OPTICAL, OPTOMECHANICAL AND DENSITY FUNCTIONAL THEORY MODELLING INVESTIGATION OF CALIXARENE LANGMUIR-BLODGETT THIN FILM FOR DRUG ENCAPSULATION

NUR FARAH NADIA BINTI ABD KARIM

SULTAN IDRIS EDUCATION UNIVERSITY

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NUR FARAH NADIA BINTI ABD KARIM

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Nur Farah Nadia Binti Abd Karim
2024

ABSTRACT

The research aim is to create a calixarene-based nanosensor targeting para-aminobenzoic acid (PABA) using Langmuir-Blodgett (LB) method. The properties of the LB film were assessed. The optical and optomechanical characteristics were examined with ultraviolet visible (UV-vis) spectroscopy and optical tweezers (OT). The host-guest binding energy was calculated using DFT method. Calix[4]arene (C4) and calix[8]arene (C8) solutions with concentration of 0.47 mM and 0.23 mM respectively, were prepared and different PABA concentrations (0.01 to 0.71 mM) was used to study the interactions. The thin films were optically analysed at wavelength of 250 to 400 nm. Microclusters with radii of 0.5-1.5 μm were optically trapped at various power density (0.23 to 2.49 MW/cm2). Complex's binding energy were calculated using optimisation calculation. C4 and C8 monolayers effectively trapped PABA, resulting in 1:1 and 1:2 stoichiometry ratios. C8 was significantly more sensitive towards PABA, detecting even at 0.01 mM concentration while C4 was more stable owning to its higher collapse pressure, 60 mN/m. Both complex monolayers showed highest absorbance at 0.47 mM, aligning with Langmuir studies. C4-PABA's band gap (4.0001 eV) is smaller than C4's (4.0259 eV), and C8-PABA's (4.2155 eV) is slightly smaller than C8's (4.2205 eV) suggesting a potential interaction between the host and guest. OT effectively captured and differentiated between the host and host-guest microclusters, utilising the corner frequency, f_c. The DFT method shows that C8 encapsulates PABA better than C4, as C8-PABA's binding energy (-0.05031 Ry) is higher than that of C4-PABA (-0.00839 Ry). The DFT method shows that C8 encapsulates PABA better than C4, as C8-PABA's binding energy (-0.05031 Ry) is higher than that of C4-PABA (-0.00839 Ry). The band gap from the DFT aligns with the Tauc plot, indicating that C8-PABA (2.6208 eV) is more thermodynamically stable than C4-PABA (2.4327 eV) due to its higher band gap. The calixarene nanosensor for PABA was developed using the LB method and the incorporation of PABA was confirmed. This research could lead to the development of PABA nanosensors that lessen PABA's skin impacts in medical and pharmaceutical applications.

OPTIK, OPTOMEKANIK DAN MODEL TEORI FUNGSIAN KETUMPATAN FILEM NIPIS LANGMUIR-BLODGETT KALIKSARENA UNTUK MEMERANGKAP DADAH

ABSTRAK

Kajian ini bertujuan untuk membangun pengesan nano bagi memerangkap asid paara-aminobenzoik (PABA) menggunakan teknik Langmuir-Blodgett (LB). Sifat-sifat filem nipis LB dikaji. Sifat- sifat optikal dan optomekanikal dianalisis menggunakan spektroskopi ultraviolet (UV-Vis) and pengepit optik (OT). Tenaga pengikat bagi kompleks perumah-tetamu dikira menggunakan teori fungsian ketumpatan (DFT). Larutan kaliks[4]arena (C4) and kaliks[8]arena (C8) dengan kepekatan 0.47 mM dan 0.23 mM disediakan. Pelbagai kepekatan PABA (0.01 ke 0.71 mM) disediakan untuk mengkaji interaksi. Sifat optik filem nipis dianalisis di panjang gelombang antara 200 ke 400 nm. Mikrogugusan dalam radius antara 0.5 dan 1.5 μm diperangkap secara optik dipelbagai ketumpatan kuasa (0.23 ke 2.49 MW/cm2). Tenaga pengikat kompleks dikira melalui pengiraan optimum. Monolapisan C4, C8, berkesan memerangkap PABA, menghasilkan nisbah stoikiometri 1:1 dan 1:2. C8 sangat sensitif terhadap PABA, mengesan walaupun pada kepekatan 0.01 mM tetapi monolapisan C4 lebih stabil dengan tekanan runtuhnya yang lebih tinggi, 60 mN/m. Kedua-dua kompleks monolapisan menunjukkan penyerapan tertinggi pada kepekatan 0.47 mM, sejajar dengan kajian Langmuir. Jurang jalur C4-PABA (4.0001 eV) adalah lebih kecil daripada C4 (4.0259 eV), dan C8-PABA (4.2155 eV) lebih kecil sedikit daripada C8 (4.2205 eV) menunjukkan potensi interaksi antara perumah dan tetamu. OT secara berkesan menangkap dan membezakan antara mikrokluster perumah dan perumah-tetamu, menggunakan frekuansi pepenjuru,f_c. Kaedah DFT menunjukkan bahawa C8 merangkum PABA lebih baik daripada C4, kerana tenaga pengikat C8-PABA (-0.05031 Ry) lebih tinggi daripada C4-PABA (-0.00839 Ry). Jurang jalur dari DFT sejajar dengan plot Tauc, menunjukkan bahawa C8-PABA (2.6208 eV) lebih stabil secara termodinamik berbanding C4-PABA (2.4327 eV) disebabkan jurang jalurnya yang lebih tinggi. Nanosensor calixarene untuk PABA telah dibangunkan menggunakan kaedah LB dan penggabungan PABA telah disahkan. Penyelidikan membawa kepada pembangunan nanosensor PABA yang boleh mengurangkan kesan PABA ke atas kulit dalam aplikasian di dalam bidang perubatan dan farmaseutikal.

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LIST OF SYMBOLS

A	Area
A_0	Mean Molecular Area
B_0	Bulk modulus
B_1	First derivative of bulk modulus with respect to the pressure
c	Concentration
E	Energy
E_0	Equilibrium Energy
E_c	Correlation Energy
E_x	Exchange energy
E_{xc}	Exchange correlation energy
F	Force
F_g	gradient force
F_s	scattering force
I	Intensity of transmitted light
I_0	Intensity of the incident light
k_T	optical stiffness
k	Spring constant
l	length or path of light travel
l_x	lengths in *x* plane
l_y	lengths in *y* plane
n_m	Refractive index of medium

n_p	Refractive index of particle
P	laser power density
r	Molecular Radius
r^*	effective radius
T_0	Kinetic energy of a non-interacting electron in the Hartree approximation
V_0	Equilibrium Volume
V_{eff}	Effective potential
V_H	Hartree potential
V_{xc}	Exchange correlation potential
W	Laser power
α	Absorption coefficient
c	Speed of light
d	Laser beam diameter
f_c	corner frequency
h	Plank's constant
ρ_{in}	Initial electron density
ρ_{out}	Output electron density
υ	Frequency
x	Displacement
ΔE	Binding energy
ΔP	Change in momentum
ΔV	Surface potential
ΔV-A	Surface potential area
ΔV_{max}	Maximum Surface Potential

ε	molar extinction coefficient
ε_0	vacuum permittivity
ε_r	relative permittivity
$\mu_\perp$	Effective Dipole Moment
$\mu_{\perp max}$	Maximum Effective Dipole Moment
γ	Surface pressure of water
γ_o	Surface pressure of water with the presence of research material
Π	Surface pressure
Π-A	Surface pressure area
η	fluid viscosity
λ	Wavelength

