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Atomistic insight into 2D COFs as antiviral agents against SARS-CoV-2

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HIGHLIGHTS

• This work suggests COFs as highly tunable structures to combat the SARS-CoV-2.
• Coarse-grained molecular simulations have been used to study the interaction between COFs and SARS-CoV-2 spike protein.
• The results show that COFs can deform the spike protein well and cause the virus to fail.

ABSTRACT

The recent pandemic of COVID-19 has raised global health concerns. Preventing severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) activity in the body is a very promising method to overcome the COVID-19 pandemic. One of the prevention methods is constraining the binding process among the human cell receptor-ACE2 and coronavirus spike protein. In the research done, the effect of deformation of the spike protein structure, due to the covalent organic frameworks (COFs), in reducing the interactions of ACE2 and the spike protein by the computational method was investigated. In this regard, atomic analysis of the interactions of ACE2 and the spike protein is provided using a molecular dynamics simulation. First, we investigated the interactions of the three different COFs, including COF-78, DAAQ-TPP, and COF-OEt, with the spike protein by analyzing the bond energies, as well as structural changes of the spike protein. Then, intermolecular interactions of the deformed spike protein along with ACE2 were assessed to clarify the protein’s fusion after the deformation. As indicated by the results, although all introduced COFs deformed the spike protein in an effective way, COF-78 showed the best performance in the prevention of spike protein-ACE2 interactions by changing the molecular structure of the protein. Indeed, the interaction analysis of the deformed spike protein by COF-78 with the ACE2 showed that their interactions had the lowest absolute value of energy, along with the least amount of hydrogen bonds, in which the compaction of the protein was lower compared to the other deformed proteins. Moreover, having a high contact area with an aqueous media as well as severe fluctuations during the simulation time confirmed the positive performance of COF-78. In the current study, we aimed to introduce novel materials and COVID-19 prevention methodology that can be used in face masks and for surface disinfection.
1. Introduction

The current public health emergency of international concern (PHEIC) is the emerging COVID-19 pandemic due to the quick and rapid spread of the SARS-CoV2 coronavirus [1]. SARS-CoV-2 is the third highly pathogenic pneumonia coronavirus, coming after SARS-CoV-1 and MERS-CoV (middle east respiratory syndrome-coronavirus) to become a pandemic [2]. The main transmission mode of SARS-CoV-2 is a distribution of droplets in the exhaled breath of human subjects, although an airborne transmission is also feasible [1,2]. The coronavirus can cause pneumonia, severe upper and lower respiratory infections, and kidney failure with a relatively high risk of mortality [4]. Fever, dry cough, myalgia, fatigue, dyspnea, and chest pain seem to be the most common symptoms of COVID-19, whereas headache, dizziness, abdominal pain, diarrhea, nausea, and vomiting are less commonly observed [5,6].

Three inevitable subjects are emphatically discussed to overcome this virus pandemic: developing an efficient vaccine, synthesis and/or discovery of an effective drug to inhibit the virus’s progression in the body, and developing a simple, rapid, and low-cost technique with higher precision to diagnose infections [7]. Since no definitive vaccine or drug has been discovered yet to prevent or cure COVID-19, research into the prevention of this disease is still important. The following protocols have proven to be crucial in the prevention of this disease as well as other viral diseases: observing social distance, wearing face masks, disinfecting the hands regularly, consuming body-strengthening vitamins, etc. [8–10].

SARS-CoV-2 is an enveloped particle that contains positive-stranded RNA in its spherical shape. Four structural proteins were found in this virus, including the nucleocapsid (N) inside the membrane protein (M) and the envelope (E), comprised of glycoprotein spikes (S) [11]. Two recognized pathways of the entrance of SARS-CoV-2 to the cells of an individual are either by way of endosomes or plasma membrane fusion. In both mechanisms, the interaction is through the heavily glycosylated spike protein, where each monomer contains two subunits (S1 and S2) [12,13]. The S1 subunit contains the receptor-binding domain (RBD) for binding to the host cells protein-based receptor, which is also known as angiotensin-converting enzyme 2 (ACE2) [14]. Discovering a compound that can block the creation or disrupt the RBD-ACE2 complex has been suggested as a reasonable strategy to make it more difficult for coronavirus to enter cells, which could at least significantly slow the epidemic until the virus disappears [15].

