevin piston method implemented in NAMD [33,34] with a damping time of 0.1 ps, while maintaining a pressure of 1 atm. The temperature was set to 310 K and controlled using a Langevin thermostat with a damping coefficient of 1 ps^{-1}. Long-range electrostatic interactions were calculated using the particle-mesh Ewald (PME) method [35]. The switching distance for non-bonded electrostatics and van der Waals interactions was 10 Å with a cutoff distance of 10 Å. The integration time step was 1 fs.

Each system was solvated with explicit TIP3P water molecules [36] prior to minimization, heating and equilibration. The TIP3P water model [36] has been broadly tested and used in biomolecular atomistic MD simulations using the NAMD 2.8 software [30] particularly in conjunction with the CHARMM27 force field [31,32]. Here, the TIP3P model is expected to generate a realistic ensemble of confirmations for the FF peptides, which are the focus of our study. However, for a more accurate (yet slower to compute) representation of the dielectric properties as well as of the water conformational dynamics, a newer higher-order model (e.g., TIP4P or TIP5P) or polarizable versions of the non-polarizable models could be used, but at a significantly increased computational cost [37]. While an improved, more detailed water model is expected to react better than TIP3P to an external electric field, it may not affect significantly the conformational dynamics of the solvated peptides [37].

For the monomeric FF systems (Fig. 1A), the box size was approx. 22,500 $Å^3$ (or 30 × 30 × 25 Å). For the 64-FF systems (Fig. 1B), the box size was approx. 400,000 $Å^3$ (or 77 × 87 × 60 Å). Total atom numbers for each system including water molecules are reported in Table 1. Systems were prepared for MD simulation as described in our previous papers using also similar NPT MD studies [38–40] of larger amyloid peptides such as Alzheimer's amyloid-beta (Aβ, [41–43]) or human amylin (hIAPP, [44]).

Single-FF systems were minimized for 1000 steps with the backbone fixed in place, and then 1000 steps with the entire system free to move. The system was heated to 310 K over 3 ps. This was followed by 5 ps of