LIST OF ABBREVIATIONS

0D	Zero-Dimensional
1D	One-Dimensional
2D	Two-Dimensional
3D	Three-Dimensional
ASCII	American Standard Code for Information Interchange
BFGS	The Broyden-Fletcher-Goldfarb-Shanno
BS	Boltzmann Statistics
C4	Calix[4]Arene
C6HCA	Calix[6]Arene Hexacarboxylic Acid
C8	Calix[8]Arene
C8OCA	Calix[8]Arene Octo-Carboxylic Acid
CCDC	Cambridge Crystallographic Data Centre
CHCl3	Chloroform
CIF	Crystallographic Information File
CPM	Curcumin-Loaded Phosphorylated Amphiphilic Calixarene
CVD	Chemical Vapour Deposition
DFT	Density Functional Theory
DI	Deionised
DNA	Deoxyribonucleic Acid
DOS	The Density of State

EOS	Birch-Murnaghan Equation of State
ET	Equipartition Theorem
EV-GGA	Engel Vosko Generalized Gradient Approximation
FDA	Food And Drug Administration
G	Gaseous
GGA	Generalised Gradient Approximation
GGA-PBE	Generalized-Gradient-Approximation with Perdew-Berke-Erzndof Parametrizations
GUI	Graphical User Interface
HDMS	1,1,1,3,3,3-Hexamethyldisilazane
HK	Hohenberg-Kohn
IUPAC	The International Union of Pure and Applied Chemistry
JRE	The Java Runtime Environment
L	Liquid
L1	Liquid-Expanded
L2	Liquid-Condensed
LB	Langmuir-Blodgett
LDA	Local Density Approximation
MBE	Molecular Beam Epitaxy
NA	Numerical Aperture
OSCal	Optical Stiffness Calculator
OT	Optical Tweezers
OTC	Over The Counter
PABA	Para-Amino Benzoic Acid
PBE	Perdew, Burke, and Ernzherh

PBEsol	Perdew, Burke, And Ernzherh Generalized Gradient Approximation for Solids and Surfaces
PDOS	Partial Density of States
PSD	Power Spectrum Density
PTX	Paclitaxel
PVD	Physical Vapour Deposition
QE	Quantum Espresso
QM	Quantum Mechanical
QPD	The Quadrant Photodiode
S	Solid
SAMs	Self-Assembled Monolayers
SCF	Self-Consistent Field
SPOT	Surface Potential Sensor
TDOS	Total Density of States
TMZ	Temozolomide
TNBC	Triple-Negative Breast Cancer
USB	Universal Serial Bus
USPP	Ultrasoft Pseudopotentials
UV	Ultraviolet
UV-Vis	Ultraviolet-Visible
WD	Walking Distance

CHAPTER 1

INTRODUCTION

1.1 Introduction

Nanotechnology is a multidisciplinary scientific field-leading today. It is a unique convergence of knowledge from various disciplines such as physics, chemistry, biology, medicine, informatics, and engineering. The primary focus of this field is to observe, measure, manipulate, assemble, control, and produce matter at an incredibly small scale (Kumar et al., 2020; Bayda et al., 2019; Hornyak et al., 2018). This burgeoning field is making significant advances for humanity, from medicine to computing, energy production to material science and the possibilities are limitless (Madkour, 2019).

Over the past decade, the field of nanotechnology has seen extensive research and has made significant strides in the realm of human health. It has been successfully

integrated into various biomedical applications, such as bio-detection, drug delivery, and notably in cancer-related areas, where it has been used for diagnostic imaging and treatment. Furthermore, the advancements in nanotechnology have led to the development of nanomaterials with unique properties and functionalities. These novel nanomaterials have found applications in a wide range of fields. They have contributed to improvements in medical and healthcare sectors (Genwa & Kumar, 2019), played a role in the electrical and electronics industry (Lu et al., 2016), enhanced sensing technology (Mustafa & Andreescu, 2020), and even found their way into cosmetics (Effiong et al., 2019). The revolution of nanotechnology continues to impact numerous other fields, demonstrating its vast potential and versatility.

Nanomaterials have become well-known in technology advancement due to their ability to be tuned and adjusted in terms of physical, chemical, and biological properties. It also performs phenomenally over bulk-size material due to the high surface area per volume ratio. Surface properties have a significant impact on the material's structure (Vatankhah et al., 2015) and result in a transition from chemically inert matter to highly reactive material (Lowry et al., 2014), affecting its strength and electrical properties (Jeevanandam et al., 2018). Moreover, nanomaterials often exhibit unexpected visual properties. This is because they are of a size that allows them to confine their electrons, leading to the manifestation of quantum effects. These quantum effects play a dominant role in determining the behavior of the material, significantly influencing the optical, electrical, and magnetic properties of the materials.

Materials at the submicron scale can be categorized based on their dimensions into zero-dimensional (0D), one-dimensional (1D), two-dimensional (2D), or three-dimensional (3D) structures (Abd Karim, 2019). In the case of 0D nanostructures, such as quantum dots and nanoparticles, all directions are confined to nanoscale dimensions. However, in 1D nanostructures (nanotubes and nanowires), the material has one growth direction: significantly faster than another two directions. Conversely, 2D nanostructures which include nanosheets and self-assembled monolayers have two fast growth directions, and only one direction is limited to nanoscale dimensions. Figure 1.1 displays examples of nanomaterials in different sizes. These nanoscale matters are not just another step in the materials' miniaturization but require different production approaches.

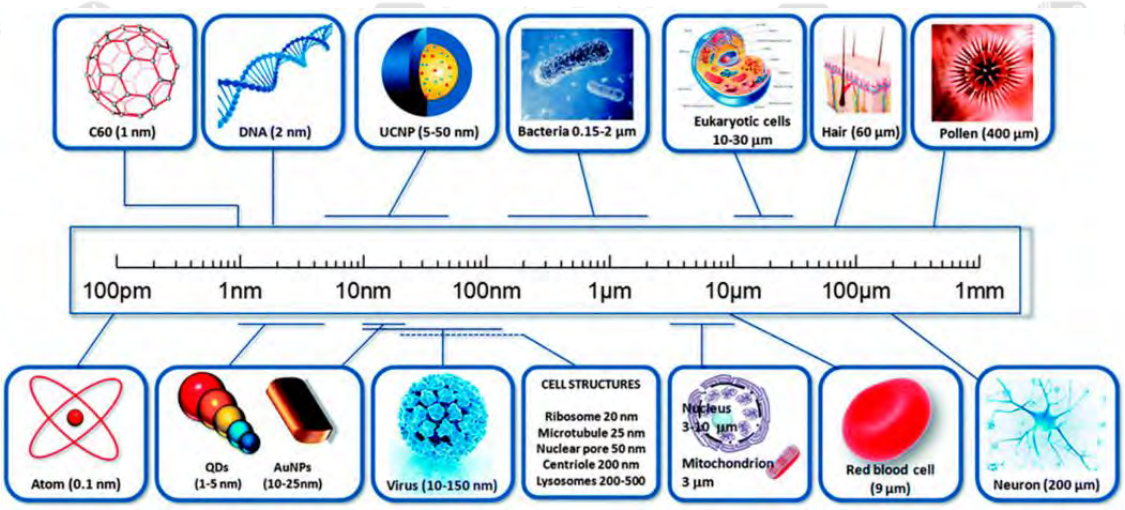


Figure 1.1. A comparison of various nanomaterial sizes. Adapted from Badya et al., 2020

The development of methodologies, techniques, tools, and instruments to examine and work with the matter at scales ranging from the tiniest atomic to the largest macromolecular greatly benefited nanomaterials and nanotechnology research. A Nobel winner, Dr. Richard Feynman, gave the first talk about nanotechnology

during the American Physical Society's annual meeting in 1959 at Caltech, entitled "There's Plenty of Room at the Bottom" (Feynman, 1959). He had prophesied the unfathomable brilliance this discipline would achieve as the law of nature does not restrict the ability to work at even the atomic and molecular. He also vividly explained the potential for developing small, delicate tools that could be used to manufacture and modify objects at the nanoscale or even smaller (Feynman, 1992). The concept of modern technology was thus planted and he is frequently regarded as the father of modern nanotechnology (Bayda et al., 2019). Dr. Feynman's proposed method is known as a top-down approach in modern technology; it complements the bottom-up method, which has been widely used in recent years.

