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========== **TRANSLATIONS OF PUBLISHED ARTICLES** ==========

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On The Choice of Force Fields for Studying the Molecular Dynamics of Ion Peptides and Their Dimers

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Abstract. The paper presents comparative data on the impact of force fields AMBER (ff03, ff99SB, and ff96) on the results of experiments on molecular dynamics of dimer peptide molecules formed of ion-peptide NH_2-$(RADA)_4$-COOH in anti-parallel β-conformation at two temperatures (300 K and 320 K). It is shown that MD simulation in explicit water environment is the most informative approach. The use of different force fields has a significant influence on the stability of the initial molecular conformation of the peptide over time. Finally, MD simulation in ff99SB environment provides significant stability of anti-parallel β-structure of the dimer at 300 K, while ff96 not only ensures the highest stability of the initial peptide in β-conformation at higher temperatures, but also enhances retention of anti-parallel β-conformation, which determines the ability of NH_2-$(RADA)_4$-COOH peptides to self-organization.

Key words: *RADA16, force fields, molecular dynamics, MD, ff03, ff99SB, ff96, AMBER.*

INTRODUCTION

Molecular dynamics (MD) is an advanced tool to study characteristics of macromolecule structures such as conformational stability over the time period, polypeptide folding, including details of supramolecular structure formation and system thermodynamics. Important issues for proper MD are the compliance of physical model properties to general concepts of classical Newtonian mechanics, which is essential to obtain sufficient sampling volume of conformational states by modeling physics of the studied chemical structure. There is a need for recognizing differences in the results obtained *in silico* with those obtained by physico-chemical methods, such as nuclear magnetic resonance (NMR), circular dichroism (CD) or infrared (IR) spectrophotometry [1].

Considerable efforts are made to improve the methods of biomolecular structure modeling by using empirical force field parameters with corresponding solvent models, different water molecule parameters and the methods of electrostatic interaction assessment [2–7]. Parameters for the atom-to-atom interactions are of particular importance since the biggest problem is usually to choose a proper potential force field to run the MD experiment. Many

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attempts have been made to improve convergence of the modeling results obtained for peptides studied with the use of different potential force fields like AMBER [8, 9], CHARMM [10], GROMOS96 [11] and OPLS [12]. Prime efforts have been focused on improving the parameters of atom-to-atom interactions in peptide structures to define complex physical criteria of mutual transition between α-helical and β-sheet states.

Protein folding results, when approached *in silico* with different force fields, show only a limited similarity [13], which further emphasizes the need for careful choosing MD-experiment conditions. A possibility was shown to use polypeptides in natural conformation as the initial state of the molecule in modeling experiments, which is important to simulate molecules of polar or self-assembling peptides as having numerous transient or short-time living conformations [13]. Comparative test on different force fields performance has not been made for NH_2-$(RADA)_4$-COOH self-assembling peptide, despite the grown computing powers emerged [14–20]. Nevertheless, adequate sampling of conformational space and suitable time intervals usage enables us to expect that the ensembles of structures would be identified, corresponding to the forms observed under physiological conditions, while they were shown as more stable objects during *in silico* experiments. Polar peptides NH_2-$(RADA)_4$-COOH in water are known to form the peptide complexes made of cross placed β-sheet structures, which look like fibrils up to 90 nm in length. These filaments can compose three-dimensional interconnected networks of fibers. Self-assembled bi-layered structures of amyloid-like complexes are formed by anti-parallel peptide molecules, arranged perpendicular to the longitudinal axis of the filament body [21].

Needless to say that use of the method of molecular modeling provides a unique opportunity for studying the properties of biological macromolecules and stage-marks of the fundamental processes during peptides self-arrangement. Molecular dynamics is a useful method to gain the data, which can be used to account for thermodynamics of protein folding, kinetic of molecule interactions and secondary structure formation [22]. Compliance with the terms of typical secondary structure formation by polypeptide chain is often a limiting factor in studying protein state transitions, polypeptide aggregating or complex structure stability by the method of molecular dynamics. Noteworthy, comparison of different conditions affecting the secondary structure stability within the polypeptide molecules during MD experiment is a practical approach to study self-assembling structures.

