UNIVERSITI PUTRA MALAYSIA

STRUCTURE AND DYNAMICS OF CUTINASE ENCAPSULATED IN ISORETICULAR METAL ORGANIC FRAMEWORK-74-VI

TUAN NURUL AZURA BINTI TUAN KOB @ YAAKUB

FS 2020 50

STRUCTURE AND DYNAMICS OF CUTINASE ENCAPSULATED IN ISORETICULAR METAL ORGANIC FRAMEWORK-74-VI

By

TUAN NURUL AZURA BINTI TUAN KOB @ YAAKUB

Thesis Submitted to the School of Graduate Studies, Universiti Putra Malaysia, in Fulfilment of the Requirements for the Degree of Master of Science

Disember 2019

Abstract of thesis presented to the Senate of Universiti Putra Malaysia in fulfilment of the requirement for the degree of Master of Science

STRUCTURE AND DYNAMICS OF CUTINASE ENCAPSULATED IN ISORETICULAR METAL ORGANIC FRAMEWORK-74-VI

By

TUAN NURUL AZURA BINTI TUAN KOB @ YAAKUB

December 2019

Chair : Muhammad Alif Bin Mohammad Latif, PhD
Faculty : Science

Cutinase is a serine hydrolases enzyme that is widely used as a biocatalyst to produce industrially important chemicals ranging from pharmaceuticals to biological and food additives. However, low thermal stability and lack of efficient recovery are the limitation of cutinase. Enzyme immobilization is one of the techniques used to improve enzyme stability and activity. Recently, immobilization with porous materials such as metal-organic frameworks (MOFs) have shown to improve the thermostability of enzymes even in extreme conditions. Here, quantum mechanics (QM) calculations and molecular dynamics (MD) simulations were performed in order to investigate the structural stability of cutinase when encapsulated within an IRMOF-74-VI. *Ab initio* calculations were performed on the crystal structure of IRMOF-74-VI to obtain partial atomic charges for IRMOF-74-VI atoms. Then, MD simulations of cutinase and cutinase-IRMOF-74-VI in water were performed at different temperatures (300, 350, 400, 450 and 500 K) and 1 atm pressure. The encapsulated cutinase showed greater stability than the free enzyme. Although the average root mean square deviation (RMSD) value increased for both systems with temperature, the cutinase-IRMOF-74-VI exhibited lower RMSD values when compared to free-cutinase especially at 500 K. IRMOF-74-VI was able to control the strong fluctuations at higher temperatures and thereby, helped retain the cutinase structure. The key interactions that maintained the stability of cutinase were identified, such as hydrophobic interactions between amino acid residues of Pro193 and Thr45 with aromatic ring of IRMOF-74-VI. In addition, ion pair interactions between Arg96 residue and carboxylate group of IRMOF-74-VI was found to have a distance of 4.53 Å and was classified as a strong salt bridge. MD simulations also have been employed to study the effect of encapsulation towards stability and flexibility of cutinase in different solvents (water, ethanol and hexane) at room temperature. Cutinase-IRMOF-74-VI in water and ethanol produced lower RMSD values (0.14 ± 0.006 and 0.17 ± 0.017 nm respectively) compared to cutinase-IRMOF-74-VI in hexane (0.24 ± 0.015 nm). Further analysis also showed that cutinase-IRMOF74-VI complex was more stable in polar solvent. Cutinase-IRMOF-74-VI exhibited the highest number of intermolecular interactions with hexane compared to water and ethanol, leading to the least stable conformation between the three solvents. These findings demonstrate the potential for cutinase-encapsulation applications

in cage-like pore frameworks by showing that encapsulation of cutinase with IRMOF-74-VI helps to retain the structural integrity at high temperature. However, IRMOF-74-VI destabilized cutinase in hexane compared to higher polarity solvents which are ethanol and water. This information can be used to optimize cutinase-MOF applications and develop new cutinase-specific MOF for biocatalysis and biosensing purposes. The interactions between cutinase and IRMOF-74-VI under different temperatures and solvents would be beneficial as guideline for future rational design of enzyme-MOF biocatalysts.

Abstrak tesis yang dikemukakan kepada Senat Universiti Putra Malaysia sebagai memenuhi keperluan untuk ijazah Master Sains