Generally, there are two basic approaches to fabricating nanomaterials: top-down and bottom-up (Arole & Munde, 2014; Iqbal et al., 2012; Vaseghi & Nematollahzadeh, 2020). Both methods can be performed in gas, liquid, supercritical fluids, solid states, or even vacuum. The synthesized nanoparticles' properties and structure can be designed depending on the experimental condition employed. The synthesis of nanoparticles allows the particle size, shape and geometry, size distribution, composition, and degree of agglomeration to be controlled. Hence, these parameters create the nanomaterials' new physical and chemical properties for different applications (Habiba et al., 2014).

Top-down methods begin with large-scale materials that are broken down into smaller, nanoscale pieces through mechanical, chemical, or other forms of energy, such as laser irradiation. This process typically results in smaller flakes or particles with a range of sizes (Habiba et al., 2014; Lim, 2020). Conversely, the bottom-up

approach involves creating materials from atomic or molecular species through chemical reactions, allowing precursor particles to increase in size. The precursor is usually a liquid or gas that is ionized, dissociated, sublimated, or evaporated, and then condensed to form amorphous or crystalline nanoparticles.

In other words, the bottom-up approach is where the atoms or molecules continue to build up, forming significant structures (Lim, 2020). This method technically produces nanoparticles with fewer defects and contamination, homogeneous chemical composition and narrow size distribution. In addition, this approach is more straightforward and precise to fabricate nanoparticles less than 100 nm, whereas the top-down approach is preferable for synthesizing nanoparticles larger than 100 nm (Habiba et al., 2014). Figure 1.2 displays both approaches in carbon-based nanomaterial production.

Each approach, both top-down and bottom-up, has its own advantages and disadvantages. The top-down method has been instrumental in the creation of numerous synthetic nanomaterials, particularly in today's semiconductor industry. However, it is starting to reach the limits of how much it can miniaturize (Iqbal et al., 2012). In addition, it has several drawbacks, such as the creation of imperfect surfaces in the materials processed, the high cost of production in lithographic processes, the need for materials with a high surface finish, and extended etching times (Kumar et al., 2018). These surface imperfections can have a significant impact on the physical and surface properties of the nanostructure due to the large surface-to-volume ratio of the nanostructure (Lim, 2020).

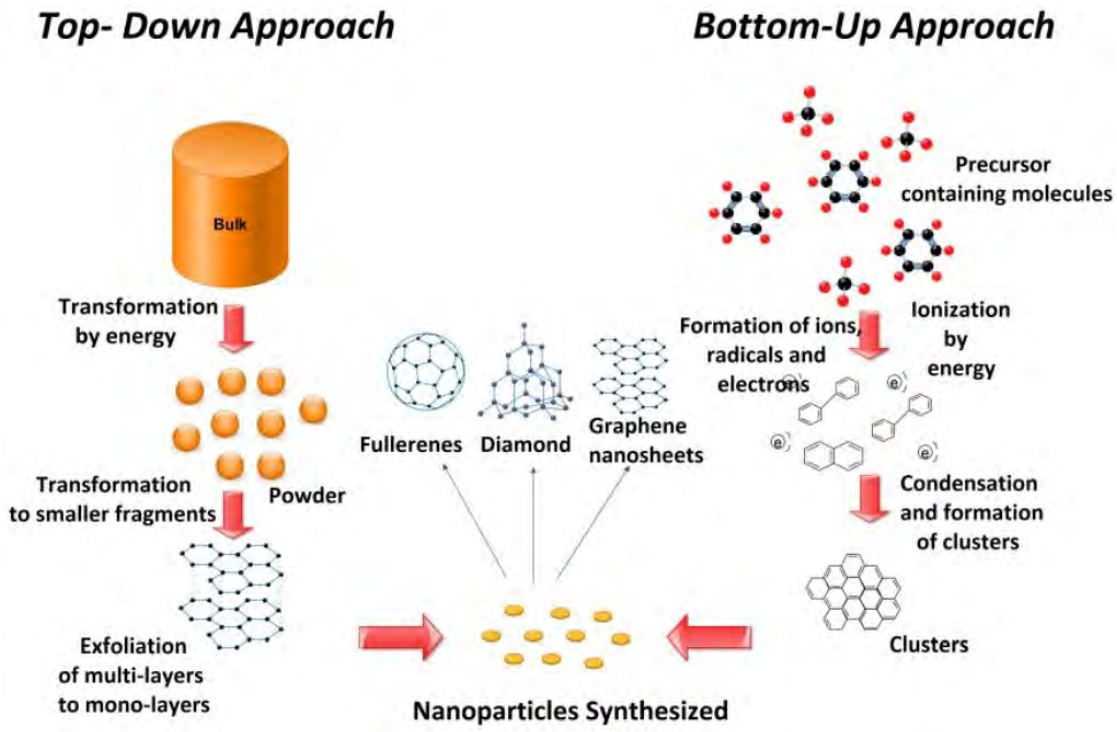


Figure 1.2. Bottom-up and top-down approaches in synthesizing carbon-based nanomaterials. Adapted from Habiba et al., 2014

Conversely, the bottom-up method is generally preferred by researchers. This approach is more practical and involves a specific chemical reaction between atoms or molecules as intermolecular interactions occur (Johal & Johnson, 2018). Furthermore, the evolution of this method is fueled by scientists' fascination with how biological structures are preprogrammed to self-assemble and self-organize through supramolecular interactions such as hydrogen bonding, van der Waals forces, electrostatic interactions, π–π interactions, and more. Supramolecular chemistry provides an intriguing tool that merges the concepts of self-assembly and molecular recognition (Iqbal et al., 2012). In addition, compared to the top-down approach, the bottom-up method can produce nanostructures with fewer defects and contaminations (Goyal, 2017).

Nanostructures can be fabricated using a variety of methods, which can be broadly categorized into top-down and bottom-up approaches. The top-down approach typically involves lithography processes, such as photolithography, soft lithography and scanning probe lithography (Vaseghi & Nematollahzadeh, 2020; Kumar et al., 2018; Iqbal et al., 2012). On the other hand, the bottom-up approach entails designing structures at the atomic or molecular level through covalent or supramolecular interactions (Iqbal et al., 2012). This approach primarily employs two methods. The first method is gas-phase syntheses, which include techniques such as plasma arching, chemical vapour deposition (CVD), and molecular beam epitaxy (MBE). The second method involves liquid phase formation techniques, such as the sol-gel method, wet synthesis, and self-assembly processes (Kumar et al., 2018).

Self-assembly is a process where atoms and molecules spontaneously interact and assemble into a stable, well-defined nano or microstructure through non-covalent bonds. The properties of the building blocks can be tailored to control the process of self-assembly and the characterization of surface patterns, such as shape and function (Kumar et al., 2018; Chen et al., 2007). This process is capable of producing a nanostructure ranging from 1 to 100 nm in size. However, when forming complex nanostructures using self-assembly, it is important to consider critical parameters like the well-defined geometry and the specific interactions between the basic units (Kumar et al., 2018). One technique that utilizes ordered molecular assemblies is the formation of Langmuir-Blodgett (LB) films.

The LB technique is a well-established method for the careful control of supramolecular structure formation in organized molecular assemblies (Oliveira Jr et

al., 2022). It has potential applications in a variety of fields, including sensors (Baratto et al., 2020), detectors (Çapan, 2019), surface coatings (de Faria et al., 2018), molecular electronic devices (Ariga, 2020) and many more. One of the main advantages of LB deposition is its ability to perfectly organize molecular arrangements, creating a thin film at the air-water interface that is maintained during the transfer process to the substrate. This can be achieved by optimizing all parameters (Hussain et al., 2018). The advantages of fabricating thin films via LB methods are as below:

- Ability to control the structure of the film and the thickness of the monolayer at the molecular level.
- Capability to uniformly and homogeneously deposit the monolayer across large areas.
- Potential to design multilayer structures with diverse layer compositions.
- Possibility to assemble individual molecules into 2D and 3D systems.
- Creation of heterostructure multilayer films composed of various molecules.
- Flexibility to deposit a monolayer on nearly any type of solid support.

