Journal of Molecular Modeling (2021) 27: 34
https://doi.org/10.1007/s00894-020-04610-2

ORIGINAL PAPER

CHARMM force field generation for a cationic thiophene oligomer with ffTK

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Received: 19 March 2020 / Accepted: 16 November 2020 / Published online: 9 January 2021

Abstract

In the present work, CHARMM force field parameters are generated for a cationic oligomer of N, N, N-trimethyl-3-(4-methylthiophen-3-yl) oxy) propan-1-aminium) which has the potential for sensing biological molecules such as nucleic acids, nucleobases. We have used ffTK (force field tool kit) to obtain potential parameters. MD simulations are performed for 20-mer and its complexes with AMP and ATP. The simulation results are analyzed to see the number of phosphates in adenosine nucleotides effects on the structure of the backbone of oligomer. The UV-VIS calculations for the conformers which possess the most probable radius of gyration are carried out and compared to the experimental ones to validate the generated force field.

Keywords Polyelectrolyte · Polythiophene · Molecular dynamics simulation · ffTK

Introduction

Conjugated polyelectrolytes (CPEs) are a kind of water-soluble macromolecules which possess excellent optical and electronic characters. They have captured the attention of many researchers during the past few decades because they show low toxicity, have good photostability in living-cell experiments, and have adjustable structural features for targeted molecule detection [15]. They are also an important part of nanomaterials for biomedical applications, solar cells, light emitting diodes, and photovoltaics studies [14]. Using CPEs, chemosensors or biosensors have been developed for sensing biologically relevant targets such as proteins [17], DNA [10], polysaccharides [5], folic acid [21], and ATP [20].

Water soluble polythiophenes (PTs), which are types of the conjugated polyelectrolytes, are widely synthesized and have an important place in the literature [2, 15]. The optical properties of these materials respond to environmental stimuli, with dramatic color shifts in response to changes in solvent, temperature, applied potential, and binding to other molecules. When the fundamental structure of polymer is twisted, the conjugation of polymer is disrupted. As a result of this property, the PTs are worth researching material to provide a unique substructure for both chemosensor and biosensor developments. Especially, cationic polythiophenes (CPTs) are represented as sensitive probe for biomolecules: DNA, RNA, and biologically active small molecules such as nucleic acids and nucleotides. The intermolecular interactions between anionic biological molecules and cationic side of CPT act to modify the conformation of conjugated backbone. These interactions could be followed by UV-visible absorption spectroscopy, fluorescence spectroscopy, and circular dichroic (CD) spectroscopy.

Molecular dynamics (MD) simulations have been performed to enlighten the experimental studies and to provide pre-experiment insight/information before setting up the experiment. They could be used to describe and understand PT interactions with large or small biomolecules to get a better insight for the biosensor capability of the polymer [12]. The parameters required to perform MD simulations are available for biomolecules and many other biologically compatible small chemical compounds in well-known databases such as CHARMM [19], GROMOS [11],

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and AMBER [4]. The parameters for nucleic acids, lipids, proteins, and carbohydrates take place in the CHARMM additive all-atom force field.

The force field parameters of a molecule whose necessary potential constants are not present in the databases can be calculated by using some ready-to-use plugins that use quantum mechanical (QM) calculations. In 1998, MacKerell group described how to produce force field parameters and the protein parameters for all-atom energy function in CHARMM program [7]. CHARMM27 database was generated by using empirical force field information for the exploration of nucleic acids. It is chosen for the simulation of lipids, DNA and RNA [8]. The CHARMM force field parameters of drug-like molecules have been developed and represented for pyrrolidine parametrization [19].

Recent studies show that ffTK [9] which is distributed as VMD [18] plugin has become quite popular for getting the force fields compatible with the CHARMM. The GUI of it is easy to produce QM input and compare QM and molecular mechanics (MM) results. The parametrization steps depend on the CHARMM parametrization technique described in Vanommeslaeghe et al.'s article [9]. Pavlova and Gumbart generated macrolide antibiotics parameters using the force field toolkit. They divided molecule into 40 or less atoms; this provided to simplify QM calculations [12]. In another study, CHARMM-compatible force field parameters were generated by ffTK for atrazine molecule.9 Pavlova et al. produced CHARMM compatible force field parameters for cobalamin compound by using ffTK in 2018. They optimized all bonded terms with the ffTK and validated by comparison with the experimental data (x-ray crystal structures). This work showed a better agreement with the reference data compared to the previous studies. They concluded that, parametrization with ffTK could be a suitable method for corrinoids and large bio-molecules [13]. Li C. and coworkers have conducted studies on the development of colorimetric ATP sensor which is based on cationic polythiophene (see Fig. 1). They observed a bathochromic/red shift by 138 nm in the absorbance spectra of CPT when ATP concentrations are increased. The color of the solution changed from yellow to red. The authors proposed that exposure to ATP were due to the formation of an electrostatic complex between the cationic polymer and anionic ATP, which led to increased planarity of the conjugated thiophene polymer backbone. At equimolar ATP concentration, the complex planarity is enough to produce polymer aggregation through hydrophobic effects. The positively charged CPT attracted to the negatively charged ATP with much stronger interaction than other biologically active phosphates like adenosine monophosphate (AMP) and adenosine diphosphate (ADP). According to their results, ATP forms supramolecular complexes and has influence on PT's structure and mode of aggregation.