Scientists are trying to discover new ways to diminish the spread of the COVID-19 virus, especially in very vulnerable areas like public places and healthcare facilities. Nanotechnology-based products are impressive in eliminating viruses and other pathogens no matter their biological structure, drug-resistant profile, or physiology [16]. In comparison with other nano systems, covalent organic frameworks (COFs) present distinct advantages for nanomedical and therapeutic applications due to their pore size, structure tenability [17], biocompatibility [18], and various functionality [19]. COFs are discovered in π-stacked layered molecules, where novel characteristics are expected to emerge from the interaction of the electrically linked component frameworks [20]. Unique characteristics of COFs such as permanent porosity and high surface area, versatile electronic behaviors, and high thermal and chemical stability make them superior candidates in various fields [21–24]. Indeed, COFs can efficiently interplay with other structures via electron-donor–acceptor interactions, π-π interactions, and hydrophobic interactions [25]. Tian et al. [26] constructed a novel composite nano material by growing small Au nanoparticles on COF nanosheets for the multiplexed identification of the hepatitis A virus DNA (HAV) and the hepatitis B virus DNA (HBV). Moreover, the COF nanosheets based on 1,3,5-tris (4-aminophenyl) benzene (TAPB) and 1,3,5-benzene-tricarbalddehyde (BTCA) were synthesized by Zhou et al. [27] for applications to be a nanocarrier for synergistic phototherapy, as well as immunotherapy.

In this critical time, in order to develop more protective routes and facilitate rapid drug discovery, computational algorithms are applied to predict the drug-target interactions and binding stability [28]. As mentioned, in the process of the SARS-CoV-2 invasion to the host cell, the binding of the spike protein to the ACE2 receptor plays a vital role in the virus-cell membrane fusion. Moreover, the high affinity belonging to the spike protein and ACE2 increases the infectivity of SARS-CoV-2. Focusing on the atomic-level details of the spike protein, as well as the ACE2 receptor binding region, is of great significance for designing and screening small molecules that inhibit fusion and subsequently for the advancement of a new protection way [29]. Despite the fact that there are many approved nanotechnology-based antiviral products, this study aimed to focus on using COFs in face masks.

In the present study, the molecular dynamics simulations study was carried out to assess the inhibitory effect of COFs (COF-78, DAAQ-TFP, and COF–OEt) on the formation of the spike protein–ACE2 complex by deforming the protein structure so as to declare the best inhibitor among the selected molecules. The results of this study can pave the way in the future for the development and design of the face masks based on COFs against COVID-19.

The remainder of this study is as follows: First, we explain the method that was used in the research in Section 2. Then, the results are presented in Section 3, and the conclusion of the paper is drawn in the last section.

2. Materials and methodology

The performance of each COF is assessed in two distinct steps. First, the impact of COF on the deformation of spike protein is simulated, and then interactions of deformed spike protein and ACE2 are scrutinized in a separate simulation. To have an accurate interpretation, the interaction of spike protein structure obtained from simulation in aqueous solution and ACE2 is also considered a basis of reference for comparison.

In this research work, all-atoms simulations were conducted by the GROMACS software package [30]. The initial structures of ACE2 and spike protein were extracted via the RCSB site with the code 6MOJ. The molecular structure of COFs, including COF-78 (C_{108}H_{24}N_{12}O_{8}) [31], DAAQ-TFP (C_{32}H_{24}N_{2}O_{4}) [32], and COF–OEt (C_{12}H_{21}O_{6}) [33], were obtained from the Material cloud site. Using Gaussian 09 software, the density functional theory (DFT) calculations were conducted to optimize the structure of COFs. The ESP charge of atoms was obtained via employing a b3lyp optimization algorithm with the basis set of 6–31 + +. To do simulations, in the first step, energy minimization of the system was performed at 100 kJ/mol. Then, the pressure and temperature of the simulation system reached equilibrium in three steps with different time steps of 20 fs, 0.01 fs, and 1 fs within 3 ns. Note that the Parrinello-Rahman and Nose Hoover [34] algorithms were used to keep the pressure and temperature constant at 1 bar and 300 K, respectively. The cut-off radius was considered 2.5 nm for both electrostatic and van der Waals (vdW) interactions. In the final stage, simulations were run with 2 fs time step at 300 ns. General procedure of MD simulations is also shown in Fig. 1. Regarding coarse-grained (CG), simulations were performed with Martini force field. Calculations of Martini force field parameters were done using a reference article [35]. The simulation time for CG was 3000 ns with a time step of 30 fs.