The LB technique enhances sensor development by enabling surface-based sensing, paving the way for new functional sensing devices (Wales & Kitchen, 2016). This method involves the self-assembly of amphiphilic molecules into an organized monolayer, known as Langmuir films, at the air-water interface. These films are then vertically transferred to a solid substrate, resulting in LB thin films (Oliveira et al., 2022; Wales & Kitchen, 2016). Figure 1.3 illustrates the process of creating LB thin

films. A comprehensive explanation of Langmuir and LB thin films formation is provided in Chapter 2.

The LB technique is a promising approach in the formation of thin films and excels in depositing self-assembled monolayers onto solid surfaces. It enables precise control over the thickness of the monolayer and provides uniform monolayer deposition over a relatively large area. Unlike traditional self-assembled monolayers (SAMs), the film with multiple layers or even with different compositions can be successfully achieved by consecutive dipping (Wales & Kitchen, 2016). Furthermore, Langmuir and LB films are widely used as mimetic systems and are often considered good models for examining cellular membrane processes (Fernández et al., 2021).

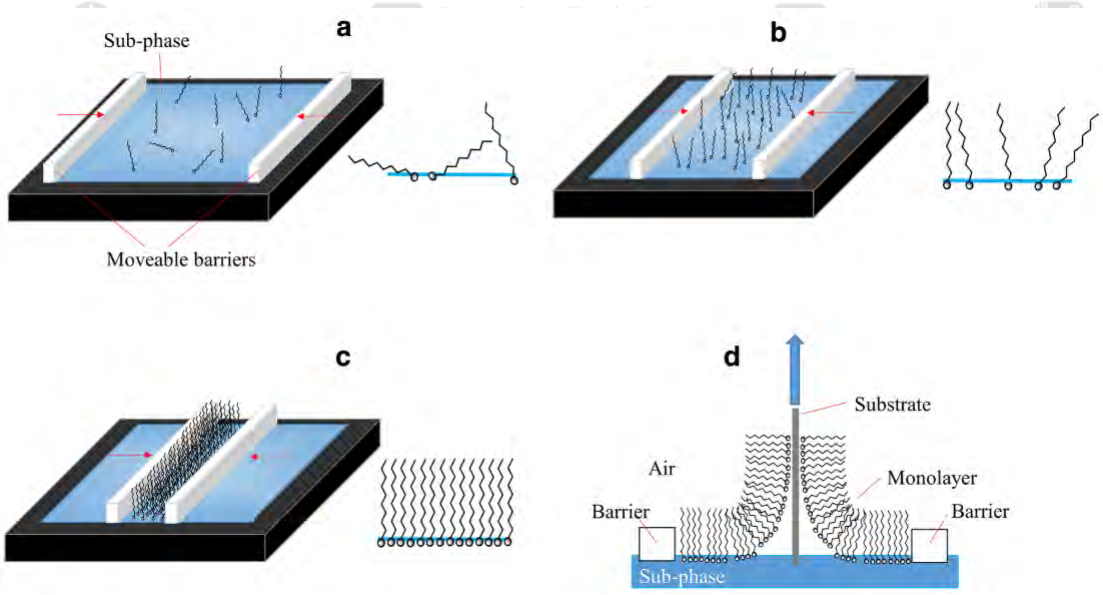


Figure 1.3. Schematic diagram of the LB thin films formation. (a) The spread amphiphilic on the Langmuir trough results in a 2D gaseous arrangement. (b) The surface area is reduced as both barriers move toward the molecules, causing molecular interaction. (c) The amphiphilic are self-assembled and form a monolayer as the compression goes on. (d) The thin film monolayer was vertically transferred onto a substrate. Adapted from Wales & Kitchen, 2016

As new nanomaterials and nanotechnology techniques emerge, the potential to develop nanosensors has garnered increased interest from researchers focused on the sensor revolution. Nanosensors are sensing devices that detect physical and chemical changes, monitor biomolecules and biochemical alterations in cells, and measure toxic and polluting substances in industry and the environment. According to Khanna, a sensor is classified as a nanosensor if it meets one of the following criteria: the sensor is of nanosize, the sensor's sensitivity is at the nanoscale, or the distance between the sensor and the object in space is measured in nanometers (Khanna, 2016).

The reduction in sensor size can yield several benefits. These include exceptional selectivity, especially when using nanomaterials, small, portable devices that can be transported anywhere, rapid response times with increased sensitivity, low manufacturing costs, the capability to detect multiple analytes simultaneously, and minimal sample preparation or pretreatment procedures, as depicted in Figure 1.4. Therefore, constructing a nanosensor from nanomaterials using a bottom-up approach like the LB technique can result in a well-structured, compact, and uniformly arranged sensor.

The advancement of nanosensors has been facilitated by the diversification of nanomaterial production processes and the exploitation of their unique properties. Examples of nanostructured materials used in nanosensor manufacturing include nanoscale wire, carbon nanotubes, thin films, and polymer nanomaterials (Abdel-Karim et al., 2020). These nanomaterials are then employed in nanosensor development to enhance sensitivity by improving their catalytic activity, conductivity, and biocompatibility (Kaya et al., 2019). Mohd Azmi (2020) claims that calixarene is

the most promising supramolecule for use in nanosensors because of its unique host-guest properties, which make it a great sensing element (Mohd Azmi et al, 2020).

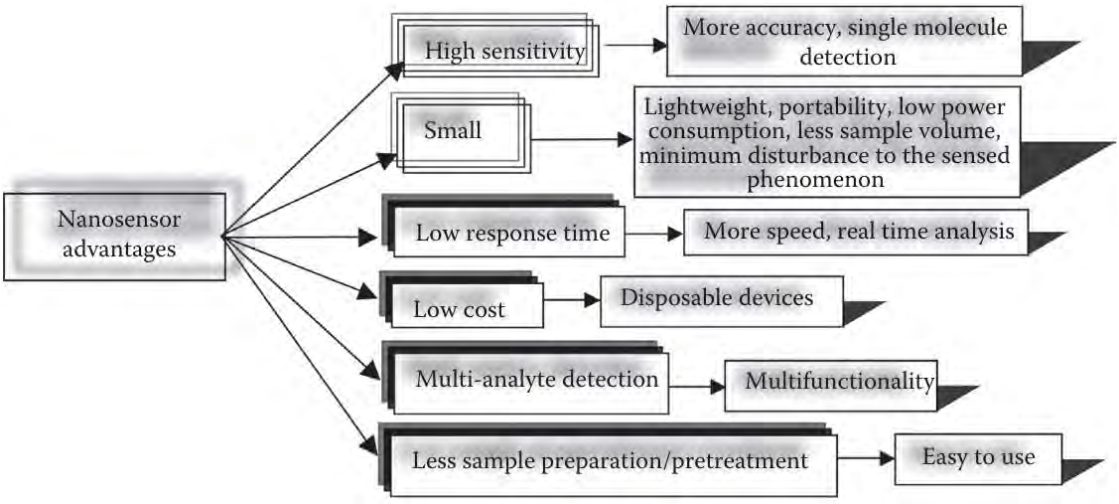


Figure 1.4. The advantages of nanosensors. Adapted from Khanna, 2016

1.2 Research Background

The construction of intelligent nanomaterials using responsive host macrocycles has become a focal point in recent times. A variety of distinct molecular hosts have been meticulously crafted for guest recognition. Owing to their adaptable host-guest characteristics and their ability to self-assemble into supramolecular structures through noncovalent interactions, these hosts are crucial in numerous areas, including polymer chemistry, materials chemistry, nanotechnology, artificial molecular machines, artificial ion channels, and others (Khalil-Cruz et al., 2021). Nonetheless, the development of these intelligent nanomaterial sensors for real-world applications is still in the early phases (Minamiki et al., 2020).