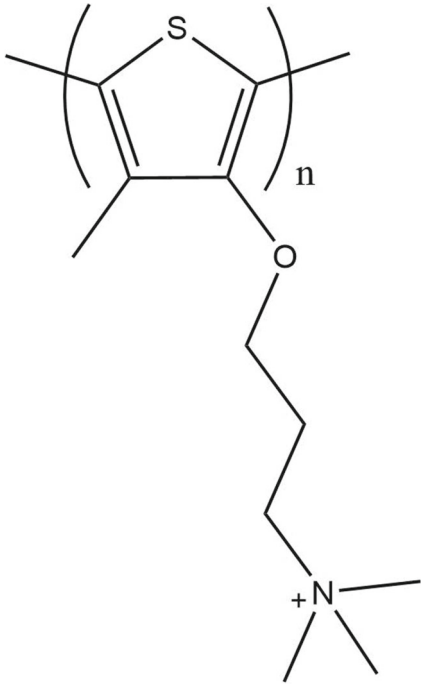


Fig. 1 The structure of Poly- N, N, N-trimethyl-3-(4-methylthiophen-3-yl) oxy) propan-1-aminium

Because ATP has a higher negative charge density than the other nucleoside phosphates. The presence of adenosine nucleotides which have different number of phosphates (AMP, ADP, ATP) in CPT solution affected the absorption maxima. While the strength of intermolecular forces was increasing, the red shift on the absorption spectrum extended. According to circular dichroism (CD), addition of AMP does not demonstrate chiral superstructure of CPT, but ATP addition makes this structure optically active. The experimental explanation of this is that it increases the planarity of the backbone, and so red shift of complex becomes much longer. When nucleobases were compared (ATP vs UTP), more-ordered aggregates are formed with ATP. They reported that, nucleobases of triphosphates play a key role on the π-stacking interactions of CPT [6].

In this work, we will present MD simulations of complexes formed by CPT and different adenosine nucleotides to explore the type of interactions between the substituents of the complex. Our aim is to find a comprehensive theoretical explanation of the experimental observations.

The essential thing for performing MD simulations is the force field definition of the interested system. CPT's CHARMM-compatible force field parameters of cationic thiophene oligomer (see Fig. 1) subjected to this study have been generated within this work since they do not exist in the current databases. For that purpose, ffTK plugin in VMD software and QM calculations via Gaussian09 [3] package were used.

The force field parameters created within this work will allow new simulations for similar PT derivatives to design new advanced materials owning important optical properties. Further on, the generated force field parameters will be used to lead new biosensor studies by exploring the formation, interactions, and the structure of complexes that consist of polythiophenes with different functional groups and biological molecules such as ssDNA, dsDNA with varying nucleotides, RNA, ATP, ADP, AMP, UTP by MD simulations.

Methods

CHARMM general force fields

CHARMM (Chemistry at Harvard Macromolecular Mechanics) was presented as a computer program which evaluates empirical energy functions for modeling macromolecular systems in 1983 [1]. To solve empirical energy functions, the terms which include internal and external interactions are required. Equation 1 includes bonds, Urey-Bradley, angles, dihedrals, impropers, and non-bonded terms (Lennard-Jones and Coulomb) where b, S, θ, χ, φ are bond distance, angle, dihedral angle, improper torsion angle and b_0, S_0, θ_0, φ_0 are the equilibrium values of them, respectively. δ and η are phase shift and the periodicity. The parameters bond (K_b), angle (K_θ), dihedral angle (K_χ), and improper dihedral angle (K_{imp}) are force constants that must be described. ϵ and $R_{\min}$ are Lennard-Jones parameters, r_{ij} is the distance between i and j atoms, and q_i and q_j are the charges on these atoms. ϵ_1 is the effective dielectric constant. MacKerell group description has been followed to produce force field parameters in this study [7].

$$
\begin{aligned}
U\left(\overrightarrow{\mathrm{R}}\right) = & \sum_{\text{bonds}} K_b(b-b_0)^2 + \sum_{UB} K_{UB}(S-S_0)^2 \\
& + \sum_{\text{angle}} K_\theta(\theta-\theta_0)^2 \\
& + \sum_{\text{dihedrals}} K_\chi(1+(\eta\chi-\delta) + \sum_{\text{impropers}} K_{\text{imp}}(\varphi-\varphi_0)^2 \\
& + \sum_{\text{nonbond}} \epsilon[(R_{\min_{ij}}/r_{ij})^{12} - (R_{\min_{ij}}/r_{ij})^6] \\
& + \frac{q_i q_j}{\epsilon_1 r_{ij}}
\end{aligned}
\tag{1}
$$

Parametrization strategy

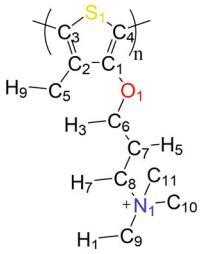
CHARMM compatible force field parameters for the thiophene oligomer (see Fig. 1) have been generated as explained in the literature [19]. The terms of energy function can also be generated by ffTK plugin at VMD that is an interface of NAMD. We use ffTK plugin to produce the absent parameters for our simulations. Details of the ffTK steps are given in the following:

1. The LJ (Lennard-Jones) parameters are necessary to develop CHARMM additive force fields, so similar atom types were taken from the CHARMM force field databases which are defined. Then, the geometry optimization run was carried out at the MP2/6-31G(d) level of theory via Gaussian09 package. The minimum energetic conformer was used to calculate Merz-Kollman charges [16].
2. In CHARMM force field, the aliphatic non-polar hydrogen charge was taken as +0.09. After setting aliphatic hydrogens, the atomic partial charges of other atoms are optimized by reproducing QM interactions with TIP3 water molecules. The water molecules were placed to possible hydrogen bond interaction sites on the most favorable structure of the compound of interest. The complexes which were created for each possible hydrogen bonds were minimized at HF/6-31(d) level of theory. For the validation of the obtained parameters, these interaction energies and distances are compared with MM calculation using the optimized partial atomic charges. Ideally, the model compound-water interaction energies and distances should be within 0.2 kcal/mol and 0.1 Å from the target interaction energies and distances, respectively.
3. The bond and angle parameters of MM were examined comparatively with QM energetically most likely structure. MP2/6-31G(d) level of theory was applied on this structure for Hessian calculations to fit the targeted bonds and angles.
4. The potential energy surface (PES) analysis was performed by using NAMD Energy plugin in VMD for the MM evaluation, and these results are compared to the corresponding QM PES with internal coordinates, ICs. Optimization of dihedral force constants was verified with PES. The dihedrals are scanned with Gaussion09 package at MP2/6-31G(d) level of theory. If the results of QM and MM have large differences (the recommended value is 0.5 kcal/mol), these steps must be repeated.