3. Result and discussion

In order to elucidate the effect of COFs on the folding of the spike protein, which plays the most important role in binding to the ACE2 receptor, the complexes between the spike protein and COFs were investigated. Fig. 2 shows the conformation of spike proteins and COFs at the first, middle, and final stages of simulation time. The outcomes of spike protein simulations in the presence of COFs reveal the compression and folding of protein particles, indicating the inhibitory effect of COFs on the formation of the spike protein–ACE2 complex. To find the best
and optimum type of COF inhibitors, first, intermolecular interactions of the COFs-spike protein complex were assessed through analyses including the number of hydrogen bonds, binding free energies (electrostatic, vdW, and total energy), and distribution of spike protein secondary structure element (SSE) during MD simulations. Then, we evaluated the interactions of deformed spike proteins with the ACE2 to compare its behavior with the original spike protein, which interacted with the ACE2 by analyzing complementary results of the radius of gyration ($R_g$), solvent accessible surface area (SASA), root-mean-square deviation (RMSD), and root-mean-square fluctuation (RMSF).

### 3.1. Evaluation of the effect of COFs on the spike protein structure

Interactions between COFs and spike proteins and the conformational stability of these complexes were firstly assessed by calculating the number of hydrogen bonds [36]. The fact is that hydrogen bonds are the most durable and stable intermolecular bonds, which are formed between hydrogen atoms and electronegative atoms such as oxygen and nitrogen [37,38]. The greater the hydrogen bonds created, the more positive the influence of COFs on the deformation of the spike protein, which is considered as one of the best ways to prevent the protein and ACE2 from interacting will result. As is seen in Fig. 3a, the mean number of hydrogen bonds was 15, 23, and 28 for DAAQ-TFP, COF-OEt, and COF-78, respectively. Since the impact of the COF-78 on the spike protein was more significant compared to other COFs, more structural deformation was also anticipated, indicating the great inhibitory influence of the COF on the fusion of the spike protein, as well as reduction of binding affinity to ACE2 receptor. Moreover, due to the greatest amount of hydrogen bonds, the COF-78 complex was more stable when compared to the DAAQ-TFP and COF-OEt complexes.

For validating the intermolecular strength of interactions and clarifying the dominancy of particular chemical energy contributing to overall stability, the estimation of binding free energies for biomolecular complexes is a useful way [39]. The average of free binding energies was obtained using MM-PBSA (Molecular Mechanics/Poisson-Boltzmann Surface Area) analysis to estimate the protein-COFs binding affinity in a dynamic state and determine the more potent COFs. In the present study, we aimed to observe the effect of three various COFs on the spike protein structure. Thus, the best conformation was selected on the basis of bonding energy (vdW and electrostatic interaction energy) or binding affinity between three interacting systems. The total binding free energy is an average of vdW and electrostatic interaction energies [40,41].

The average energy of vdW and electrostatic interactions between three various COFs and the spike protein complex, which is considered as one of the most crucial analysis for studying intermolecular interactions, are shown in Fig. 3b. Indeed, the more significant electrostatic and vdW attraction between COFs and spike proteins leads to lower stimulation energy levels, indicating the more complex stability, as well as the greater the effects of COFs on the complex of the spike protein.

The vdW energy, which refers to hydrophobic interactions, is more favorable for three complexes. In other words, the energy from the vdW bonds overcomes the energy from the electrostatic bonds for all simulations. In the comparison of results of energy analyses, although all three COF inhibitors showed good interactions with the spike protein, COF-78 had relatively higher binding affinities and more negative interaction energy with the spike protein, and subsequently, as was mentioned, the COF-78-spike protein complex showed more stability. Since interactions can deform the receptor-binding motif of the spike protein, COF-78 is the most effective structure on the deformation of the spike protein secondary structure in comparison with other selected COFs. Although, as the previous analysis illustrated, DAAQ-TFP had the most minimal influence on the deformation of the spike protein as its energy analysis indicated fewer interactions.

Interactions between COFs and a spike protein can alter the structure of the spike protein. Therefore, the distribution of spike protein secondary structures was analyzed in order to establish the effect of the best COF on the deformation of the spike protein folding. The fact is that the suitable condition of the interaction between the spike protein and ACE2 receptor occurs in the case of increasing the β-sheets and α-helices, and decreasing the coils, bends, and turns [42,43]. Fig. 3c shows the secondary structures of the spike protein both with and without the company of COFs. As is clear, the presence of COFs increased coils, bends, and turns, as well as reduced the β-sheets and α-helices. COFs were shown to have positive performance in deforming the spike protein, in which a reduction of the spike protein interactions with the ACE2 receptor occurred. Consequently, the findings declared that COF-78 was the most potent ligand among the other selected molecules for changing the folding of the spike protein motif as the increase in coil, bend, and turn structures had been the highest in the protein simulation. Furthermore, investigating the number of hydrogen bonds, as well as the energy of interaction, proved instability of the spike protein secondary structure.