Calixarenes are frequently studied as the host in host-guest system and widely used as nanosensors as its excellent sensing element (Abd Karim et al., 2022; Wong et al., 2022). The attention on calixarene increased tremendously due to its significant properties, such as molecule recognition, selectivity, solubility, and degree of hydrophobicity (Español & Villamil, 2019). It also offered promising applications, primarily in the biological and medical fields.

Calixarene is well-known and extensively used due to its superior cavity and rim abilities, making it ideal for molecular platforms, binding, and host-guest interactions. Its proven selectivity towards various ions and molecules has been demonstrated repeatedly over the past decades (Mei & Ahmad, 2021). The ease of functionalization at both rims reveals a range of biological activities, including antiviral and anti-cancer properties, making it an excellent material for drug delivery systems (Español & Villamil, 2019). The unique structure of calixarene, which provides multiple binding sites, makes it an ideal material for drug sensing, encapsulation and transportation (Fan & Guo, 2021).

Para-amino benzoic acid (PABA) is a key compound in biochemistry and medicinal chemistry with applications in various industries (Krátký et al., 2020). This compound is biologically significant for healthy skin and hair, ozone, and other protection of pollutants (Naser et al., 2019). Moreover, PABA is an essential nutrient for many human pathogens. These biological and pharmaceutical properties have led to the extensive research conducted by Krátký et al., 2020.

PABA and its derivatives have been widely employed as active constituents in sunscreen cream to serve as a sunburn protectant for local application against ultraviolet (UV) B radiation and protect against dangerous consequences of solar rays (Krátký et al., 2020; Abbasi et al., 2019). According to Ozcan (2019), the employment of this active ingredients in the sunscreen is due to its chemical structure (Ozcan, 2019). However, evidence is provided at the molecular level regarding the harmful effect of PABA if used as a sunscreen ingredient (Chan et al., 2020). In fact, excessive use of this substance may also lead to skin abnormalities and allergic reactions (Naser et al., 2019) due to its deep skin penetration (Abbasi et al., 2019).

Hence, the PABA drug was identified and encapsulated by calixarene-based nanosensors through the host-guest system. The construction of PABA nanosensors is via the LB method where the trapping of the PABA by the calixarene molecule happen at the air water/interphase. The superior sensing ability and beneficial drug carrier properties of calixarene, such as its low toxicity and does not cause haemolytic activity, make it an ideal choice for hosting PABA molecules.

1.3 Motivation

The motivation for this research lies in the exploration of monolayer formation, surface potential characteristics, optical and optomechanical properties, as well as Density Functional Theory (DFT) modelling of calixarene for the entrapment of PABA. This is primarily due to the superior properties of the calixarene

macromolecule and the detrimental impacts of PABA. Over the past several decades, calixarenes have been widely utilized as molecular sensors (Priyangga et al., 2022).

Numerous reports suggesting that calixarenes serve as excellent sensing materials for the detection of minute molecules (Eddaif et al., 2019). Conversely, PABA has negative effects on users and poses a threat to marine life due to its continuous disposal through personal care products (Wu et al., 2021). Therefore, it is of utmost importance to develop a system that can alleviate these impacts.

Host-guest chemistry uses non-covalent interactions to form dynamic supramolecular assemblies, which can be adjusted in response to external stimuli, aiding in the creation of superior functional materials (Sayed & Pal, 2021). This concept has inspired the development of nanosensors and various systems that can encapsulate molecules, offering benefits like early detection of illness, toxins, or biological threats (Yang et al., 2021; Munawar et al., 2019).

Through the examination of Langmuir properties, including the surface pressure area (Π-A) isotherm, surface potential area (ΔV-A) isotherm, and the optical properties of the monolayer, it is possible to develop highly sensitive calixarene-based nanosensors for PABA detection. Furthermore, the integration of PABA into the calixarene can be ascertained and verified. The design of these highly sensitive sensors was achieved using the LB method, as the entrapment of PABA is molecule to molecules based which eventually reveals the most appropriate host to guest stoichiometric ratio.

The incorporation of PABA into the calixarene framework can also be determined through the optomechanical characterisation using optical tweezers (OT). Besides, this green method could also pave the way for advancements in water treatment technologies. The ability to manipulate and capture microcluster in an aqueous environment using a laser of a specific power could lead to innovative solutions in PABA removal from watery system. This method allows for the trapping of PABA by calixarene in a water medium. Such a technology could play a crucial role in preserving and protecting marine ecosystems and water systems by facilitating the removal of PABA substances.

The DFT method was employed to examine the host and guest at molecular levels. This approach facilitates a comprehensive understanding of calixarene and PABA at atomic levels. Furthermore, it allows for the exploration of the electronic structure of both the host and guest based on their electron density (Margraf & Reuter, 2021). Besides, these theoretical calculations can also forecast the possibility and appropriateness of the formation of the host and guest and the host-to-guest stoichiometric ratio can be expected.

1.4 Problem Statement

In recent times, there have been significant advancements in the medical field, particularly in the area of drug delivery systems. These systems are designed to deliver therapeutic agents to their intended location for specific treatments with optimal effectiveness (Obeid et al., 2017; Miele et al., 2012; Brown, 2005). While

numerous delivery systems have proven successful, there remain challenges to be addressed, such as drug stability, efficacy, and ensuring a safe dosage for the target. As a result, the development of a new drug delivery system that targets drugs could be a potential solution to these problems (Patra et al., 2018).

The design and synthesis of macrocyclic compounds in supramolecular chemistry have garnered the attention of researchers (Akceylan & Cagil, 2017) for the development in drug delivery system. This interest is due to their physicochemical properties, which include rigid cyclic structures, geometric dimensions, a hydrophobic cavity, and a hydrophilic interface (Bai et al., 2019). Macrocyclic amphiphiles have also demonstrated certain advantages in drug delivery, such as enhancing drug solubility and stability, and reducing the required drug dosage (Yuksel & Fellah, 2021).

Calixarene has gained considerable attention due to its notable properties such as molecule recognition, selectivity, solubility, and hydrophobicity (Español & Villamil, 2019). It has shown promising potential in the biological and medical fields and as a nanomaterial in the development of nanosensors. Calixarene, with its basket-like shape and adaptable cavity, has proven to be an excellent host molecule (Nag & Rao, 2022), capable of accommodating anions, cations, and neutral molecules, including drugs (Español & Maldonado, 2019; Español & Villamil, 2019). Its ability to capture guest molecules in its large core cavity through non-covalent interactions is depicted in Figure 1.5.

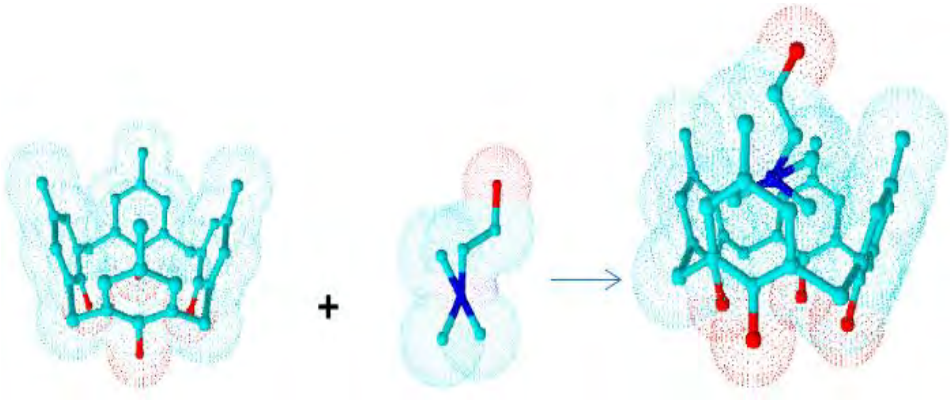


Figure 1.5. The host-guest phenomenon of calix[4]arene and guest molecules. Adapted from Español & Villamil, 2019

PABA, with its flexible structure and the capacity for modifications at both the amino and carboxyl groups, is frequently employed in the pharmaceutical industry. It has been observed to possess a variety of therapeutic properties, such as anticancer, anti-Alzheimer's, antibacterial, antiviral, antioxidant, and anti-inflammatory effects. This makes PABA an excellent candidate for use in therapeutic agents (Haroon et al., 2023).