MD simulations

In this study, MD simulations of 20-mer of N, N, N-trimethyl-3-(4-methylthiophen-3-yl) oxy) propan-1-aminium) and biological phosphates complexes were carried out through NAMD. CHARMM force field was used for nucleotides and waters, and the absent parameters for CPT were generated as described above via ffTK. The simulation box length was arranged w.r.t the complex length with initial configuration that is placed diagonally in a cubic box with one side

Table 1 The list of names, types, and charges of atoms in CPT



Atom	Type	Charge	Atom	Type	Charge	Atom	Type	Charge
S_1	SG2R50	−0.16	C_5	CG331	−0.24	C_8	CG321	−0.11
C_1	CG2R51	0.03	H_9	HGA3	0.09	H_7	HGP5	0.25
C_2	CG2R51	0.33	C_6	CG321	−0.01	N_1	NG3P0	−0.60
C_3	CG2R57	−0.14	H_3	HGA2	0.09	C_9	CG334	0.25
C_4	CG2R57	0.07	C_7	CG321	−0.17	H_1	HGP5	0.09
O_1	OG301	−0.33	H_5	HGA2	0.09			

Equivalent atoms are not taken in the structure

varying between 78 and 88 Å. TIP3 water molecules were added as solvent to the simulation box. Then, the initial systems were minimized. In this part, the cut-off for non-bonded interactions was set to 100 Å, which is more than box dimensions. After minimization step, the timestep was given taken as 2 fs and cut-off value was lowered to 14 Å. The temperature of the systems was gradually increased from 0 to 293 K. After that, equilibration step was applied as N, V, T ensemble for 10 ns. Finally, production step (N, P, T) was performed for 100 ns, and the energies and coordinates of system were saved every 0.05 ns.

Results and discussion

Parametrization of CPT

In the literature search, the force field parameters of the cationic thiophene oligomers do not exist, so the unknown parameter sets which are necessary to perform MD simulations were generated by using quantum mechanical potential energy surface scans and ffTK plugin for VMD. The obtained parameters were fitted to QM calculations via ffTK. With the four types of required files (.psf, .pdb, .par, .top), this oligomer can be part of CHARMM-based molecular dynamics simulations, so that interactions with biomolecules can be studied. ffTK plugins in VMD and Gaussian09 are the programs that we used to generate CHARMM-compatible force field parameters for the monomer of a cationic polythiophene (see Fig. 1). The dihedral parameters were found by using its dimer. The LJ/vdW parameters were identified in monomer as its constituent atoms which are named as in Table 1, then they were compared with existing parameters in the literature, and the matched ones were used.

The most favorable structure of the monomer was obtained at MP2/6-31G* level of theory. The partial charges of non-polar hydrogens are fixed to +0.09 for aliphatic. QM calculations at HF /6-31G* level of theory were used to obtain charges of monomer interacting with a water molecule.

QM calculations of the Hessian which is the second derivative of potential energy function are used to reproduce the potential energy surface by distortions along the angles and bonds. MP2/6-31G* level of theory is applied to optimized structure for Hessian calculations fitting the targeted bonds and angles data.

Bonds and angles are expressed using a simple harmonic potential. NAMD performed a short geometry optimization in the background during the ffTK optimization. The first change ensures a good fit of MM-optimized geometry and QM-optimized geometry. The optimization iterations were performed until increasing the current final objective value. The bond, angle, and dihedral parameters were determined by comparing QM and MM calculations. Some parameters were obtained from CGenFF for the thiophene derivatives (Paramchem https://cgenff.umaryland.edu/) [19]. We calculated the parameters which have penalties higher than 10 (see Table 2). According to CHARMM parameters, the difference 0.03 Å for bonds and 3° for angles is acceptable; the calculated parameters in this work were found in this range. The target QM bond and angle deviations values were obtained as 0.01 Å and 2.67° respectively for our calculations. On the other hand, for all parameters, the maximum deviations are 0.07 A and 9.53° for distances and angles respectively, belong to the parameters taken from CGenFF list (see Fig. 2).

The relaxed PES scan with dihedrals was performed at the MP2/6- 31G* level of theory and refinement was

Table 2 The list of high penalty parameters

Type	Penalty
CG2R51 OG301	45
CG2R51 CG2R51 OG301	39
CG2R51 CG2R51 CG2R51 OG301	45
CG331 CG2R51 CG2R51 OG301	46
CG331 CG2R51 CG2R51 SG2R51	115
OG301 CG2R51 CG2R51 SG2R51	111
CG2R51 CG2R51 OG301 CG321	94
CG324 CG321 CG321 OG301	17

