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Theoretical Study of the Interaction of IRMOF-1 (MOF-5) with Valine, Alanine, and Norleucine Amino Acids

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Abstract

We have investigated by density functional theory the interaction of representative amino acids such as valine (Val), alanine (Ala) and norleucine (Nle) with a suitably functionalized organic linker of the IRMOF-1 (MOF-5) metal-organic framework. The binding energy value of -8.19 kcal/mol, -9.32 kcal/mol, and -5.64 kcal/mol were obtained via molecular docking for Val-MOF-5, Ala-MOF-5, and Nle-MOF-5 complexes, respectively. Also, the intermolecular energy value and internal energy value for each of the complexes were found to very low, confirming their high stabilities and strong bonding between MOF-5 and the amino acids. This is very promising for possible pharmaceutical applications of MOF-5.

Keywords: MOF-5, valine. alanine, norleucine, docking

1.0 Introduction

MOF-5 (also known as IRMOF-1) is one of the most typical representatives of the MOFs family. It is a three-dimensional framework structure composed of terephthalic acid and metal cluster Zn4O [Qasem *et al*., 2018], firstly synthesized by Yaghi et al. [Li *et al*., 1999]. MOF-5 has open skeleton structure, controlled pore structure and pore surface area and high thermal stability function [Sabo *et al*., 2007; Guo et al., 2018; Bakhtiari and Azizian, 2018], which has been widely studied in gas storage [Liu *et al*., 2019] and separation [Ozen and Ozturk, 2019], electrochemistry [Cendrowski *et al*., 2018], catalysis, and medicine [Motakef-Kazemi, *et al*., 2016].

One of the major directions of nanobiotechnology research is currently focused on the interactions between biomolecules and nanoporousmaterials (Turner *et al*., 1995; Wadu-Mesthrige *et al*., 2001). The fabrication of structureswith functional surfaces on which proteins will be immobilized without losing their biological activity remains a major goal. Initially, carbon nanotubes (CNTs) were studied for drug delivery. Both theoretical (Mavrandonakis, *et al*., 2006) and experimental (Bradley, *et al*., 2004; Kostarelos, 2010; Bianco, *et al*., 2005) investigations have proved that nanomaterials are good candidates for the encapsulation of proteins, taking into account the fact that functionalized CNTs exhibit low toxicity and are not immunogenic (Kostarelos, 2010; Bianco, *et al*., 2005). Nevertheless, the axial porosity of CNTs together with their graphitic surface places limits on the variety of biological reactants and potential applications (Koukaras, *et al*., 2011).

The 3D periodic structure of MOFs consists of inorganic primary building units (pbu), which are linked via secondary organic building units (sbu), commonly referred to as the organic linker. The almost unlimited variety of organic linkers that can be used for their skeleton provides them with a large range of pore dimensions along with a great diversity of interaction sites. These advantages

of MOFs, compared with other nanoporous materials, lead to the consideration of MOFs as drug vehicles for improving drug delivery by increasing their bioavailability and biostability, ensuring progressive drug release under physiological conditions. In the work of Horcajada *et al*., (2006;2011) using iron(III) carboxylate MOFs, they demonstrated and verified for the first time the remarkable capacity for drug encapsulation and controlled delivery of such MOFs and their biocompatibility. By examining the adsorption and delivery capabilities of MOFs with different porosities, they showed that the combination of high and regular porosity with the presence of organic groups within the framework may cumulate the advantages to achieve both a high drug loading and a controlled release. Equally significant are the results of their invitro and invivo studies, which reveal low to no cytotoxicity and toxicity of the studied MOFs.

Theoretical study of amino acid interaction with MOFs has received consideration over the years. Koukaras *et al*., (Koukaras *et al*., 2011) investigated by density functional theory the interaction of representative amino acids such as glycine and tyrosine with a suitably functionalized organic linker of the IRMOF-14 metal-organic framework for various sites and ways of approach. It was found that the only active site with nonmarginal interaction energy is the one introduced by the strategic replacement of a linker hydrogen by a hydroxyl unit. The magnitude of the interaction energies of 9.8 kcal/mol for glycine and 10.8 kcal/mol for tyrosine were recorded.

In this work, we examine the “direct” interaction of two very important amino acids, alanine (ALA), norleucine (Nor), and valine (VAL) with the organic part of a strategically modified IRMOF-1 framework.