STRUKTUR DAN DINAMIK ENKAPSULASI CUTINASE DALAM RANGKAIAN ORGANIK LOGAM-74-VI

Oleh

TUAN NURUL AZURA BINTI TUAN KOB @ YAAKUB

Disember 2019

Pengerusi : Muhammad Alif Bin Mohammad Latif, PhD
Fakulti : Sains

Cutinase ialah serine hidrolasi enzim yang digunakan secara meluas sebagai biomangkin untuk menghasilkan bahan kimia perindustrian penting yang terdiri daripada farmaseutikal untuk bahan tambahan biologi dan makanan. Walau bagaimanapun, kestabilan haba yang rendah dan kekurangan pemulihan cekap adalah kekurangan cutinase. Enzim enkapsulasi adalah salah satu teknik yang digunakan untuk meningkatkan kestabilan enzim dan aktiviti. Baru-baru ini, rangkaian organik logam (MOFs) telah ditunjukkan untuk meningkatkan kestabilan termal enzim walaupun dalam keadaan suhu yang melampau. Di sini, mekanik kuantum (QM) pengiraan dan dinamik molekul (MD) simulasi telah dijalankan untuk menyiasat kestabilan struktur cutinase apabila terkandung dalam rangkaian organik IRMOF-74-VI Pengiraan *ab initio* telah dilakukan ke atas struktur kristal IRMOF-74-VI untuk mendapatkan caj atom separa untuk setiap atom IRMOF-74-VI. Kemudian, MD simulasi cutinase dan cutinase-IRMOF-74-VI di dalam air telah dijalankan pada suhu yang berbeza (300, 350, 400, 450 dan 500 K) dan tekanan 1 atm. Cutinase terkandung menunjukkan kestabilan yang lebih besar daripada enzim sahaja. Walaupun akar purata min nilai sisihan persegi (PGPR) meningkat untuk kedua-dua sistem dengan suhu, cutinase-IRMOF-74-VI dipamerkan nilai PGPR lebih rendah jika dibandingkan dengan cutinase sahaja terutama pada 500 K. IRMOF-74-VI dapat mengawal kestabilan pada suhu yang lebih tinggi dan membantu mengekalkan struktur cutinase tersebut. Interaksi utama yang mengekalkan kestabilan cutinase telah dikenal pasti, seperti interaksi hidrofobik antara amino asid Pro193 dan Thr45 dengan cincin aromatik IRMOF-74-VI. Di samping itu, interaksi pasangan ion antara Arg96 dan kumpulan karboksilat daripada IRMOF-74-VI didapati mempunyai jarak 4.53 Å dan telah diklasifikasikan sebagai jambatan garam yang kuat. MD simulasi juga telah digunakan untuk mengkaji kesan enkapsulasi ke arah kestabilan dan fleksibiliti cutinase dalam pelarut yang berbeza (air, etanol dan heksana) pada suhu bilik. Cutinase-IRMOF-74-VI dalam air dan etanol dihasilkan nilai PGPR lebih rendah (0.14 ± 0.006 dan masing-masing 0.17 ± 0.017 nm) berbanding cutinase-IRMOF-74-VI dalam heksana (0.24 ± 0.015 nm). Analisis selanjutnya juga menunjukkan bahawa cutinase-IRMOF74-VI kompleks adalah lebih stabil dalam pelarut kepolaran yang tinggi. Cutinase-IRMOF-74-VI dipamerkan bilangan tertinggi interaksi antara molekul dengan heksana berbanding air dan etanol, yang membawa kepada kestabilan yang rendah bagi perbandingan ketiga tiga pelarut. Dapatan

ini menunjukkan potensi untuk aplikasi cutinase-enkapsulasi dalam sangkar seperti rangkaian organik logam dengan menunjukkan bahawa pengkapsulan cutinase dengan IRMOF-74-VI membantu untuk mengekalkan integriti struktur pada suhu tinggi. Walau bagaimanapun, IRMOF-74-VI mengurangkan kestabilan cutinase dalam heksana berbanding pelarut kepolaran lebih tinggi seperti etanol dan air. Maklumat ini boleh digunakan untuk mengoptimumkan aplikasi cutinase-MOF dan membangunkan MOF cutinase yang baru khusus untuk tujuan biocatalisis dan biosensor. Interaksi antara cutinase dan IRMOF-74-VI di bawah suhu dan pelarut yang berbeza akan memberi manfaat sebagai panduan untuk masa depan dalam reka bentuk pemangkin biologi enzim-MOF.

ACKNOWLEDGEMENTS

In the name of Allah SWT, the Most Gracious and the Most Merciful. First of all, I would like to express my gratitude to Allah S.W.T. With His mercy and blessings, I was able to complete my master. Foremost, I would like to express my sincere gratitude to my research supervisor, Dr Muhammad Alif Muhammad Latif for the continuous support, for his patience, motivation and immense knowledge. His guidance helped me in all the time of research and writing of this thesis.

I also would like to thank all my lab mates, postgraduates from Macromolecular Simulation Laboratory, Department of Chemistry, Faculty of Science, for the guidance and help during my research.

Further thanks to my family especially for my mother, Sakinah binti latiff for her continuous support and advices for me to finish my project. Her prayer gave me strength to complete this project in success. My next appreciation goes to my friends and everyone else who helped me in all ways, especially when I needed any help. Without them, I could not have completed the project successfully.