Based on previous research done, PABA poses therapeutic properties which not only benefits to human, but also beneficial for agriculture field. According to Laborda (2019), PABA has the ability to cure and protect the plant from various of plant pathogens (Laborda et al., 2019). Due to its ability to absorb ultraviolet (UV) B rays and provide protection against sunburns PABA is widely known as a UV-blocking sunscreen applied to the skin (McKinnon et al., 2022; Horozić et al., 2019).

However, several studies has reported this substance can harm to human skin such as producing skin irritation, allergies, and contact dermatitis (Nitulescu et al., 2023; Naser et al., 2019; DeLeo, 2018) . Deep penetration of PABA into the skin

increase the potential adverse effects experience by the users (Abbasi et al., 2019) and potentially increased the risk of skin cancer (Ngoc et al., 2019). Therefore, there is urge in development of nanosensors to encapsulate PABA. Figure 1.6 illustrates possible mechanism of a calixarene-based nanosensors for PABA molecules entrapment.

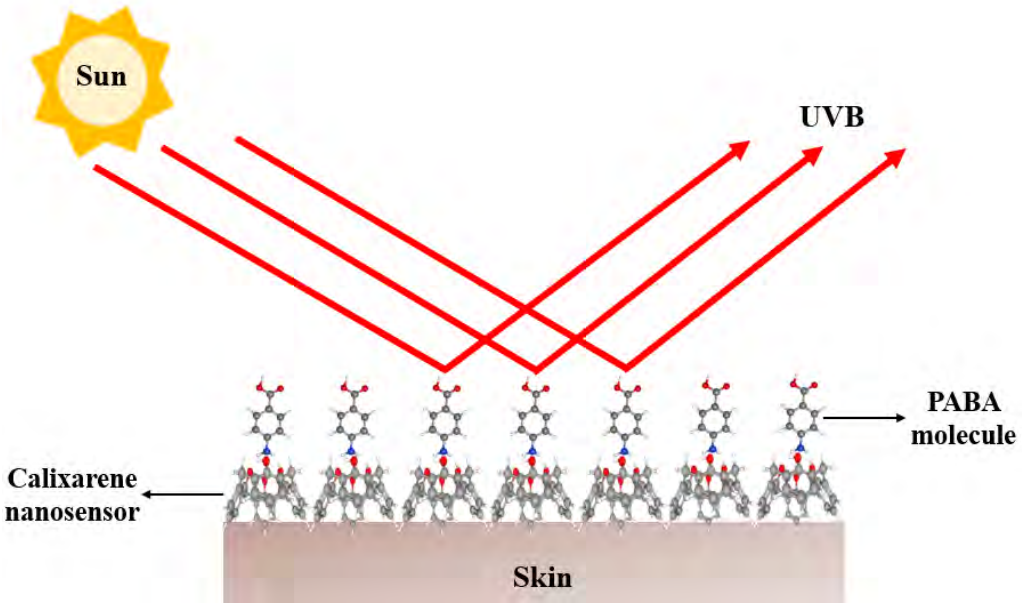


Figure 1.6. The potential mechanism of calixarene nanosensors in trapping PABA molecules

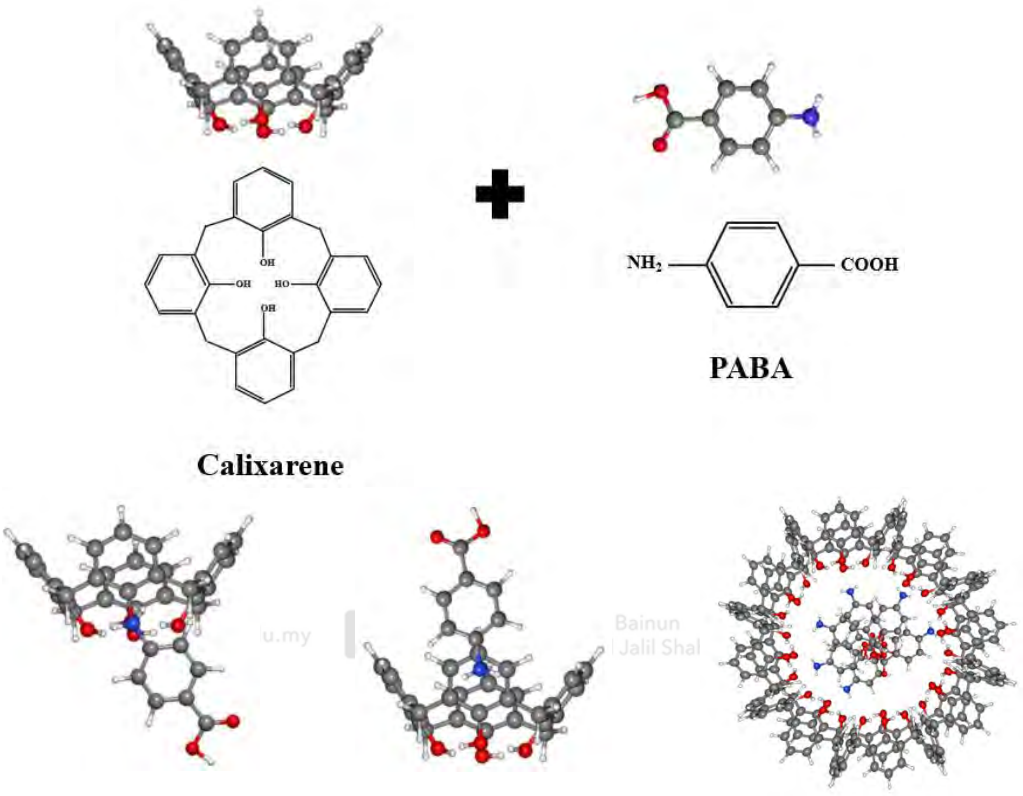
Moreover, through sunscreen application, PABA is continuously released into the water ecosystems, raising concerns about health-related problems such as deoxyribonucleic acid (DNA) damage and increased photosensitivity (Tsoumachidou et al., 2017). According to research reported by Mao in 2011, PABA absorbs solar energy, which indicates both its photoreaction behavior in natural waterways (Mao et al., 2011) and it is toxic to the aquatic environment (Sun et al., 2024; Wheate, 2022; Mao et al., 2011). Therefore, removing this organic contaminant from watery environments is necessary if its effects on ecological life are eliminated.

Recent years have seen numerous impressive efforts to degrade PABA using some of the most cutting-edge oxidation processes, including photolysis, photocatalysis, and photo electrocatalysis (Khan et al., 2020). Nevertheless, the present industrialized and technological era has given no option except to develop natural, green, and renewable energy sources to substitute the non-renewable traditional and contaminative fossil fuels as a result of severe environmental pollution.

The interaction of photons on the host and host-guest molecules was investigated. This observation was focused on the optical trapping of calixarene and calix-PABA microclusters since the trapping irregular microclusters in the water is challenging (Gong et al., 2018) and there is limited research on irregular microcluster trapping using OT (Mahadi et al., 2022). The most crucial component of optical trapping is to have stable optical trapping. The optical stiffness, k_τ serves as a parameter for the strength of the trapping spot, and the trapped microcluster's corner frequency, f_c used to determine the k_τ. These two variables demonstrate the OT's strength to hold the microstructure. The optical trapping of calix-PABA complex path a way toward countless manipulation of microsensing applications.