The results presented in this paper represent molecular dynamics (MD) data on NH_2-$(RADA)_4$-COOH peptide dimers in extended conformation, studied at different force potential fields AMBER (ff96, ff99SB, ff03) at two temperatures (300 K and 320 K). Experiments on molecular dynamics of peptides were conducted both in vacuum and explicit water. The initial state of NH_2-$(RADA)_4$-COOH dimers was in antiparallel β-sheet conformation, which is predominant for this type of peptides. Below we present the description of model peptide structures design, setting MD-experiments under different conditions and data analysis. The conclusions are summarized in the final section of the paper.

METHODS

Model peptides

The virtual molecule of the dimer peptide NH_2-$(RADA)_4$-COOH was created by docking two NH_2-$(RADA)_4$-COOH models as anti-parallel chains in extended conformation. Docking software HEX6.1 was used so that the models geometry was taken into account and surface charges were set “on” as an option [23]. At the same time, the program GRAMM-X gave virtually identical results, when it worked with the molecule shape only [24]. These two approaches yielded nearly identical results, but the most stable peptide complex was chosen

fot further analysis. The dimer structure was further used as an initial object of research on peptide complex stability by investigating the effects of different force fields on NH_2-$(RADA)_4$-COOH dimer structural characteristics. The goal was to find more suitable media to monitor the peptides in extended conformation during the state transition, taking into account the fact that these polar peptides are self-assembling in normal saline by forming hydro-gels, composed of filaments made of anti-parallel β-sheet structures, which are the main building motif of the filament internal organization.

Sample preparation

3-D models of 16-mer NH_2-$(RADA)_4$-COOH peptide dimer structures were built as a segment of anti-parallel β-sheet from the peptide monomer which was created by using HyperChem 8 software [25]. Protonation state of the charged amino acid residues corresponded to pH7 and corresponding PDB files were used for further MD experiments.

Molecular dynamics

Molecular dynamics of polypeptide dimers in explicit water and data analysis were performed by using AMBER11 package [26].

The system with periodic boundary conditions (PBU) consisted of the peptide complex immersed in media of 6551 water molecules. The parameters of the water molecule corresponded to TIP3P model [27]. Molecular dynamic runs were modeled in three AMBER force fields ff96 [28], ff03 [8, 29] and ff99SB [9] at 300 K and 320 K. We used the same protocol to obtain 6 MD trajectory of 10 ns length each.

Firstly, the system energy was minimized with fixed atom position coordinates of dimer peptide to resolve atoms clashes by streamline interactions and more balanced distribution of water molecules in the PSU cell. Limited heating of the system at constant volume was performed by using the procedure of molecular dynamics in NVT-ensemble, while some position coordinates of atoms at the peptide dimer were also fixed. These calculations are necessary in order to adjust properly water molecules surrounding the model dimer, relative to the cell boundaries of PSU. The latter step of heating lasted for 10 ps.

Further two stages of energy minimization were steadily performed, when the model was affected by partially weakening forces to fix atom positions in the dimer molecule model. During the next step, the whole system was heated unconditionally by NVT-ensemble procedure either to 300 K or to 320 K at constant volume. NVT-type simulation lasted for 10 ps, after that simulation was continued in NPT-ensemble at constant pressure for 15 ps. For this purpose the cell was adjusted to periodic boundary conditions to achieve the desired density of fluid in the system.

As a result of these operations, the system was brought to the starting conditions to calculate experimental MD trajectories of 11 ns at constant pressure of 1 atm.

Data analysis

To determine the type and composition of the secondary structures in the analyzed models of polypeptides we used the classification system proposed by Kabsh and Sander [30]. To analyze the thermodynamics we estimated Gibbs energy (ΔG) of each saved instant geometry peptide. The calculations took into account the Gibbs energy of the molecular mechanical (MM) and the excess energy of the peptide chemical potential, the evaluation of which is made by the generalized Born method (GBSA) [31]. Conformational stability was evaluated by comparing the number of amino acid residues found in β-conformation, as well as the length of non-interrupted continuous stretch of amino acid residues in β-conformation. These values were estimated for each saved instant geometry state of dimer peptide chains and further identified by averaging them over the MD trajectory. B-value layer was determined

according to the values of the angles φ (C'-N-Cα-C ') and ψ (N-Cα-C'-N) peptide backbone, which were found by the Bioinformatics Toolbox 3.6 in MATLAB R2010b. The boundary conditions for the angles φ and ψ, which are stored within β-conformation of the peptide bonds were in the ranges ($-105° < \varphi < -180°$) and ($105° < \psi < 180°$).