This thesis was submitted to the Senate of Universiti Putra Malaysia and has been accepted as fulfilment of the requirement for the degree of Master of Science. The members of the Supervisory Committee were as follows:

Muhammad Alif Mohammad Latif, PhD
Senior Lecturer
Centre of Foundation Studies for Agricultural Sciences
Universiti Putra Malaysia
(Chairman)

Mohd Farid Ismail, PhD
Senior Lecturer
Faculty of Sciences
Universiti Putra Malaysia
(Member)

_____
ZALILAH MOHD SHARIFF, PhD
Professor and Dean
School of Graduate Studies
Universiti Putra Malaysia

Date:

Declaration by graduate student

I hereby confirm that:

- this thesis is my original work;
- quotations, illustrations and citations have been duly referenced;
- this thesis has not been submitted previously or concurrently for any other degree at any other institutions;
- intellectual property from the thesis and copyright of thesis are fully-owned by Universiti Putra Malaysia, as according to the Universiti Putra Malaysia (Research) Rules 2012;
- written permission must be obtained from supervisor and the office of Deputy Vice-Chancellor (Research and Innovation) before thesis is published (in the form of written, printed or in electronic form) including books, journals, modules, proceedings, popular writings, seminar papers, manuscripts, posters, reports, lecture notes, learning modules or any other materials as stated in the Universiti Putra Malaysia (Research) Rules 2012;
- there is no plagiarism or data falsification/fabrication in the thesis, and scholarly integrity is upheld as according to the Universiti Putra Malaysia (Graduate Studies) Rules 2003 (Revision 2012-2013) and the Universiti Putra Malaysia (Research) Rules 2012. The thesis has undergone plagiarism detection software.

Signature: _____ Date: _____

Name and Matric No.: _____

Declaration by Members of Supervisory Committee

This is to confirm that:

- the research conducted and the writing of this thesis was under our supervision;
- supervision responsibilities as stated in the Universiti Putra Malaysia (Graduate Studies) Rules 2003 (Revision 2012-2013) are adhered to.

Signature: _____
Name of Chairman of Supervisory Committee: _____

Signature: _____
Name of Member of Supervisory Committee: _____

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

MOFs	metal organic framework
SBUs	secondary building units
IRMOFs	isoreticular MOFs
COFs	covalent organic frameworks
MD	molecular dynamics
QM	quantum mechanics
GCMC	Grand Conical Monte Carlo
DOT	2,5-dioxidoterephthalate
ZIF	zeolite imidazolate framework
CD-MOFs	cyclodextrin-based MOFs
RMSF	root mean square deviation
UiO	Universitetet i Oslo
MIL	Materials of Institut Lavoisier
CCDC	Cambridge Crystallographic Data Centre
PME	Particle Mesh Ewald
RMSF	Root Mean Square Fluctuation
Arg	arginine
pdb	Protein Data Bank
PET	polyethylene terephthalate

CHAPTER 1

INTRODUCTION

1.1 Overview

Enzymes have been applied as catalysts for manufacturing of industrially applicable chemicals ranging from pharmaceuticals to biological and food additives. Enzymes have rapidly improved in terms of their catalytic performance, yet their uses in industrial applications are limited by the low thermal stability, denaturation and lack of efficient recovery. Daniel *et al.* (1996) also discovered that in aqueous solution, enzymes can only be active at a temperature up to 85°C and at higher temperature; the denaturation of the enzymes becomes faster. Without any support or protection, enzymes are not stable and their functions becomes very limited. Cutinase is one of those enzymes having the same limitation. Cutinase tends to deactivate and degrade at high temperature. Carvalho *et al.* (1998) had discovered that cutinase possess a very short half-life in water.

Several successful strategies have been proposed to improve the thermal stability of enzymes using either immobilization, encapsulation or biomineralization approaches (Mateo *et al.*, 2007). Normally, physical adsorption such as immobilization or encapsulation was preferred, since the methods do not change the initial structure of the catalyst and do not interrupt its active site (Krajewska *et al.*, 2014). Over the past few years, protein encapsulation in metal organic framework (MOF) has been developed as a new potential application area of these materials. Other than encapsulation methods, conjugation and infiltration also were other methods used for stabilizing biomolecules by MOFs. The metal cluster of MOFs are also called as secondary building units (SBUs). There are variety of SBUs types in MOFs such as triangle, trigonal prism and octahedron. MOFs also can be made up by different types of organic linker either ditopic, tritopic, tetratopic, or multitopic linkers (Sharmin & Zafar, 2016). Currently, the most recent trend regarding the designation of metal cluster and linkers in MOFs are by using mixed linker and mixed metal cluster in the same structure of MOFs (Amarajothi *et al.*, 2016). This combination of linkers or metal clusters could result in MOF with a greater catalytic activity than single metal or single linker MOFs. MOFs have been widely studied over the past decade for a variation of potential applications such as catalysis (Howarth & Hupp, 2017), gas storage (Fracaroli *et al.*, 2014), drug delivery (Erucar & Keskin, 2016), agricultural (Rieth *et al.*, 2017; Jr *et al.*, 2018) and also in the water treatment (Kumar *et al.*, 2018).