Another challenge will be the drug-trapping mechanism, as there are several potentials to encapsulate the drug, as shown in Figure 1.7. The mechanism of drug entrapment was not widely discussed previously. By studying the optical properties and validating with the theoretical calculation study by means of DFT method, the trapping mechanism and the host-guest complexes' stability and favourability reaction was revealed. By computing the host-guest complexes' binding energy, the calix[n]arene with a good absorption property for PABA drugs was determined

(Yuksel & Fellah, 2021) and the theory behind the host-guest complexes was discovered. Furthermore, this study will help envisage the molecular interactions of PABA drugs and calixarene as a host in host-guest complexes (Patra et al., 2018).



(a) (b) (c)

Figure 1.7. The calixarene, PABA and their potential mechanism of complex formation

Calixarene is chosen as a host in the complexes as their ability to form host-guest complexes in drug delivery systems, mainly for cancer treatment, is proven. In addition, there is much research on calixarene as a host in host-guest interaction; however, the calix-PABA interaction is not widely researched. This work identifies the host-guest mechanism and examines its optical and optomechanical characteristics. Several characterisations was performed to study the attachment

mechanism at air-waters interphase, the behaviour of host and guest molecules and optical properties of the host and host-guest complex formed.

1.5 Research Objectives

1. To study the surface pressure area isotherm (Π-A), surface potential ΔV and effective dipole moment ($\mu_{\perp}$) of the calix[n]arene and calix[n]arene-PABA (n=4,8) as host and the host-guest complexes using Langmuir-Blodgett (LB) technique and Surface Potential Sensor (SPOT) device respectively.
2. To characterise the optical properties of calix[n]arene and calix[n]arene-PABA (n=4,8) complexes using Ultraviolet-visible (UV-Vis) Spectroscopy.
3. To evaluate the optomechanical properties of calix [n]arene and calix[n]arene-PABA (n=4,8) as host and host-guest complexes using optical tweezer (OT).
4. To determine the binding energy of the calix[n]arene-PABA (n=4,8) complexes using the Density Functional Theory (DFT) molecular modelling.

1.6 Research Problems

1 How is the calix[n]arene and calix[n]arene-PABA film behave in terms of Π-A isotherm and ΔV and what is the pattern of $\mu_{\perp}$ of the host and host-guest complexes?

2 Is there any significant and distinct peak of the UV-Vis absorption spectra between the host, calix[4]arene (C4) and calix[8]arene (C8) and the host-guest complexes, C4-PABA and C8-PABA?

3 Is the OT capable of holding a single C4, C8 and C4-PABA and C8-PABA microcluster and are there any differences in terms of the minimum laser power density, P_{min}, and corner frequency, f_c of stable optical trapping for both host and host-guest microcluster?

4 What is the binding energy of the host-guest complex, C4-PABA and C8-PABA and which complex has the greatest binding energy calculated using DFT?

1.7 Scope and Limitations

In this research, only two types of calixarene that is C4 and C8 were utilized and act as a host. The cosmetic drugs chosen is PABA which was the targeted guest in the host-guest complexes. The first part of this research focuses on fabrication of calixarene and calix-PABA monolayer using Langmuir technique using KSV NIMA 2002 System 2 LB deposition trough with KSV SPOT probe. The Langmuir properties study is in terms of Π-A isotherm, ΔV-A isotherm, and $\mu_{\perp}$. Here, the spreading volume of the hosts, C4 and C8 and PABA solution concentration were optimised. The hosts and host-guest complexes monolayer were then transferred onto the quartz substrate using the LB method.

The deposited monolayer of the host, C4 and C8 and their respective complex, C4-PABA and C8-PABA were then undergoing optical characterisation using UV-Vis spectroscopy to observe the incorporation of PABA into the hosts, through the absorbance peak recorded and support the outcome from the Langmuir study. The optical characterisation was performed at wavelengths ranging from 240 to 400 nm. The value of optical band gap of the structures including hosts, guest and host-guest complexes were obtained by using Tauc plot method.

After that, the optomechanical characterisation of the calixarene, PABA and their respective complexes were studied using Modular Optical Tweezers, OTKB (/M) model. The wavelength of the laser used was 976 nm. The trapping of microcluster performed on the microclusters with an effective radius of 0.5 to 1.30 μm in a deionised (DI) water environment. The value of f_c of each microcluster were collected at five power density, P with an increment of 0.419 MW/cm^3 in each P. The range of P for the C4 and C8 were 0.231 to 1.907 MW/cm^3 and 0.357 to 2.023 MW/cm^3 respectively. For the host-guest complexes, the P for C4-PABA were ranging from 0.441 to 2.116 MW/cm^3 whereas the range of 0.818 to 2.493 MW/cm^3 was for C8-PABA.

The last part of this research focuses on the computational study of the calixarene and calix-PABA complexes using DFT method. Using Quantum Espresso (QE), DFT molecular modelling simulations were performed by inputting a crystallographic information file (CIF) of each structure which was obtained from the Cambridge Crystallographic Data Centre (CCDC) (Groom et al., 2016). The exchange-correlation employed in the calculation was Generalized-gradient-

approximation with Perdew-Berke-Erzndof parametrizations (GGA-PBE). The calculations were performed in terms of structure optimisation to obtain the system's total energy, self-consistent field (SCF) calculation to determine the electronic band gap and the density of state (DOS) to discover the behaviors of atoms in valence and conduction bands.

1.8 Research Significance

The sensor development worldwide still has enormous potential to be developed, utilising all kinds of nanomaterials or macroscopic substances to achieve the desired result, then further incorporating the research findings into commercially available products that can benefit humankind. This research is heading towards calixarene-based nanosensors for drug detection that will benefit the medical and pharmaceutical fields. The ability and selectivity of calixarene have been proven in the last few decades. Furthermore, the ability of calixarene to trap drugs in the drug delivery system has been successfully demonstrated several times, especially for cancer treatment (Español & Villamil, 2019).

The research on calixarene-PABA thin film, conducted using the LB technique, contributes to our understanding of how the PABA drug is trapped or encapsulated. This study is significant as it sheds light on the mechanism of drug encapsulation, specifically for PABA. In addition to this, the credibility and comprehensiveness of the findings are enhanced by comparing the experimental results with theoretical predictions. For instance, the optical band gap, which is

determined through UV-Vis spectroscopy, is compared with the energy bandgap calculated using DFT method. This comparison between experimental and theoretical results not only validates the findings but also provides a deeper understanding of the phenomena observed.

Moreover, the successful encapsulation of PABA drugs using the LB technique has broader implications. It suggests that other drugs with structures similar to PABA or drug possess PABA building block could potentially be trapped using the same technique. This creates new opportunities for the delivery of drugs and could lead to the development of more effective therapeutic strategies. Thus, the study of calixarene-PABA thin film through the LB technique is not only significant in its own right but also has far-reaching implications for the broader field of drug delivery.

The use of OT to capture the host and the host-guest microcluster has opened up new possibilities for the development of calixarene nanosensors. The calixarene nanosensors have the unique ability to be trapped PABA molecules not only at the air-water interface but also within the water itself. This is particularly useful for the removal of PABA in aqueous systems, a task that was previously limited due to the amphiphilic property of calixarene. Hence, the threaten on marine ecosystem by PABA can be reduced or eliminated.

Besides, the ability to optically trap calixarene and calix-PABA microclusters expands the capabilities of OT. Traditionally, OT has been focused on trapping entities that are spherical and solid. The trapping of irregular microcluster using OT is limited and not widely researched. However, the successful trapping of these irregular

shape microclusters indicates that OT can be used with a wider variety of shapes and materials. This could potentially lead to the development of more versatile and effective microsensors in the future.

On the other hand, DFT method have significantly deepened the understanding of the host, guest, and host-guest molecules at atomic levels. This method has been instrumental in exploring the electronic structure of calixarene, PABA, and the calix-PABA structure, based on their electron density. It provides a comprehensive notion of the electronic properties of these molecules, offering insights into their behaviours and interactions. The distribution of electrons within these structures and how the distribution influences the properties and interactions can be understanding.