RESULTS AND DISCUSSION

Investigation of the energy characteristics of molecular dimers NH_2-$(RADA)_4$-COOH, formed by the model peptides in three conformations (Fig. 1) reveals the similarity of the dynamic behavior of the dimers in explicit aqueous environment. Despite the fact that the minimal value of Gibbs free energy corresponds to the dimer of the form of α/β (Fig. 2,a), the difference between the free energies of the three models of dimers with dispersion is negligible (Fig. 2). Since the comparison of polar dimer energy in different but frozen peptide conformations was proved unpromising, it became obvious that for these purposes the analysis of peptide structures is required. In modeling aqueous media with generalized Born method we obtained poor results, since the peptide dimer structures (α/β, β/β, β/π) at 300 K quickly collapsed into a state of weakly evolving globules (data not shown). Thus, the use of explicit water environment to study polar peptide dynamics was a non-alternative approach and was considered by the authors as an indispensable factor *in silico* experiments with NH_2-$(RADA)_4$-COOH. Consideration of changes in the properties of dimers (α/β, β/β, β/π) at 300 K in explicit water environment allowed us to make a conclusion about the dominant contribution of the initial conformation of the peptides into the stability of the structure during the considered period of time. The weak dynamics of α-helical molecule NH_2-$(RADA)_4$-COOH α/β (Fig. 2,a) in this experiment cannot be considered to be one of the initial components of larger oligomers formed by anti-parallel β-peptide structure [21].

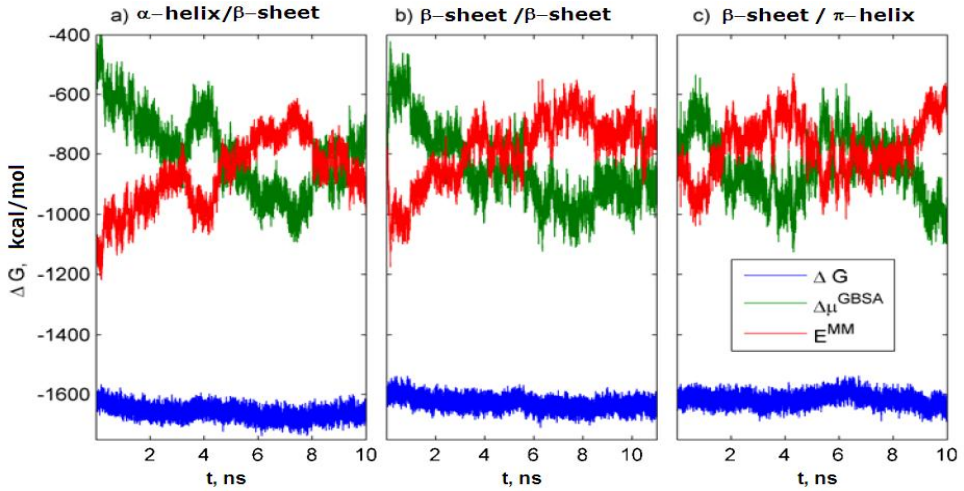

Fig. 1. Decomposition of Gibbs energy of NH_2-$(RADA)_4$-COOH dimers in explicit water: ΔG – Gibbs energy, Δ_{μ}^{GBSA} – estimation of excess chemical potential by generalized Born method, E^{MM} – molecular-mechanical energy.