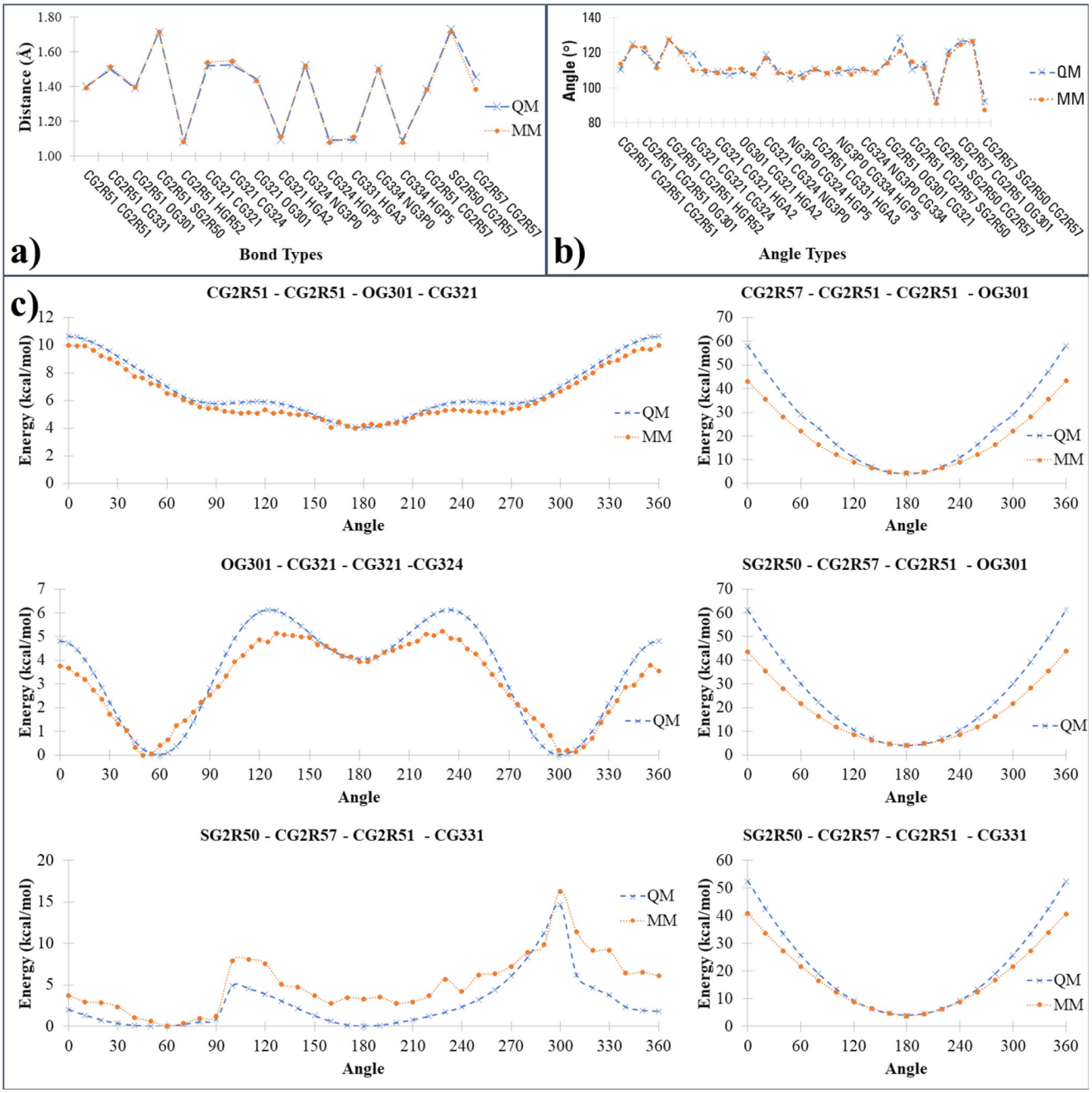


Fig. 2 The comparison QM and MM data **a** for the bond fitting, **b** for the angle fitting, and **c** for the dihedral optimization

applied to catch good fitting of QM-MM as shown in (see Fig. 2). Dihedral scan parameters were fitted as described in the computational methods part. The root-mean square error (RMSE) value for our calculated dihedral parameters was obtained as 0.6 kcal/mol. After all refinement, the result demonstrates that MM data nearly fit to the target QM data. 0.5 kcal/mol is recommended RMSE value for the compatible-CHARMM force field. Although the RMSE was not the same as the recommended value, it was nearly well-matched.

Simulations of CPT

The only experimental data which can be compared to validate the generated force field of the cationic PT subject to this work is the UV-VIS spectra of the complexes with biological molecules (ATP, ADP, AMP, and DNA). There is no X-ray or NMR data available in the literature to our knowledge for this system. The UV-VIS calculations have been performed for the conformer of the backbone of the complex and oligomer composed of 20 monomers which

Table 3 The computational and experimental UV-VIS absorption λ_{max} values with TD/HF/3-21G level of calculations

	20mer	20mer+AMP	20mer + ATP
λ(nm)	292	302	305
λ^{*}_{exp}(nm)	400	416	538

*The experimental λ_{max} (Li et al. 2006)

has an average radius of gyration and end to end distance given in Table 3 at TD/HF/3-21G level of theory in water. Both experimental and theoretical results showed that, the oligomer responded as a red shift in the absorption spectra upon the complexation with AMP and ATP. However the simulation results provide a small red shift. The errors in absorption wavelength calculations can be explained by the accounts; the calculations involve only one 20mer with 5 ATP or 10 AMP molecules but in experiments stacking of complexes were supposed to form, also due to the size of the system and computational demands a low level of theory was used in the UV-VIS calculations. To observe the effect of the number of phosphate groups on CPT complexes, two different systems were prepared with ten AMP and five ATP molecules. These molecules have the same adenine group but the number of phosphate sides linking to adenine is different.

$$\mathrm{RMSD} = \sqrt{\frac{1}{N}\sum_{i=1}^{N}(\vec{r}_{1,i} - \vec{r}_{0,i})^2} \qquad (2)$$

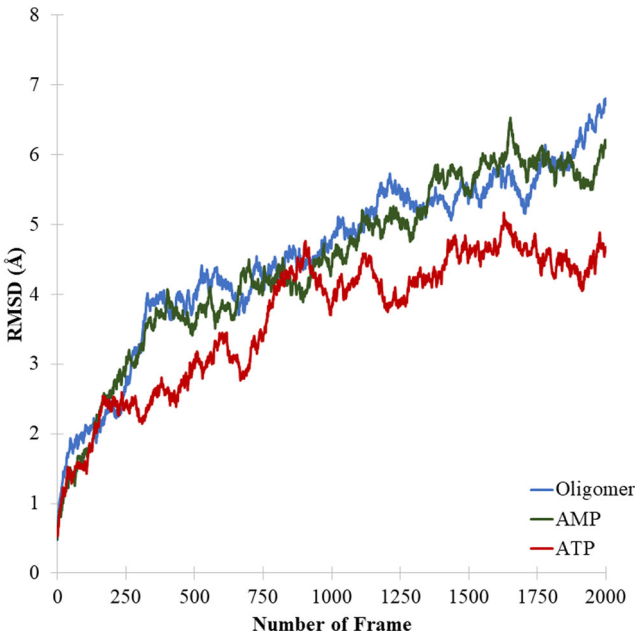


Fig. 3 Time evolution of RMSD of 20-mer in water (blue), ATP (red), and AMP (green) complexes