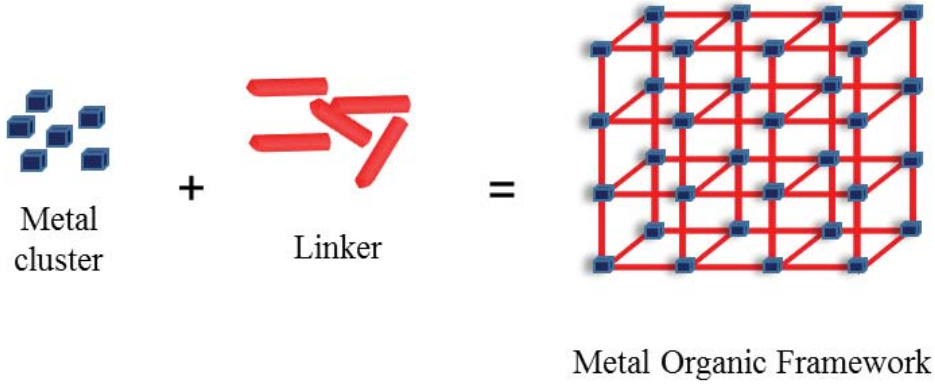

Figure 1.1: Schematic representation of a MOF system

MOFs are compounds that are made up by combinations of various metal ions connected by organic linker (Figure 1.1). One of the most interesting features of MOFs is the concept of the reticular chemistry in its design and synthesis. MOFs and covalent organic frameworks (COFs) are the established materials that used the concept of reticular chemistry. Isoreticular synthesis also provided a way to increase the pore apertures of MOFs, which allows for big molecules such as enzymes to enter the pore.

1.2 Problem Statement

MOFs have already shown their ability to increase the stability and performance of enzymes. Even at elevated temperatures and pressure, MOF can act as a protective layer, enabling the enzymes to retain their high activity (Li *et al.*, 2016). Although MOFs can improve the stability and performance of enzymes, the behavior and intermolecular interactions between MOFs and enzymes are not yet being fully understood. The encapsulation mechanism which stabilizes enzymes is important to be unveiled in order to further improve the biocatalyst composite. Such information can be the basis of modification for the current MOFs or as guidelines to design new MOFs for biocatalytic applications.

In some cases, the structures of the MOFs are too complicated to be solved experimentally (Liang *et al.*, 2015) thus computational methods are used to explore further the intermolecular interaction of the enzyme encapsulated in the MOFs. Specifically, this project examined a cutinase enzyme, encapsulated in IRMOF-74-VI (Figure 1.2) to test the effect of encapsulation towards the stability of the enzyme at different temperatures and solvent systems.

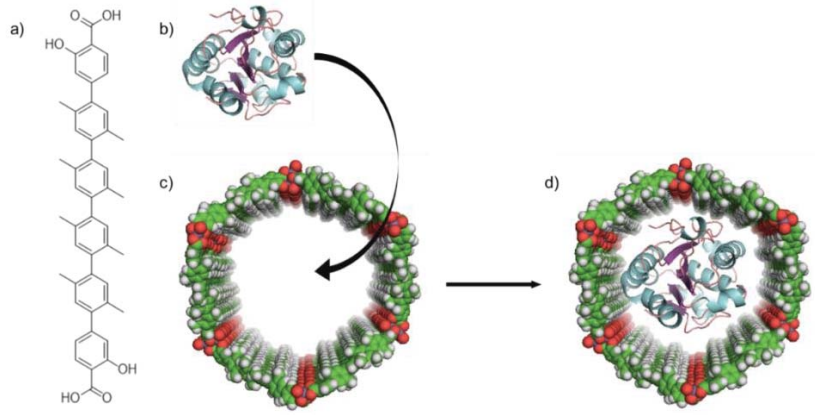

Figure 1.2: Graphical representation of cutinase encapsulation in IRMOF-74-VI. (a) 2,5-dioxidoterephthalate (DOT) as the organic linker, (b) cutinase, (c) IRMOF-74-VI and (d) cutinase-IRMOF-74-VI composite

1.3 Objectives

The main goal of this research is to determine the structural and dynamics properties of cutinase encapsulated in IRMOF-74-VI by using molecular dynamics simulation methods. Therefore, four specific objectives were pursued;

i) To model and parameterize the structure of IRMOF-74-VI for application in MD simulations,
ii) To determine the effect of encapsulation in IRMOF-74-VI towards the structural stability of cutinase at different temperatures,
iii) To elucidate the intermolecular interactions between IRMOF-74-VI and cutinase,
iv) To determine the effect of different solvent towards the structural stability of cutinase-IRMOF74-VI composite.

REFERENCES

Abdelnaby, M., Alloush, A.M., Qasem, N.A., Al-Maythalony, B.A., Mansour, R.B., Cordova, K.E., & Hamouz, O.C. (2018). Carbon dioxide capture in the presence of water by an amine-based crosslinked porous polymer. *Journal of Material Chemistry*. *A*, *6*, 6455–6462.

Armstrong, C. T., Mason, P. E., Anderson, J. L. R., & Dempsey, C. E. (2016). Arginine side chain interactions and the role of arginine as a gating charge carrier in voltage sensitive ion channels. *Nature*, *6*, 1–10.

Baldridge, K.K., Greenberg, J.P., Elbert, S., Mock, S., & Papadopoulos, P.M. (2002). QMView and GAMESS: Integration into the World Wide Computational Grid. *ACM/IEEE SC 2002 Conference (SC'02)*, 64-64.