The rising incidences of infectious and terminal diseases such as Covid-19, cancer, Ebola, etc., has necessitated a constant search for newer drug candidates to combat this ugly trend. Sadly, many

drug candidates with proven superb therapeutic potentials have little or no application owing to their low bioavailability and biostability within the biological system. This constitutes a great danger to drug discovery and development and poses humanity to an immense risk. To circumvent this bottleneck, a need to explore MOFs (MOF-5 in this case) for sound drug vehicles has become necessary.

2.0 Materials and methods

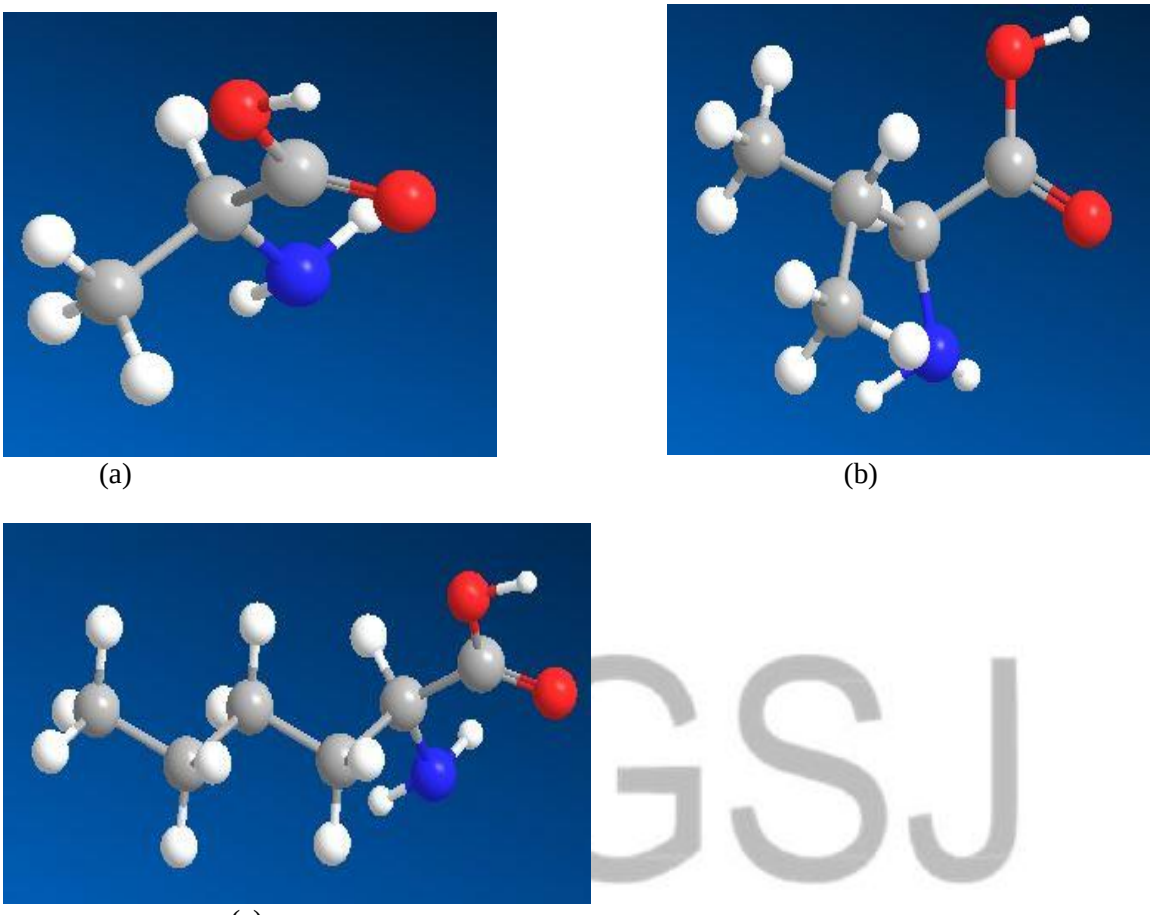
2.1. Molecular docking studies

Molecular docking studies were performed to provide a theoretical perspective for possible molecular interactions of MOF-5 with the target proteins (amino acids). The materials used in this study are experimental data from the X-Ray Diffraction results for alanine, norleucine, and valine which can be downloaded in the protein data bank (PDB) http://www.rscb.org/pdb. The drug vehicle, MOF-5 was taken from https://pubchem.ncbi.nlm.nih.gov. The theoretical binding affinities were determined by energy minimization from docking calculation results. Molecular optimization was performed using the Density Functional Theorem (DFT).