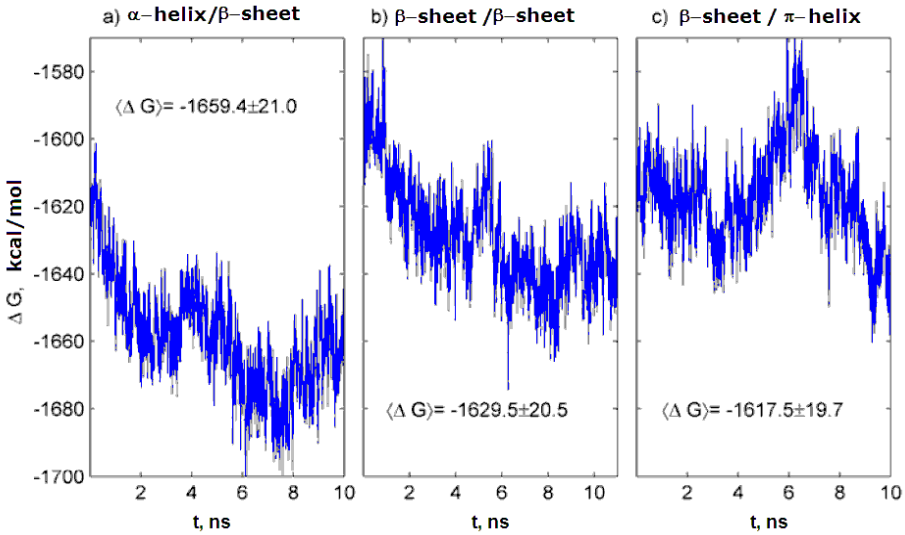

Fig. 2. Dynamics of Gibbs energy of NH_2-$(RADA)_4$-COOH dimers in explicit water.

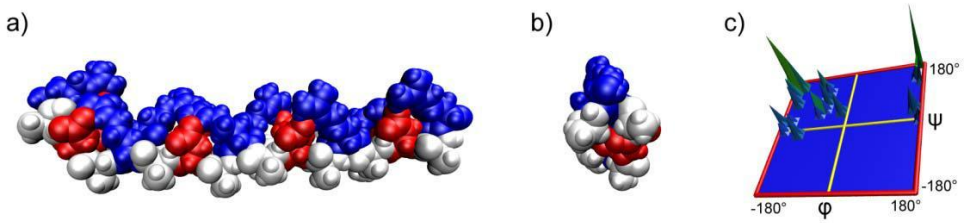

Fig. 3. Molecule obtained by docking of NH_2-$(RADA)_4$-COOH peptide dimer with the use of HEX6.1 (a – front view, b – right view, c – Ramachandran map).

The aim of this work was to study the peptide dimer structure which could act as a possible self-assembling component of the bigger protofilament complex. Anti-parallel β-sheet of NH_2-$(RADA)_4$-COOH peptide dimer is a prime structure to study stability and conformational state (Fig. 3,a and 3,b). The authors intentionally avoided common potential fields, such as OPLS and GROMOS96, since they require inner parameter set optimization in order to make them applicable for studying polar peptides in explicit water [2]. Instead, the environment was modeled with AMBER force fields ff96, ff99SB and ff03. AMBER force fields in this work allowed using the same procedure for sample preparation and controlling conditions during MD-experiments.

Comparison of Figure 3,c and Figure 4 shows the efficacy of potential field usage for modeling dynamics of NH_2-$(RADA)_4$-COOH peptide dimers, resulted in relative stabilization of β-conformation.

Besides, the results of molecular dynamics investigation of NH_2-$(RADA)_4$-COOH dimers at temperatures 300K and 320K show that the use of ff99SB most effectively stabilizes β-conformation of ion peptides (Fig. 3,c) at 300 K (Fig. 4) although on the time interval from 4 to 7.5 ns the ff96 force field demonstrated similar performance (Fig. 5,a and 5,b). Even more determined picture was gained by modeling polar peptides with ff96 at 320K (Fig. 5,b and 5,d). The increase in temperature led to alterations in stability of β-structures on anti-parallel chains of NH_2-$(RADA)_4$-COOH peptide dimer, which initially contained amino-acid residues entirely in β-conformation.