Barde, N. P., Patil, S. D., Kokne, P. M., & Bardapurkar, P. P. (2015). Deriving time dependent Schrödinger equation from Wave-Mechanics , Schrödinger time independent equation, Classical and Hamilton-Jacobi equations. *Leonardo Electronic Journal of Practices and Technologies*, *26*, 31–48.

Borders, C. L., Broadwater, J. A., Bekeny, P. A., Salmon, J. E., Lee, A. E., Eldridge, A. M., & Pett, V. B. (1994). A structural role for arginine in proteins : Multiple hydrogen bonds to backbone carbonyl oxygens. *Protein Science*, *3*, 541-548.

Breneman, C. M., & Wiberg, K.B. (1990). Determining Atom-Centered Monopoles from Molecular Electrostatic Potentials . The Need for High Sampling Density in Formamide Conformational Analysis. *Journal of Computational Chemistry*, *11*, 361–373.

Brooks, B.R., Brooks, C.L., MacKerell, A.D., Nilsson, L., Petrella, R.J., Roux, B., Won, Y., Archontis, G., Bartels, C., Boresch, S., Caflisch, A., Caves, L.S., Cui, Q., Dinner, A.R., Feig, M., Fischer, S., Gao, J., Hodošček, M., Im, W., Kuczera, K., Lazaridis, T., Ma, J., Ovchinnikov, V., Paci, E., Pastor, R.W., Post, C.B., Pu, J., Schaefer, M., Tidor, B., Venable, R.M., Woodcock, H.L., Wu, X., Yang, W., York, D.M., & Karplus, M. (2009). CHARMM: The biomolecular simulation program. *Journal of computational chemistry*, *30*(10), 1545-614.

Bueno-pérez, R., García-pérez, E., & Gutiérrez-sevillano, J. J. (2010). A Simulation Study of Hydrogen in Metal – Organic Framework. *Adsorption Science & Technology*, *28*, 8–10.

Bussi, G., Donadio, D., & Parrinello, M. (2007). Canonical sampling through velocity rescaling. *Journal of Chemical Physics*, *126*, 1–7.

Butova, V. V, Soldatov, M. A., Guda, A. A., Lomachenko, K. A., & Lamberti, C. (2016). Related content Metal-organic frameworks : structure, properties, methods of synthesis and characterization. *Russian Chemical Review*, *85*(3), 280-307.

Carvalho, C. M. L., & Aires-barros, M. R. (1998). Cutinase structure, function and biocatalytic applications. *Electronic Journal of Biotechnology*, *1*(3), 1–14.

Chen, S., Su, L., Chen, J., & Wu, J. (2013). Cutinase: Characteristics, preparation, and application. *Biotechnoogy Advances*, *31*, 1754–1767.

Chen, Y., Han, S., Li, X., & Zhang, Z. (2014). Why Does Enzyme Not Leach from Metal − Organic Frameworks (MOFs)? Unveiling the Interactions between an Enzyme Molecule and a MOF. *American Chemical Society*, *53*, 10006–10008.

Christenholz, C. L., Obenchain, D. A., Peebles, R. A., & Peebles, S. A. (2014). Rotational Spectroscopic Studies of C − H ⋯ F Interactions in the Vinyl Fluoride ⋯ Di fluoromethane Complex. *Journal of Physical Chemistry A*, *118*, 1610−1616.

Davis, M. E. (2002). Ordered porous materials for emerging applications. *Nature*, *417*, 813–821.

DeLano, W. L. (2002). Pymol: An open-source molecular graphics tool. *CCP4 Newsletter on Protein Crystallography*, *40*, 82-92.

Delivery, G. (2017). Multiscale simulations reveal IRMOF-74-III as a potent drug carrier for gemcitabine delivery. *Journal of Materials Chemistry B*, *5*, 3277–3282.

Deng, H., Grunder, S., Cordova, K. E., Valente, C., Furukawa, H., Hmadeh, M., Gándara, F., Whalley, A. C., Liu, Z., Asahina, S., Kazumori, H., O'Keeffe, M., Terasaki, O., Stoddart, J. F., & Yaghi, O. M. (2012). Large-Pore Apertures in a Series. *Science*, *336*, 1018.

Duan, X., Liu, Y., You, X., Jiang, Z., Yang, S., & Yang, S. (2017). High-level expression and characterization of a novel cutinase from Malbranchea cinnamomea suitable for butyl butyrate production. *Biotechnology for Biofuels. Biotechnology for Biofuels*, *10*(223), 1–14.

Dubbeldam, D., Walton, K. S., Ellis, D. E., & Snurr, R. Q. (2007). Exceptional Negative Thermal Expansion in Isoreticular Metal – Organic Frameworks. *Angewandte Chemie International Edition*, *46*, 4496–4499.

Erucar, I., & Keskin, S. (2016). Efficient storage of drug and cosmetic molecules in bio-compatible MOFs : A molecular simulation study. *Industrial & Engineering Chemistry Research*, *55*(7), 1929-1939.