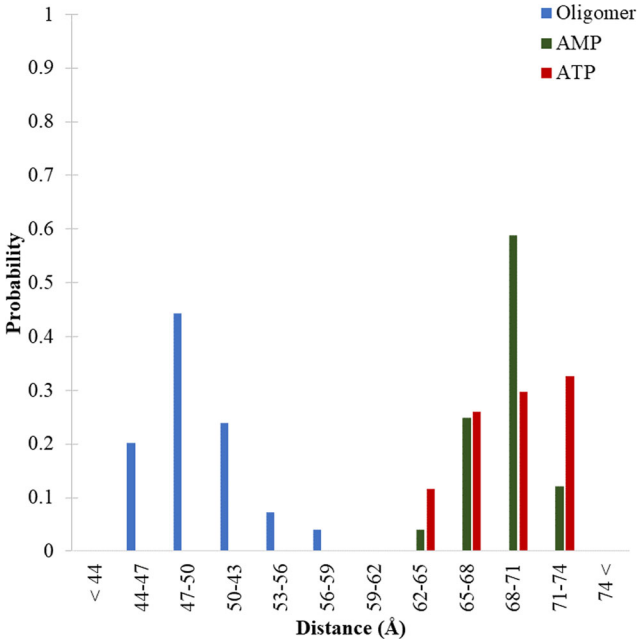


Fig. 4 R_{ee} distributions(normalized) of 20-mer in water (blue), ATP (red), and AMP (green) complexes

The equilibration of simulations is achieved as shown in Fig. 3 which has time evolution of root mean square deviations (RMSD) calculated by using Eq. 2 where N and $\vec{r}$ are number of atoms and position vector of these atom, respectively. The small RMSD values illustrate that the structural changes w.r.t the initial configuration

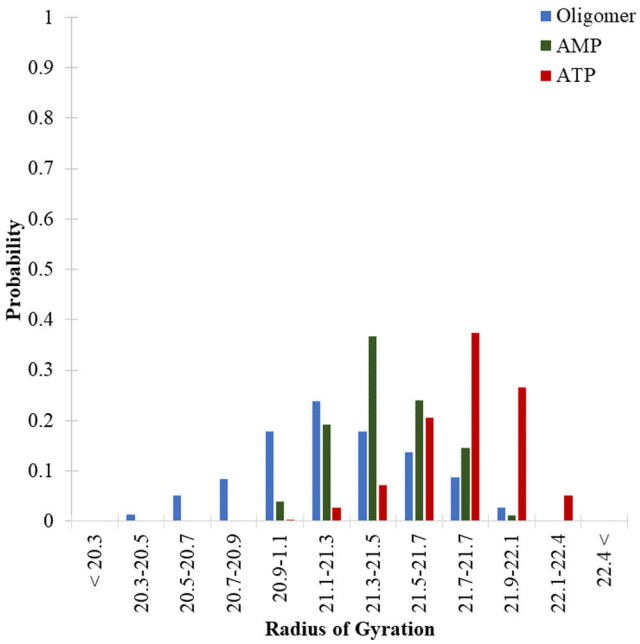


Fig. 5 Distributions (normalized) of radius of gyration of 20-mer in water (blue), ATP (red), and AMP (green) complexes

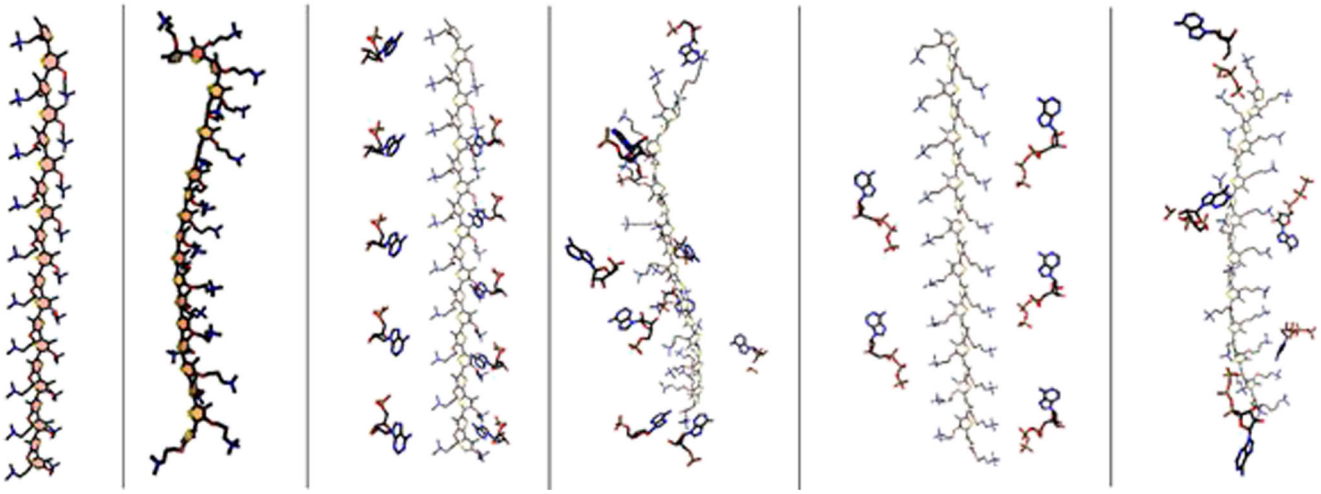


Fig. 6 The snapshots of initial (left) and average R_g positions (right) of **a** 20-mer, **b** ATP complex, and **c** AMP complex