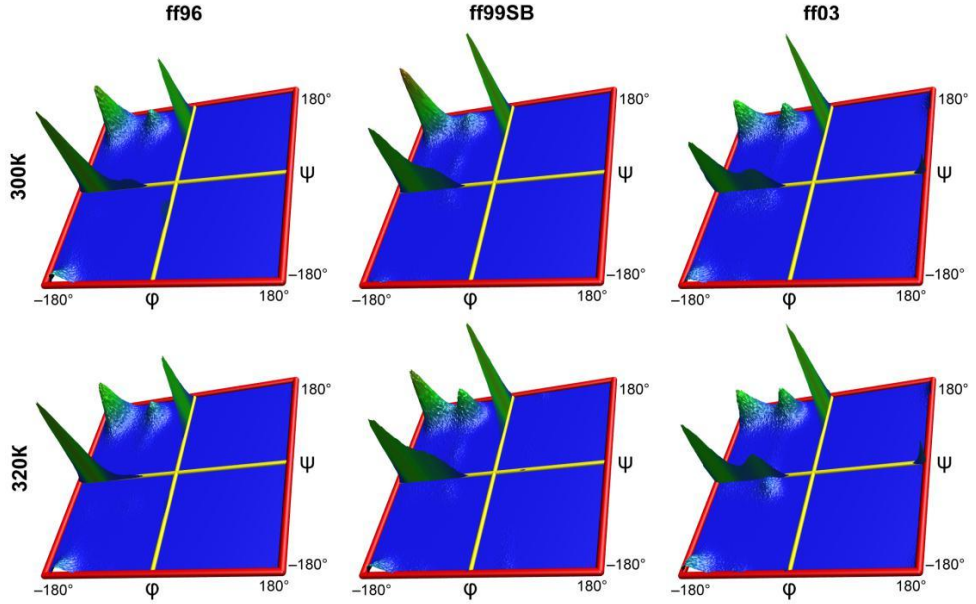

Fig. 4. Ramachandran maps of NH_2-(RADA) $_4$-COOH dimer, constructed on the basis of the results of MD modeling during 11 ns with the use of different force fields.

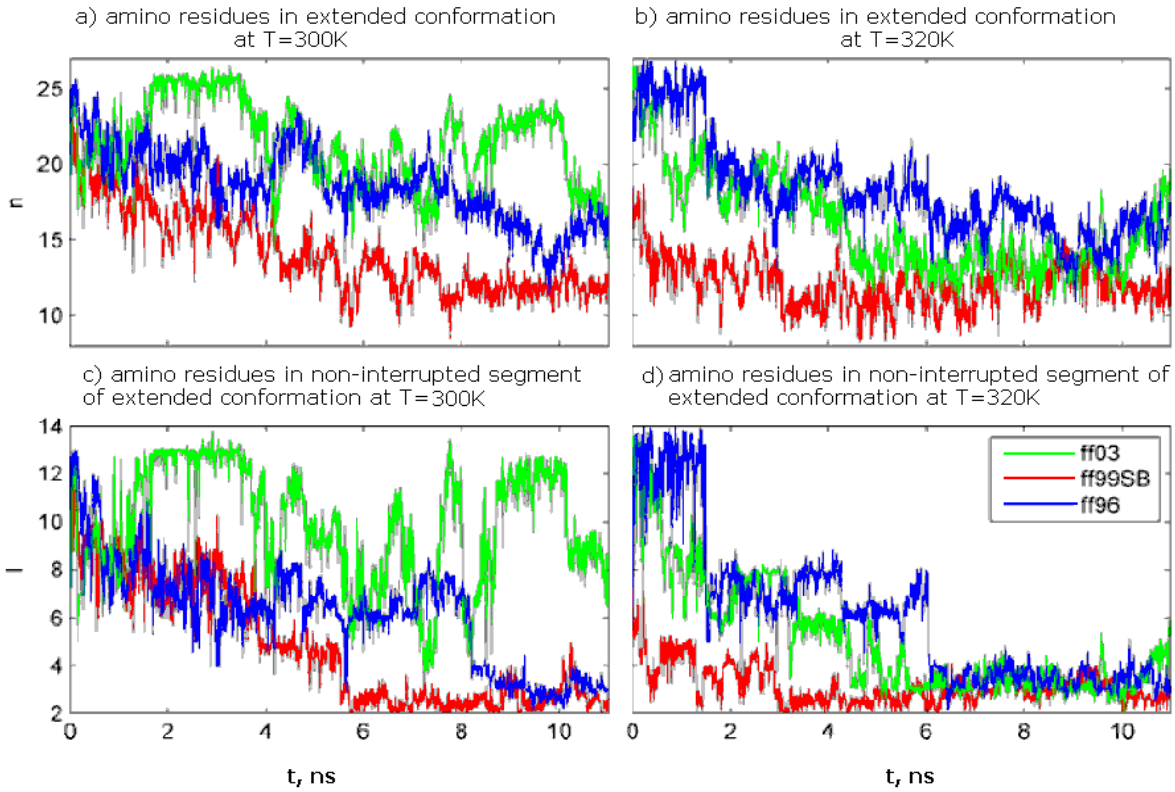

Fig. 5. Stability of antiparallel β-conformation in different models of the potential fields of NH_2-$(RADA)_4$-COOH dimer.