Essmann, U., Perera, L., Berkowitz, M. L., Darden, T., Lee, H., & Pedersen, L. G. (1995). A smooth particle mesh Ewald method. *Journal of Physical Chemistry*, *103*, 8577–8593.

Furukawa, H., Cordova, K.E., O'keeffe, M., & Yaghi, O.M. (2013). The chemistry and applications of metal-organic frameworks. *Science*, *341:6149*, 1230444.

Ferrario, V., Pellis, A., Cespugli, M., Guebitz, G.M., & Gardossi, L. (2016). Nature Inspired Solutions for Polymers: Will Cutinase Enzymes Make Polyesters and Polyamides Greener? *Catalysts*, *6*, 205.

Garberoglio, G. (2012). OBGMX: A web-based generator of GROMACS topologies for molecular and periodic systems using the universal force field. *Journal of computational chemistry*, *33*(27), 2204-8.

Grillo, M. E., Andzelm, J. W., Govind, N., Fitzgerald, G., & Stark, K. B. (2004). 10 Computational Materials Science with Materials Studio : Applications in Catalysis. *Computational Materials Science*, *221*, 207–208.

Gromiha, M. M., Santhosh, C., & Ahmad, S. (2004). Structural analysis of cation – π interactions in DNA binding proteins. *International Journal of Biological Macromolecules*, *34*, 203–211.

Groom, C. R., Bruno, I. J., Lightfoot, M. P., & Ward, S. C. (2016). The Cambridge Structural Database, *Acta Crystallographica Section B: Structural Science*, *72*(2), 171-179.

Heinig, M., & Frishman, D. (2004). STRIDE : a web server for secondary structure assignment from known atomic coordinates of proteins. *Nucleic Acids Research*, *32*, 500–502.

Hess, B. (2008). P-LINCS : A Parallel Linear Constraint Solver for Molecular Simulation. *Journal of Chemical Theory and Computation*, *4*, 116–122.

Howarth, A., & Hupp, J. (2017). Enzyme encapsulation in metal – organic frameworks for applications in catalysis. *19*, 4082–4091.

Hu, X., Gao, Z., Wang, Z., Su, T., Yang, L., & Li, P. (2016). Enzymatic degradation of poly (butylene succinate) by cutinase cloned from Fusarium solani. *Polymer Degradation Stability*, *134*, 211–219,

Hu, Z., & Jiang, J. A. (2016). Helical peptide confined in metal-organic frameworks: Microscopic insight from molecular simulation. *Microporous and Mesoporous Materials*, *232*, 138–142.

James, M., Murtola, T., Schulz, R., Smith, J. C., Hess, B., & Lindahl, E. (2015). GROMACS : High performance molecular simulations through multi-level parallelism from laptops to supercomputers. *SoftwareX*, *2*, 19–25.

Jelesarov, I., & Karshikoff, A. (2009). Defining the role of salt bridges in protein stability. *Methods Mol. Biol. 490*, 227-260.

Keskin, S., & Kizilel, S. (2011). Biomedical Applications of Metal Organic Frameworks. *Industrial & Engineering Chemistry Research*, *50*(4), 1799-1812.

Kotzabasaki, M., Galdadas, I., Tylianakis, E., Klontzas, E., Cournia, Z., & Froudakis, G. E. (2017). Multiscale simulations reveal IRMOF-74-III as a Potent Drug Carrier for gemcitabine delivery. *Journal of Materials Chemistry B*, *5*, 3277--3282.

Kumar, P., Bansal, V., Kim, K. H., & Kwon, E. E. (2018). Metal-organic frameworks (MOFs) as futuristic options for wastewater treatment. *Journal of Industrial and Engineering Chemistry*, *62*, 130–145.

Lee, S. H., Song, W. S., & Kim, H. R. (2009). Cutinase Treatment of Cotton Fabrics. *Fibers and Polymers*, *10*, 802–806.

Leng, X., Huang, H., Yin, X., Ni, J., Wang, W., Sai, N., & You, L. (2018). Zirconium-Porphyrin PCN-222 : pH-responsive Controlled Anticancer Drug Oridonin. *Evid Based Complement Alternat Med*, *2018*, 3249023. doi: 10.1155/2018/3249023.

Li, L., Vorobyov, I., & Allen, T.W. (2013). The different interactions of lysine and arginine side chains with lipid membranes. *The journal of physical chemistry. B, 117*(40), 11906-20.

Li, P., Modica, J. A., Howarth, A. L., Vargas, E. L., Moghadam, P. Z., Snurr, R. Q., Mrksich, M., Hupp, J. T., & Farha, O. K. (2016). Toward Design Rules for Enzyme Immobilization in Hierarchical Mesoporous Metal-Organic Frameworks. *Chem*, *1*, 154–169.

Lian, X., Fang, Y., Joseph, E., Wang, Q., Li, J., Banerjee, S., Lollar, C., Wang, X., & Zhou, H. Enzyme–MOF (metal–organic framework) composites. *Chemical Society Reviews*, *46*, 3386–3401 (2017).