($\overrightarrow{r}_{0,i}$) at the propagation part of the simulation does not alter much.

$$R_g = \sqrt{\frac{\sum_{a=1}^{N} m_a (r_a - r_{\text{com}})^2}{\sum_{a=1}^{N} m_a}} \tag{3}$$

The distribution of end to end distance (R_{ee}, the distance between H-atoms on the first and the last thiophene of 20-mer) which will be used as a measure of spatial extent of the CPT backbone and the oligomer (20-mer) radius of gyration (R_g) calculated by using Eq. 3 where $N, \overrightarrow{r}$, m, and $\overrightarrow{r}_{\text{com}}$ are number of atoms, position vector, mass of atom, and center of mass vector respectively, to indicate compactness of the system, are given in Figs. 4 and 5, respectively.

The complexes with ATP and AMP have the longer average (69 Å) and most probable end to end distances than 20 mer in water (49 Å). Based on our simulation results, it can be concluded that, the backbone of oligomer gets stretched with the addition of AMP and ATP.

Figure 5 shows that, there is a correlation between the number of phosphate groups on adenine and the compactness of the backbone structure of the oligomer in the complex. The most probable/average value of R_g increases with increasing number of phosphate groups. 20-mer in water have more compact structure than both complexes. The initial configuration at the very beginning of the simulation and position at average R_g at the production part snapshots of 20-mer and its complexes are given in Fig. 6. These structures reflect the findings obtained from R_g and R_{ee} analyses; the most elongated one is ATP complex, and the least one is 20-mer.

We have examined cation − anion and π − cation interaction in order to achieve the dominant interaction present in the complexes or to answer if there is a specific interaction for ATP, so that it can be attributed to spectroscopic behavior of its complex.

The cation − anion interaction and π − cation interaction were calculated using the distance between nitrogen atom of CPT and O atom on phosphate group of adenine molecule and between adenine six-membered ring and nitrogen atom of CPT, respectively (see Fig. 7). The threshold distance was taken as 6.5 Å.

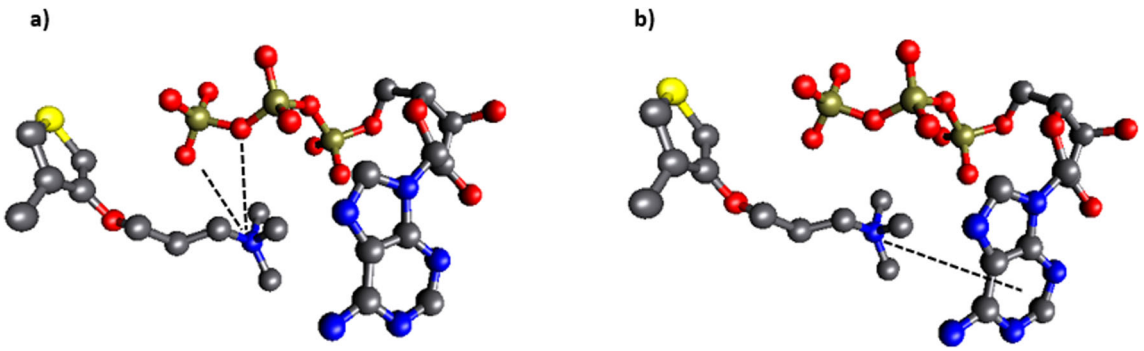


Fig. 7 The representation of **a** the cation − anion interaction, and **b** π − cation interaction between 20-mer and phosphate group of adenine molecules

Conclusions

The normalized cation anion interactions were computed by counting the distances which are less than the threshold value and dividing this value by the total number frames and corresponding number of possible interactions. According to Fig. 8, ATP complex has higher cation − anion interaction strength than AMP complex. On the contrary, AMP complex which shows a minor shift in the experimental absorption spectra have stronger π −cation interaction. It seems that both electrostatic interactions play an important role on the structural and spectroscopic behavior of complexes, and ATP complex has weak π − cation interaction which might be connected to strong red shift of CPT in UV-VIS spectra with the addition of ATP.

We have also considered hydrogen atoms of ATP and AMP close to N, O, and S atom on the backbone of the oligomer and H atoms on the oligomer near to O and N atoms on the adenine phosphate moieties to quantify interactions (the threshold distance in our calculations was taken as 3.5 Å). ATP and AMP have different numbers of oxygen atoms (5 ATP and 10 AMP were used in the complexations) and so the number of H-interactions is different in each complex. We have considered this situation and reflected this effect dividing the normalized hit number by probability of H-interaction in each case. It should be noted that, we did not mention these interactions as hydrogen bonds since the angles were not considered. Hydrogens on the side groups and on the backbones of oligomer were considered separately to differentiate their contributions to these interactions which are shown in the Fig. 9. AMP complex have drastically higher amounts of H-interactions than ATP in most cases. The only considerable interactions present in ATP complex are between H atoms in the side groups of oligomer and N or O atoms in ATP, which may be due to electrostatic interactions. The strong interactions in AMP complex are observed on the 'H at the backbone (methyl group); N atom at AMP' and 'S atoms of thiophene; H atoms of AMP'; in other words, AMP most likely interact with the backbone of oligomer through the H-interactions which is completely absent in ATP complex. Once again, the red shift in ATP complex might be explained by the presence of weak interactions with the complex constituents.