### 3.2. Evaluation of behavior of the deformed spike proteins in the presence of ACE2

As previously mentioned, the interaction of COFs with the spike protein culminated in the deformation of the spike protein structure. The goal of the research is also investigating the interactions of deformed spike protein with the ACE2 so as to assess COFs that have a more positive impact on the fusion reduction of the spike protein into the ACE2. Therefore, we firstly analyzed the energy of interaction to evaluate the intermolecular strength and then quantified the compactness of the spike protein after the interaction with ACE2. Moreover, the number of hydrogen bonds created between the deformed spike protein and ACE2 was compared. Finally, with the use of RMSD and RMSF, the stability of the system was analyzed.

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Fig. 1. The general procedure of MD simulations employed for this research work.
3.2.1. Evaluation of the interaction energy between the deformed spike protein and ACE2 interaction as well as compactness of spike protein

The evaluation of interaction energy in terms of the type and quantity is a significant parameter when it comes to the interaction between a deformed spike protein and the ACE2. Essentially, the high absolute amount of energy is an indication of the stronger interactions among the different particles. In more detail, the greater absolute amounts of the interaction energy between the deformed spike protein and the ACE2 receptor signify the imperfect influence of COFs on the deformation of the spike protein. Fig. 4a illustrates the energy resulting from vDW and the electrostatic interaction between the deformed spike protein and the ACE2 receptor. The results reveal that the vDW interactions are the dominant interactions in which their absolute values are approximately two times higher than the electrostatic energy in all simulation cases. Moreover, although the deformation of the spike protein has reduced the interaction energy of this protein and the ACE2 receptor, the lowest absolute interaction energy is related to the case in which the spike protein was deformed by COF-78, followed by COF-OEt, and DAAQ-TFP. Therefore, it can be inferred that the stronger interaction of COF-78 with the spike protein deforms the structure of the protein in such a way that creates greater prevention in the formation of the perfect protein-ACE2 complex in comparison with other cases.

It is indisputable that the stronger attraction energy of the deformed spike protein and the ACE2 has led to more shrinkage in the protein. Therefore, the study of the spike protein compaction is a good indicator to compare the effect of COFs in preventing the interaction of spike protein and the ACE2.
protein and the ACE2. The compactness of the protein structure can be assessed by the Gyration Radius analysis, which involves determining the root-mean-square of the distance of particles from their center-of-mass \[44\]. By definition, the lower the value of \(R_g\), the more compressed the protein is that is being studied. Therefore, concerning the spike protein, the difference between the initial and final values of \(R_g\) was considered as an index to compare the spike protein compaction. To explain further, if the final value of \(R_g\) is less than its initial value, the compaction of spike protein particles is increased, and this indicates high interactions of spike protein with the ACE2. Fig. 4c demonstrates the compaction index value of the spike protein. The negative values of the compaction index of deformed spike proteins after interaction with the ACE2 presented an increase in the final value of \(R_g\) compared to its initial value, and thus a decrease in the compaction of this protein. This was due to the deformation of the spike protein structure by COFs, which resulted in decreasing the interaction of the protein with the ACE2 receptor. The COF-78 was the most effective of the COFs in deforming the structure of spike protein, as the compaction of the protein was further reduced compared to other cases. Fig. 4c shows the structure of the spike protein as well as the ACE2 after interaction.

3.2.2. Evaluation of hydrogen interactions of spike protein and ACE2, as well as the stability of their interactions

As mentioned, the strongest types of intermolecular interactions among the spike protein and the ACE2 are the hydrogen bonds, which play a vital role in their binding \[45\]. The reduction in the number of hydrogen bonds created between deformed spike proteins and the ACE2 receptor reflects the beneficial impact of COFs on the structure of spike protein which prevents them from binding. It is notified that increasing the number of hydrogen bonds between the spike protein and aqueous media results in reducing the number of hydrogen bonds between the spike protein and the ACE2. This means that the hydrogen interactions of the protein and aqueous media lead to an increase in their contact area, which prevents the formation of the perfect complex of the protein and the ACE2 receptor. So that a quantified comparison of the effectiveness of COFs on the deformation of the protein can be made, the number of hydrogen bonds of the spike protein and the ACE2 in terms of their contact area with aqueous media is shown in Fig. 5a. Considering the results, the deformation of spike proteins by COFs not only reduced their hydrogen bonds with the ACE2, but also increased the contact area of the spike proteins and aqueous media. It is worth mentioning that although there was a reduction in the number of hydrogen bonds of all deformed proteins with the ACE2, the deformation of the spike protein by COF-78 had further reduced the hydrogen bonds. In fact, COF-78 had the most influence in preventing interaction between the spike protein and the ACE2 receptor.