Furthermore, DFT method serve as a powerful tool for validating the experimental outcomes of this research. This theoretical calculation supports the experimental band gap and host to guest ratio results. In essence, the use of the DFT method in this research has not only deepened the understanding of the molecules involved but also provided a robust theoretical framework that supports and validates the experimental findings. This highlights the importance of theoretical calculations in scientific research, as the method complement experimental work and contribute to a more comprehensive and accurate understanding of the phenomena being studied.

1.9 Contribution of Knowledge

The research conducted on drug entrapment, specifically focusing on the sensing substance calixarene and utilizing the LB approach, has opened up new avenues of understanding in the field of drug encapsulation. This area of study is particularly intriguing as it employs the concept of host-guest chemistry, a fascinating aspect of molecular science that allows for the trapping of water-soluble drugs.

The LB approach, a technique known for its simplicity and cost-effectiveness, enables the formation of a monolayer with a molecular organization that is impeccably ordered. The particles within this layer are uniform in size and exhibit controlled morphology, two critical factors in the production of nanosensors. These nanosensors hold significant potential for application within the pharmaceutical industries, where precision and consistency are paramount.

Moreover, the host substance in this study, calixarene, possesses hydroxyl units within its scaffold. This unique characteristic allows it to sense and capture the guest non-covalently, paving the way for the development of intelligent supramolecular sensors designed specifically for drug entrapment.

The principles of molecular host-guest chemistry continue to stimulate the creation of receptors, resulting in a wide variety of synthetic systems with the ability to encapsulate molecules. This principle, when combined with the results of this study, which demonstrate the formation of calixarene nanosensors for PABA drug entrapment not only at the air-water interface but also within the water environment,

can be utilized to further advance the development of drug capture and delivery systems, and broaden the application of calixarene nanosensors. This could potentially lead to more efficient and versatile drug delivery methods in the future which beneficial to biomedical and pharmaceutical field.

A keen insight of each structures including calixarene, PABA and their respective complexes at their atomic levels is essential. This in-depth knowledge facilitated a comprehensive understanding of the changes in properties and behaviours when transitioning from a pure substance to a complex structure. This understanding is vital as it provides a foundation for further research and development in this field.

1.10 Thesis Overview

The thesis is meticulously organized into five chapters, each focusing on a different aspect of the research. This structure allows for a logical progression of ideas and findings, guiding the reader through the various stages of the research. From the initial introduction of the hosts and guest drug to the final conclusions and recommendations, each chapter builds upon the previous one, culminating in a comprehensive exploration of the fabrication of host-guest complexes using the LB technique.

Chapter 1 provides general information regarding nanotechnology, the top-down and bottom-up approaches that are synonymous with nanotechnology for creating nanomaterials, the LB method as one of the bottom-up approaches in

developing perfectly organized nanomaterials for nanosensors application, and the properties of nanosensors. Then, the materials used, calixarene and PABA, were introduced in the research background. The significant properties of calixarene were described, as well as the ability of this macromolecule to encapsulate the drugs. In addition, the role of calixarene and PABA as host-guest complexes was explained in terms of their interaction. Next, the motivation and research problem clearly explained the gap in previous research related to drug sensing and encapsulation development. This chapter also listed the research objectives and problems, scope and limitation, research significance, and knowledge contribution. Lastly, the general thesis overview is presented to aid comprehension of the study's overall framework.

Chapter 2 focused on the literature review of the research. First, the calixarene and PABA's background, including their history, synthesis, and applications as a sensor in the biomedical field, were discussed. Next, the thin film technology was introduced, and several popular deposition methods were reviewed in terms of the benefits and drawbacks of each technique. Then, the development of the study material's fabrication method, the Langmuir and LB techniques, along with the theory of film formation and its characteristics, were thoroughly described and presented. After that, the UV-Vis spectroscopy and OT were presented, and the theory underlying each instrument was explained in depth. The instrument was used for optical and optomechanical evaluation. Finally, the DFT computational method theory is also discussed in this chapter. All the theories and reviews were based on previous research done by other researchers.

Chapter 3 highlights the procedures for calixarene-PABA sample preparation and characterization. Firstly, the materials used, the hosts, and the guest were stated. Then, the solution and Langmuir film preparation for fabricating the C4, C8, and calix[n]-PABA monolayer using the LB method was explained in detail. Next, the steps for precleaning the material before moving the monolayer were outlined, and the process for transferring the monolayer onto the quartz for optical measurement was then clarified. Finally, the optical and optomechanical characterization of the thin film sample and the DFT method was defined comprehensively. This part also included a summary of the scientific instruments, software, and steps for computational calculation and the parameter utilized.

Chapter 4 presents the result and discussion after conducting the experiment and collecting the data of the Langmuir properties results of calixarene and calix-PABA such as Π-*A* isotherm, Δ*V*-*A* isotherm and $\mu_{\perp}$calculation. The optical analysis of the sample solution and deposited thin films were performed using UV-Vis spectroscopy. The properties of calixarene and calixarene-PABA solution and films were determined in terms of the absorbance and the absorbance coefficient of both types of samples. The optical bandgap of each sample was defined using the Tauc plot method. The sample solution of different calix[n]arene concentrations was examined to ensure it obeys the beer-lambert law. Then, the optomechanical properties of the calix[n]arene and calix[n]-PABA microcluster were analyzed by means of the OT. By manipulating the microcluster with a laser, it is possible to examine its properties, including the f_c, k_τ, and P, in order to ascertain the stable optical trapping of a single microcluster. Finally, the theoretical calculation of each material and complex was computed using DFT. The calculations were performed in terms of the total energy of

each material and the binding energy to determine the most stable host for trapping the PABA guest. Each sample's density of state, DOS, fermi level, and bandgap were also computed. This computational calculation was done to validate the optical band gap which has been determined using the Tauc plot method. The research findings were analyzed to identify the theoretical underpinnings of each occurrence and presented according to the objectives stated in chapter 1.

Chapter 5 serves as the culmination of the study, drawing together the threads of the research that has been conducted. This research was grounded in experimental results and utilized the DFT method as a key tool in its analysis. This final chapter plays a crucial role in not only summarizing the findings of the study but also in identifying areas where further research is needed. It highlights certain gaps in the current understanding of calixarene and PABA complexes, pointing out these areas as potential avenues for future exploration. Chapter 5 also provides a list of suggestions and recommendations for future studies. These recommendations are based on the findings of the current study and aim to guide future researchers in their exploration of calixarene and PABA complexes.

1.11 Summary

The field of nanotechnology has seen remarkable advancements, making it theoretically possible to create nanosensors as small as one billionth of a meter. The fabrication of nanomaterials fundamentally relies on two primary approaches: the top-down and bottom-up techniques. The top-down technique involves the reduction of

bulk materials to the nanoscale, while the bottom-up technique involves the assembly of atomic and molecular components to create nanoscale materials.

Each of these techniques has its own set of advantages and disadvantages, and the choice between them often depends on the specific requirements of the nanomaterials being produced. They each impart unique characteristics to the nanomaterials created, influencing their properties and potential applications. However, among these two, the bottom-up technique is currently the most favoured approach among researchers. This preference is due to its ability to produce nanomaterials with more precise control over their size, shape, and chemical composition.

This research specifically focuses on the LB method, a prominent example of a bottom-up approach. The LB method is renowned for its ability to produce high-quality thin films of nano complexes. These thin films possess drug-sensing properties, making them highly beneficial for biomedical applications. The potential of the LB method to improvise the drug delivery systems and improve patient outcomes serves as a significant motivation for this study. By advancing the understanding of this method and its applications, new possibilities in the field of nanotechnology can be unlock and contribute to the development of more effective and targeted therapeutic strategies. Thus, the study is not only an exploration of the LB method but also a step towards the future of nanomedicine.