Liang, K. Ricco, R., Doherty, C. M., Styles, M. J., Bell, S., Kirby, N., Mudie, S., Haylock, D., Hill, A. J., Doonan, C. J., & Falcaro, P. (2015). Biomimetic mineralization of metal-organic frameworks as protective coatings for biomacromolecules. *Nature Communications*, *6*, 1–8.

Longhi, S., Czjzek, M., Lamzin, V., Nicolas, A., Cambillau, C., & Aiguier, J. (1997). Atomic Resolution (1.0 A) Crystal Structure of Fusarium solaniCutinase: Stereochemical Analysis. *Journal of Molecular Biology*, *268*, 779-799.

Maiangwa, J., Ali, M.S., Salleh, A.B., Rahman, R.N., Normi, Y.M., Shariff, F.M., & Leow, T.C. (2017). Lid opening and conformational stability of T1 Lipase is mediated by increasing chain length polar solvents. *PeerJ*. DOI 10.7717/peerj.3341

Malde, A.K., Zuo, L., Breeze, M.L., Stroet, M., Poger, D., Nair, P.N., Oostenbrink, C., & Mark, A.E. (2011). An Automated Force Field Topology Builder (ATB) and Repository: Version 1.0. *Journal of chemical theory and computation, 7*(12), 4026-37.

Margreitter, C., Petrov, D., & Zagrovic, B. (2013). Vienna-PTM web server : a toolkit for MD simulations of protein post-translational modifications. *Nucleic Acids Research*, *41*, 422–426.

Mark P., & Nilsson, L. (2001). Structure and Dynamics of the TIP3P , SPC , and SPC / E Water Models at 298 K. *Journal of Physical Chemistry A, 105*, 9954–9960.

Martínez, L., Andrade, R., Birgin, E. G., & Martínez, J. M. (2009). Software News and Update Packmol : A Package for Building Initial Configurations. *Journal of Computational Chemistry, 30*(13), 2157-2164.

Matak, M. Y., & Moghaddam, M. E. (2009). The role of short-range Cys171 – Cys178 disulfide bond in maintaining cutinase active site integrity : A molecular dynamics

simulation. *Biochemical and Biophysical Research Communications, 390,* 201–204.

Mateo, C., Palomo, J. M., Fernandez-lorente, G., Guisan, J. M., & Fernandez-lafuente, R. (2007). Improvement of enzyme activity, stability and selectivity via immobilization techniques. *Enzyme and Microbial, 40*, 1451–1463.

Miller, D. L. (1979). Prevention of Fungal Infection of Plants by Specific Inhibition of Cutinase A Relationship Between DNA Helix Stability and Recognition Sites for RNA Polymerase, *Science, 205*, 0–1.

Mu, W., Liu, D., Yang, Q., & Zhong, C. (2010). Microporous and Mesoporous Materials Computational study of the effect of organic linkers on natural gas upgrading in metal – organic frameworks. *Microporous and Mesoporous Materials, 130(1–3)*, 76–82.

Nikolaivits, E., Makris, G., & Topakas, E. Immobilization of a Cutinase from Fusarium oxysporum and Application in Pineapple Flavor Synthesis. (2017). *Journal of Agricultural and Food Chemistry, 65*, 3505−351.

Ougherty, D. E. A. D. (1999). Caution - π interactions in structural biology. *Proceedings of the National Academy of Sciences of the United States of America*, *96*, 9459–9464.

Phillips, J. C., Braun, R., Wang, W. E. I., Gumbart, J., Tajkhorshid, E., Villa, E., & Poincare, H. (2005). Scalable Molecular Dynamics with NAMD. *Journal of Computational Chemistry, 26*(16), 1781-1801.

Ping, L. F., Chen, X. Y., Yuan, X. L., Zhang, M., Chai, Y. J., & Shan, S. D. (2017). Application and comparison in biosynthesis and biodegradation by Fusarium solani and Aspergillus fumigatus cutinases. *International Journal of Biological Macromolecules. 104*, 1238–1245.

Plimpton, S. (1995). Fast Parallel Algorithms for Short – Range Molecular Dynamics. *Journal of Computational Physics, 117*, 1–42.

Press, P. (1977). Biological Significance of Methylated Derivatives of Lysine. *Life Sciences, 20*, 385-392.

Reilly, E. O., & Turner, N. J. (2015). Enzymatic cascades for the regio- and stereoselective synthesis of chiral amines. *Perspectives in Science, 4*, 55–61.

Rieth, A. J. (2017). Moisture Farming with Metal-Organic Frameworks. *Chem, 2*, 751–759.

Ruiter, M.V., Mejia-Ariza, R., Cornelissen, J.J., & Huskens, J. (2016). Hierarchical Pore Structures as Highways for Enzymes and Substrates. *Chem, 1(1)*, 29–31.

Salomon-ferrer, R., Case, D. A., & Walker, R. C. (2012). An overview of the Amber biomolecular simulation package. *Focus article, 00*, 1–13.

Sanchez, C., Shea, K. J., & Kitagawa, S. (2011). Hybrid materials themed issue.

Chemical Society Reviews, *40*, 926–940.

Schleich, W. P., Greenberger, D. M., Kobe, D. H., & Scully, M. O. (2013). Schrödinger equation revisited. *PNAS*, *110*, 10–15.