Under these conditions, the model of the ff96 field has a distinct advantage in the area of experimental trajectories of 0–6 ns (Fig. 5,d). The final phase of the experiment is characterized by similar results for all the three force fields (Fig. 5,c and 5,d, Table 1). Taking into account relatively high tolerance of filamentary complexes NH_2-$(RADA)_4$-COOH to high temperatures it should be recognized that the use of model conditions ff96 provides more adequate conditions for the simulation of ionic dimers of peptides in the temperature range of 300–320 K. At the same time, the effectiveness of the potential field in the study of dimers ff99SB NH_2-$(RADA)_4$-COOH is limited to a temperature close to room temperature

(Fig. 5,c), which is probably explained by the changed parameters of torsion interactions implemented in ff99SB [31]. Unexpectedly, the least effective force field to secure extended conformation of anti-parallel β-peptide dimer was ff03 (Fig. 5). At the same time, this fact was indirectly confirmed by the results obtained by simulation of the alanine tripeptide. Both these data may indicate a system error, which appears when traditional AMBER force fields are used and manifested as prevailing α-helical over β-sheet structures during MD experiments with polypeptides [9].

CONCLUSION

Different results were obtained in modeling NH_2-$(RADA)_4$-COOH peptide dimers by using three potential fields and two temperatures, which reflects easy motility of peptide complexes and different characteristics of the force fields. In comparing β-sheet peptide structures at 300–320 K, the AMBER ff96 force field looks preferable, which is clearly manifested on time intervals: 0–8 ns at 300 K (Fig. 5,c) and 0–6 ns at 320 K (Fig. 5,d). AMBER ff99SB force field had limited ability to hold peptides in extended conformation at 320K (Fig. 5,c).

Table 1. Stability of β-conformation of NH_2-$(RADA)_4$-COOH peptide dimer. The data are presented as pairs of mean and standard deviation values over the samples of 55000 and 10000 instant geometries saved for the intervals of 0–11 ns and 9–11 ns, respectively

Temperature, K	300			320		
Force field	ff96	ff99SB	ff03	ff96	ff99SB	ff03
0–11 ns						
Portion of residues in β-conformation, %	58.09±8.99	66.91±9.53	44.19±9.28	56.84±11.16	55.22±12.34	37.56±6.28
Number of residues in β-conformation in chain A	9.44±1.30	10.94±1.47	6.78±1.36	9.22±1.95	8.62±1.75	5.66±0.76
Number of residues in β-conformation in chain B	9.15±1.58	10.47±1.58	7.36±1.61	8.97±1.62	7.45±1.84	6.36±1.25
Number of residues in continuous β-layer	6.15±2.18	9.86±2.37	4.77±2.54	6.06±2.99	5.08±2.40	3.11±0.77
9–11 ns						
Portion of residues in β-conformation, %	47.53±4.43	64.53±8.72	36.97±3.34	47.72±5.53	46.38±7.09	37.50±4.03
Number of residues in β-conformation in chain A	8.09±0.59	10.87±1.56	5.84±0.51	7.94±1.08	8.25±1.20	5.31±0.65
Number of residues in β-conformation in chain B	7.12±0.83	9.78±1.23	5.99±0.56	7.33±0.69	6.59±1.07	6.69±0.64
Number of residues in continuous β-layer	3.02±0.36	10.43±1.75	2.71±0.52	3.41±0.42	3.50±0.72	2.93±0.44

Peptide molecules in extended conformation demonstrate extremely high volatility of structural elements (Fig. 5,a), which limits the use of ff99SB in experiments on the study of polar polypeptide conformations and structure stability. Increasing temperature leads to sharp destabilization of segments of polypeptide structure in extended conformation (Fig. 5,b), probably due to diminished torsion stiffness value and screwed electrostatics which were implemented in the force field.

The results obtained with standard AMBER ff03 force field while studying the extended conformation stability of NH_2-$(RADA)_4$-COOH peptides are moderate. Nevertheless, this force field is indeed a carefully balanced system, which could perform more stably and reproducibly as compared to ff99SB. Therefore AMBER ff03 can be used to analyze

molecular dynamics and stability of macromolecules, including different in size NH_2-$(RADA)_4$-COOH peptide complexes.

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