During the simulation time, different particles present in the simulation box interact with each other to achieve their most stable status. These interactions are accompanied by fluctuations of molecules in the simulation box. Therefore, oscillations of particles in simulation systems can be considered as a perfect indicator for comparing the stability of different simulated systems. Indeed, the more fluctuations of the molecules, the lower the stability of the molecules in the simulation box will result. In our case, the strong interactions between the spike protein and the ACE2 cause more stability and less fluctuation of the spike protein particle in the simulation box. To investigate the fluctuations of the spike protein, the RMSD (root-mean-square deviation) and the RMSF (root-mean-square fluctuation) were analyzed. The RMSD analysis defines when the fluctuation of particles in the simulated system is calculated relative to a reference at different simulation times, while the RMSF analysis calculates the oscillations of all particles to a single

![Fig. 4.](a) Total, vdW, and electrostatic energy of spike protein and ACE2 interaction, (b) difference between initial and final gyration radius, and (c) conformation of spike protein and ACE2 after interaction.)
particles, and the superior the instability in the interactions of the spike protein and the ACE2 receptor. The average value of RMSF in terms of the average value of RMSD is shown in Fig. 5b. According to the results, an increase in the average values of RMSD and RMSF was related to the deformed spike proteins. This means that in the case of the deformation of the spike protein by COFs, interactions of this protein with the ACE2 receptor have less stability. Moreover, the most significant instability in the molecular structure of a deformed spike protein was related to the deformation of the protein by COF-78. In other words, COF-78 is the best nanoparticle to change the structure of the spike protein as seen by the result analysis of the protein, and the ACE2 interactions revealed that in this case the fusion of the protein was minimized compared to other deformed proteins.

4. Conclusion

The binding of the spike protein to the ACE2 allows coronavirus activity in the body. Preventing the binding of the spike protein to ACE2 by changing the structure of the protein is one of the best ways to prevent the coronavirus epidemic. In the current work, three different types of COFs were used to assess their performance in the deformation of the structure of the spike protein with the use of a powerful MD simulation tool. The effectiveness of COFs in changing the structure of the spike protein was investigated by using several analyses, including interaction energy, the number of hydrogen bonds, and secondary structure distribution. According to the results, COF-78 with the greatest absolute value of energy and the number of hydrogen bonds with the spike protein led to the most change in the structure of spike protein. In the next step, we simulated the deformed spike protein with the ACE2 receptor to assess the fusion capacity of the protein after the deformation. By analyzing the energy, H-bonds, gyration radius, SASA, RMSD, and RMSF results, intermolecular interactions in terms of the vDW and electrostatic, the number of hydrogen bonds created between the protein and the receptor, changes in the protein compaction, the contact area of the protein with the aqueous media, and the protein stability was investigated, respectively. In general, all introduced COF inhibited binding of the protein to the receptor by changing the protein structure. The spike protein deformed by COF-78 had the lowest interaction energy, compaction, and the number of hydrogen bonds, while its contact area with aqueous media was the highest compared to other deformed proteins. Moreover, this deformed protein had the uppermost instability, which indicated the low interaction with the ACE2 receptor. In fact, COF-78 was the best structure to prevent spike protein binding to ACE2. The results presented in this study pave the way for future applications of COFs in the manufacturing of masks and air filters. It is also suggested that the effects of the presented structures in this work be investigated in a laboratory.

CRediT authorship contribution statement

Ahmad Miri Jahromi: Conceptualization, Methodology, Software, Formal analysis, Visualization. Aida Solhjoo: Writing – review & editing, Investigation, Conceptualization. Mehdi Ghasesmi: Investigation, Conceptualization, Writing – review & editing. Mohammad Khedri: Conceptualization, Methodology, Software. Reza Maleki: Conceptualization, Writing – review & editing. Lobat Tayebe: Supervision, Conceptualization, Project administration, Investigation, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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