Hardware consists of a computer with 8 GB RAM specifications, Quad Core Processor (Intel Corei3), Microsoft Windows 10 Pro4.04 operating system. The software used for the docking simulation process is AutoDockTools-1.5.6 and AutoDock_vina 1_1_2. The preparation and analysis of the simulation results were carried out using the Discovery Studio and Pymol programs.

All of the docking experiments were performed using AutoDock Vina because it offers; more accuracy in predicting ligand-protein interactions, a shorter running time as a result of multiple core processors, and greater accuracy for ligands with more than 20 rotatable bonds.

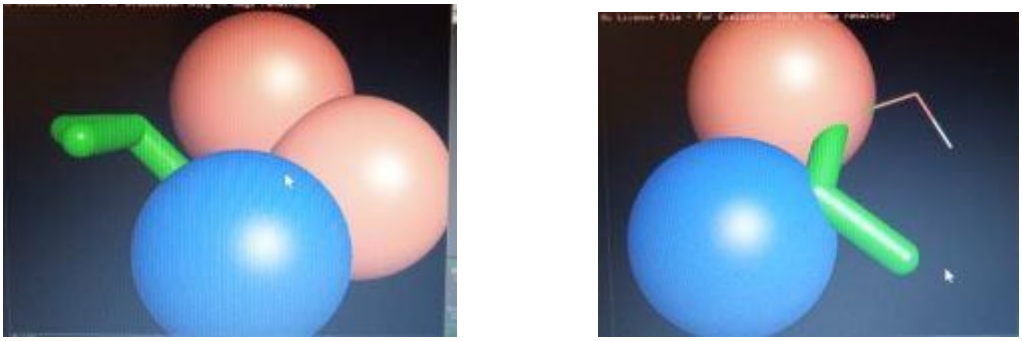
3.0 RESULTS AND DISCUSSION



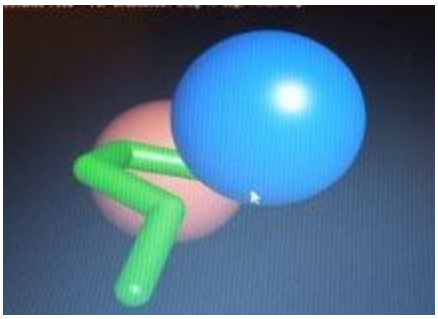
(a) (b)

(c)

Fig. 1: Optimized structures of amino acids [Black (C); white (H); red (O); blue (N)]



(a) (c)



(b)

Fig 2: Maximum interaction configurations of the amino acids with MOF-5

Table 1: **MOLECULAR DOCKING RESULT** for **IRMOF-1(MOF5)-Valine**

Parameter	value
Binding Energy	-8.19
Kl	988.55
Intermolecular energy	-9.39
Internal Energy	-1.67
Torsional Energy	1.19
Unbounded Extended Energy	-1.64
Cluster RMS	0.00
Ref RMS	19.64

Table 2: **MOLECULAR DOCKING RESULT** for **IRMOF-1(MOF5)-Alanine**

Parameter	value
Binding Energy	-9.32
Kl	147.84
Intermolecular energy	-10.21
Internal Energy	-1.25
Torsional Energy	0.89
Unbounded Extended Energy	-1.25
Cluster RMS	0.00
Ref RMS	19.51

Table 3: **MOLECULAR DOCKING RESULT** for **IRMOF-1(MOF5)-Norleucine**

Parameter	value
Binding Energy	-8.50
Kl	590.19nm
Intermolecular energy	-10.29
Internal Energy	-1.11
Torsional Energy	1.79
Unbounded Extended Energy	-1.11
Cluster RMS	0.00
Ref RMS	32

Table 4: Features of IRMOF-1 (MOF-5)

Organic linker	Pore size (Å)	Pore volume (cm^3/g)	Surface area (m^2/g)
1,4-benzene dicarboxylate	15	1.22	2297

Fig. 1 shows the DFT optimized structures of the (a) valine (Val) (b) norleucine (Nle) and alanine (Ala) amino acids. These structures are not under scale. Maximum interaction configuration of the Ala,Val,and Nle amino acids with MOF-5 is shown in Fig 2; a,b, and c, respectively. Tables 1,2,3 give the result of the molecular docking for Val, Ala, and Nle.