In this work, we have developed all-atom CHARMM force field compatible parameters sets for a cationic thiophene polyelectrolyte (N, N, N-trimethyl-3-(4-methylthiophen-3-yl) oxy) propan-1-aminium) polymer) to perform atomistic MD simulations of polyelectrolyte and its complexes with biologically active compounds. We have carried out MD simulations by using these parameter sets for the complex formation with different adenine phosphate molecules, ATP and AMP. The structural analysis was made to understand the effect of phosphates on the spectroscopic behavior of the oligo-electrolyte. Based on the simulation results, ATP and AMP complexations make the oligomer backbone more elongated. The response of the oligomer to the addition of ATP as a strong red shift in the absorption spectra might be explained by the weak π − cation interactions in

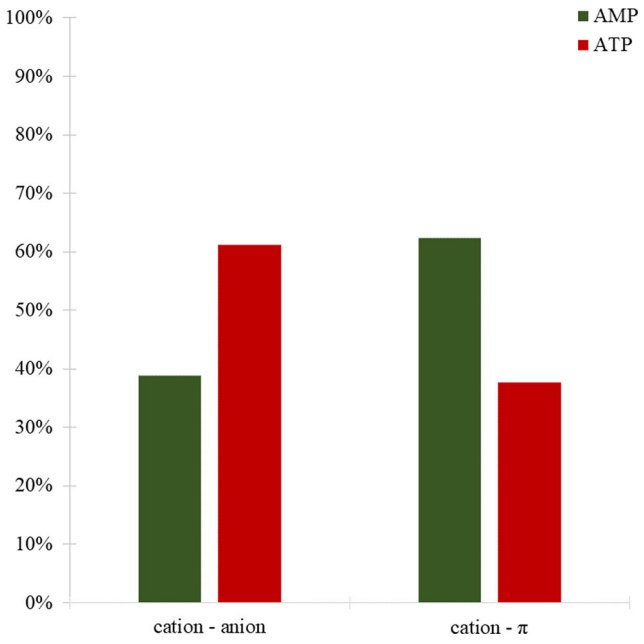


Fig. 8 Normalized cation − anion and π −cation interactions between 20-mer and AMP, ATP along the simulations

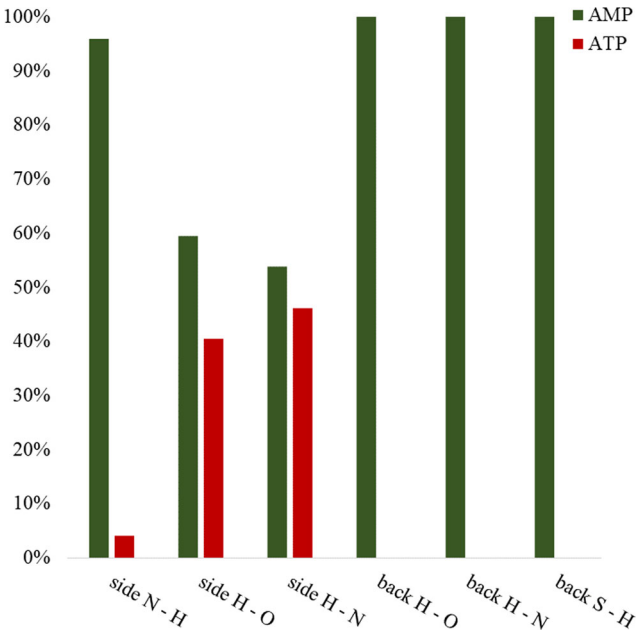


Fig. 9 Hydrogen interactions (The first and second atoms belong to the oligomer and nucleotide groups respectively; side and back refer to side chain and backbone of the oligomer respectively)

ATP complex which prevents the complex structure from a random coil form. These simulations were done only for the validation of the force field parameters. In our current studies, more detailed simulations with biological molecules and CPT are being continued.

Acknowledgments The numerical calculations reported in this paper were fully performed at TUBITAK ULAKBIM, High Performance and Grid Computing Center (TRUBA resources). We would like to give thanks to Ümit Hakan Yıldız for inspirations to this study.

Funding This work was supported by the "Scientific and Technological Research Council of Turkey," TUBITAK, under the project numbers 119Z100.