Siu, S. W. I., Pluhackova, K., & Bo, R. A. (2012). Optimization of the OPLS-AA Force Field for Long Hydrocarbons. *Journal of Chemical Theory and Computation*, *8*, 1459−1470

Sokalingam, S., Madan, B., Raghunathan, G., & Lee, S. (2013). In silico Study on the Effect of Surface Lysines and Arginines on the Electrostatic Interactions and Protein Stability. *Biotechnology and Bioprocess Engineering*, *26*, 18–26.

Song, X., Wang, S., Hao, C., & Qiu, J. (2014). Investigation of SO 2 gas adsorption in metal – organic frameworks by molecular simulation. *INOCHE*, *46*, 277–281.

Strub, C., Alies, C., Lougarre, A., Ladurantie, C., Czaplicki, J., & Fournier, D. (2004). Mutation of exposed hydrophobic amino acids to arginine to increase protein stability. *BMC Biochemistry 6*, 1–6.

Su, L., Chen, S., Yi, L., Woodard, R. W., Chen, J., & Wu, J. (2012). Extracellular overexpression of recombinant Thermobifida fusca cutinase by alpha-hemolysin secretion system in E.coli BL21 (DE3). *Microbial Cell Factories*, *11*, 8-14.

Sulaiman, S., Yamato, S., Kanaya, E., Kim, J., Koga, Y., Takano, K., & Kanaya, S. (2012). Isolation of a novel cutinase homolog with polyethylene terephthalate-degrading activity from leaf-branch compost by using a metagenomic approach. *Applied and environmental microbiology*, *78*(5), 1556-62 .

Svozil, D., Sponer, J., Iii, T. E. C., Laughton, C. A., & Orozco, M. (2007). Refinement of the AMBER Force Field for Nucleic Acids : Improving the Description of a / g Conformers. *Biophysical Journal*, *92(11)*, 3817–3829

Tatb, H. (2011). Novel MOFs with tetrahedral cavity assembled from. *INOCHE*, *14(4*), 601–605.

Thumarat, U., & Nakamura, R. (2012). Biochemical and genetic analysis of a cutinase-type polyesterase from a thermophilic Thermobifida alba AHK119. *Application Microbiol Biotechnololy*, *95*, 419–430.

Turner PJ. XMGRACE, Version 5.1.19. (2005) Center for Coastal and Land-Margin Research, Oregon Graduate Institute of Science and Technology, Beaverton.

Usman, K.A., Buenviaje, S.C., Edañol, Y.D., Conato, M.T., & Payawan, L.M. (2018). Facile Fabrication of a Potential Slow-Release Fertilizer Based on Oxalate-Phosphate-Amine Metal-Organic Frameworks (OPA-MOFs). *Materials Science*, *936*, 14-19.

Vanommeslaeghe, K., Hatcher, E., Acharya, C., Kundu, S., Zhong, S., Shim, J., & Darian, E. (2009). CHARMM General Force Field : A Force Field for Drug-Like Molecules Compatible with the CHARMM All-Atom Additive Biological Force Fields. *Journal of Computational Chemistry*, *31*(4), 671-690.

Velde, G. T. E., Bickelhaupt, F. M., Baerends, E. J., Guerra, C. F., & Gisbergen, S. J. A. V. A. N. (2001). Chemistry with ADF. *Journal of Computational Chemistry*, *22*(9), 931–967.

Wang, Y., He, M., Gao, X., Zhang, Y., Zhong, H., & Long, P. (2018). Two NbO-type MOFs based on linear and zigzag diisophthalate ligands : exploring the effect of ligand-originated MOF isomerization on gas adsorption properties. *Inorganic Chemistry Frontier, 5*, 2811-2817.

Wong-Ng, W., Culp, J.T., & Chen, Y. (2016). Crystallography of Representative MOFs Based on Pillared Cyanonickelate (PICNIC) Architecture. *Crystals 2016, 6*, 108; doi:10.3390/cryst6090108

Wu, X., Yang, C., & Ge, J. (2017). Green synthesis of enzyme / metal - organic framework composites with high stability in protein denaturing solvents. *Bioresources Bioprocess*, *4*(24), 0–7.

Xu, J., Jiang, M., Sun, H., & He, B. (2010). An organic solvent-stable protease from organic solvent-tolerant Bacillus cereus WQ9-2: purification, biochemical properties, and potential application in peptide synthesis. *Bioresource technology*, *101*(20), 7991-4.

Zhang, H., Lv, Y., Tan, T., & Van Der Spoel, D. (2016). Atomistic Simulation of Protein Encapsulation in Metal-Organic Frameworks. *Journal of Physical Chemistry B*, *120*(3), 477–484.

Zhang, L., Liand, F., & Luo, L. (2018). Preparation Methods of Metal Organic Frameworks and Their Capture of Preparation Methods of Metal Organic Frameworks and Their Capture of CO_2. *IOP Conf. Series: Earth and Environmental Science*, *108*, 042104. doi:10.1088/1755-1315/108/4/042104