Successful docking of all the amino acids revealed significant binding with MOF-5. Valine docked with the composite showed significant binding, yielding a binding affinity of -8.19 kcal/mol. The interaction of this amino acid with the composite (Fig. 2a) showed a high affinity interaction, as the ligand fit inside the core pocket region of the MOF. Internal energy of -1.6 kcal/mol in the Val-MOF-5 complex measures the stability of the complex. The low values of this parameter shows a significant binding interaction between the ligand (MOF-5) and the receptor (Val amino acid).

Results obtained by docking Ala to MOF-5 showed binding affinity of -9.32 kcal/mol (Fig. 2b). Internal energy of -1.25 kcal/mol in the Ala-MOF-5 complex measure the stability of the complex. The low values of these parameters shows a significant binding interaction between the ligand (MOF-5) and the receptor (Ala amino acid).

The docking of IRMOF-1 with the Nle amino acid revealed that the ligand had a high-affinity interaction with the protein with a binding energy value of -5.64 kcal/mol (Fig. 2c). -1.34 kcal/mol gives the internal energy of the Nle-IRMOF-1 complex. The low value of this parameter reveal the high stability of the complex and existence of significant binding of the amino acid to the MOF.

3.1 Influence of Hydrogen bond

Hydrogen bond refers to a special class of attractive intermolecular forces that arises due to the dipole-dipole interaction between a hydrogen atom that is bonded to a highly electronegative atom lying in the vicinity of the hydrogen atom. The observed intermolecular energy of -9.39 kcal/mol, -10.21 kcal/mol, and 7.43 kcal/mol were recorded for Val-MOF-5, Ala-MOF-5 complex and Nle-IRMOF-1 complex, respectively. The low values of intermolecular energies show that hydrogen bond most likely plays a significant role in the docking mechanism and binding modes selection. This result is in agreement with the findings of Fikrika *et al*., 2009 wherein molecular docking studies was carried out on catechin and its derivatives as anti-bacterial inhibitor for glucosamine-6-phosphate synthase. It was found by the authors that hydrogen bond most likely plays a profound role in the binding of the catechin and its derivatives to the enzyme, glucosamine-6-phosphate synthase

3.2 Influence of surface area, pore sizes and pore volumes

Basically, the adsorption of the drug depends on the availability of internal surface area in the carriers as well as the pore sizes and pore volumes present in the frame works. 15Å, 1.22 $cm^3/_g$, 2297 $m^2/_g$ give the pore size, pore volume, and surface area, respectively of IRMOF-1. The high binding affinity of the studied amino acids to the composite (MOF-5) could be attributed to the large values of the pore size, pore volume and surface area. Pore size can accommodate reaction with N atom on the amino acid to be easily accessible to the bonding groups on the organic linkers on MOF-5. This result is in consonance with the findings of Jagannath *et al*., 2021 wherein the role of pore volume and surface area of Cu-BTC and MIL- 100 (Fe) metal-organic frameworks on the loading of rifampicin were studied via molecular docking. The authors argued that the pore volume of MIL-100(Fe) and Cu-BTC plays vital role for the drug loading.

3.3 Influence of ring on the organic linker

Presence of ring in the organic linker promotes stability through chelate effect. The organic linker in MOF-5 is 1,4-benzene dicarboxylate. The observed stability of MOF-5 complexes with the studied amino acids could be partly attributed to the ring presence on 1,4-benzene dicarboxylate. Similar observation was made by Koukaras *et al.*, 2011, in their work titled ‘’interaction of glycine and tyrosine amino acid with pyrenol based IRMOF-14’’

Summarily, the investigated amino acids displayed excellent binding affinity to the MOF-5 as evidenced by their low binding energies vis-a-viz their Intermolecular and internal energies. This observation could be attributed to the large values of the pore size, pore volume and surface area of MOF-5.

Conclusion

The docking results yielded significant binding interactions of the Val, Ala, Nle amino acids with MOF-5 (IRMOF-1). This could be attributed to the large values of the pore size, pore volume and surface area. Hence, MOF-5 could be use as vehicle for drug candidates posed with problem of low bioavailability and biostability within the biological system. Since amino acids are found everywhere in the biological system, drug encapsulated in MOF-5 could be transported to every part of the human serum.

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