References

1. Brooks BR, Bruccoleri RE, Olafson BD, States DJ, Swaminathan S, Karplus M (1983) Charmm: a program for macromolecular energy, minimization, and dynamics calculations. J Comput Chem 4(2):187–217. https://doi.org/10.1002/jcc.540040211. https://onlinelibrary.wiley.com/doi/abs/10.1002/jcc.540040211
2. Carreon AC, Santos WL, Matson JB, So RC (2014) Cationic polythiophenes as responsive dna-binding polymers. Polym. Chem. 5:314–317. https://doi.org/10.1039/C3PY01069D
3. Frisch MJ, Trucks GW, Schlegel HB, Scuseria GE, Robb MA, Cheeseman JR, Scalmani G, Barone V, Petersson GA, Nakatsuji H, Li X, Caricato M, Marenich AV, Bloino J, Janesko BG, Gomperts R, Mennucci B, Hratchian HP, Ortiz JV, Izmaylov AF, Sonnenberg JL, Williams-Young D, Ding F, Lipparini F, Egidi F, Goings J, Peng B, Petrone A, Henderson T, Ranasinghe D, Zakrzewski VG, Gao J, Rega N, Zheng G, Liang W, Hada M, Ehara M, Toyota K, Fukuda R, Hasegawa J, Ishida M, Nakajima T, Honda Y, Kitao O, Nakai H, Vreven T, Throssell K, Montgomery JA Jr, Peralta JE, Ogliaro F, Bearpark MJ, Heyd JJ, Brothers EN, Kudin KN, Staroverov VN, Keith TA, Kobayashi R, Normand J, Raghavachari K, Rendell AP, Burant JC, Iyengar SS, Tomasi J, Cossi M, Millam JM, Klene M, Adamo C, Cammi R, Ochterski JW, Martin RL, Morokuma K, Farkas O, Foresman JB, Fox DJ (2016) Gaussian09 Revision A.02. Gaussian Inc. Wallingford CT
4. Galindo-Murillo R, Robertson JC, Zgarbová M, Šponer J, Otyepka M, Jurecka P, Cheatham TE (2016) Assessing the current state of amber force field modifications for dna. J Chem Theory Comput 12(8):4114–4127. https://doi.org/10.1021/acs.jctc.6b00186. PMID: 27300587
5. Ho HA, Béra-Abérem M, Leclerc M (2005) Optical sensors based on hybrid dna/conjugated polymer complexes. Chemistry 11(6):1718–1724. https://doi.org/10.1002/chem.200400537. https://onlinelibrary.wiley.com/doi/abs/10.1002/chem.200400537
6. Li C, Numata M, Takeuchi M, Shinkai S (2006) Unexpected chiroptical inversion observed for supramolecular complexes formed between an achiral polythiophene and atp. Chemistry 1(1-2):95–101. https://doi.org/10.1002/asia.200600039. https://onlinelibrary.wiley.com/doi/abs/10.1002/asia.200600039
7. MacKerell AD, Bashford D, Bellott M, Dunbrack RL, Evanseck JD, Field MJ, Fischer S, Gao J, Guo H, Ha S, Joseph-McCarthy D, Kuchnir L, Kuczera K, Lau FTK, Mattos C, Michnick S, Ngo T, Nguyen DT, Prodhom B, Reiher WE, Roux B, Schlenkrich M, Smith JC, Stote R, Straub J, Watanabe M, Wiórkiewicz-Kuczera J, Yin D, Karplus M (1998) All-atom empirical potential for molecular modeling and dynamics studies of proteins. J Phys Chem B 102(18):3586–3616. https://doi.org/10.1021/jp973084f. PMID: 24889800
8. Mackerell AD Jr, Feig M, BrooksIII CL (2004) Extending the treatment of backbone energetics in protein force fields: limitations of gas-phase quantum mechanics in reproducing protein conformational distributions in molecular dynamics simulations. J Comput Chem 25(11):1400–1415. https://doi.org/10.1002/jcc.20065. https://onlinelibrary.wiley.com/doi/abs/10.1002/jcc.20065
9. Mayne CG, Saam J, Schulten K, Tajkhorshid E, Gumbart JC (2013) Rapid parameterization of small molecules using the force field toolkit. J Comput Chem 34(32):2757–2770. https://doi.org/10.1002/jcc.23422. https://onlinelibrary.wiley.com/doi/abs/10.1002/jcc.23422
10. Miranda OR, You C-C, Phillips R, Kim I-B, Ghosh PS, Bunz UHF, Rotello VM (2007) Array-based sensing of proteins using conjugated polymers. J Am Chem Soc 129(32):9856–9857. https://doi.org/10.1021/ja0737927. PMID: 17658813
11. Oostenbrink C, Villa A, Mark AE, VanGunsteren WF (2004) A biomolecular force field based on the free enthalpy of hydration and solvation: The gromos force-field parameter sets 53a5 and 53a6. J Comput Chem 25(13):1656–1676. https://doi.org/10.1002/jcc.20090. https://onlinelibrary.wiley.com/doi/abs/10.1002/jcc.20090
12. Pavlova A, Gumbart JC (2015) Parametrization of macrolide antibiotics using the force field toolkit. J Comput Chem 36(27):2052–2063. https://doi.org/10.1002/jcc.24043. https://onlinelibrary.wiley.com/doi/abs/10.1002/jcc.24043
13. Pavlova A, Parks JM, Gumbart JC (2018) Development of charmm-compatible force-field parameters for cobalamin and related cofactors from quantum mechanical calculations. J Chem Theory Comput 14(2):784–798. https://doi.org/10.1021/acs.jctc.7b01236. PMID: 29334459
14. Rajwar D, Ammanath G, Cheema JA, Palaniappan A, Yildiz UH, Liedberg B (2016) Tailoring conformation-induced chromism of polythiophene copolymers for nucleic acid assay at resource limited settings. ACS Appl Mater Interfaces 8(13):8349–8357. https://doi.org/10.1021/acsami.5b12171. PMID: 26956217
15. Rubio-Magnieto J, Thomas A, Richeter S, Mehdi A, Dubois P, Lazzaroni R, Clément S, Surin M (2013) Chirality in dna–π-conjugated polymer supramolecular structures: insights into the self-assembly. Chem Commun 49:5483–5485. https://doi.org/10.1039/C3CC42108B
16. Singh UC, Kollman PA (1984) An approach to computing electrostatic charges for molecules. J Comput Chem 5(2):129–145. https://doi.org/10.1002/jcc.540050204. https://onlinelibrary.wiley.com/doi/abs/10.1002/jcc.540050204
17. Thomas SW, Joly GD, Swager TM (2007) Chemical sensors based on amplifying fluorescent conjugated polymers. Chem Rev 107(4):1339–1386. https://doi.org/10.1021/cr0501339. PMID: 17385926
18. Tocci G, Joly L, Michaelides A (2014) Friction of water on graphene and hexagonal boron nitride from ab initio methods: Very different slippage despite very similar interface structures. Nano Lett 14(12):6872–6877. https://doi.org/10.1021/nl502837d. PMID: 25394228
19. Vanommeslaeghe K, Hatcher E, Acharya C, Kundu S, Zhong S, Shim J, Darian E, Guvench O, Lopes P, Vorobyov I, Mackerell AD Jr (2010) Charmm general force field: a force field for drug-like molecules compatible with the charmm all-atom additive biological force fields. J Comput Chem 31(4):

671–690. https://doi.org/10.1002/jcc.21367. https://onlinelibrary.wiley.com/doi/abs/10.1002/jcc.21367

20. Wang X, Feng Q, Wang L, Pei M, Zhao J, Zhang G (2014) A novel polythiophene derivative as a sensitive colorimetric and fluorescent sensor for the detection of atp. Des Monomers and Polym 17(1):26–32. https://doi.org/10.1080/15685551.2013.771315
21. Yao Z, Li C, Shi G (2008) Optically active supramolecular complexes of water-soluble achiral polythiophenes and folic acid: spectroscopic studies and sensing applications. Langmuir 24(22):12829–12835. https://doi.org/10.1021/la802086d