

MOLECULAR DYNAMICS SIMULATION OF GUEST DIFFUSIONAL AND
CONFORMATIONAL BEHAVIOUR OF HEXADECANE-1,16-DIOL AND
HEXADECANE IN UREA INCLUSION COMPOUND MODELS

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To my beloved *father* and *mother*, thank you for always being there.

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“In the name of Allah, the most gracious and the most merciful”

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ABSTRACT

Urea inclusion compounds are organic crystalline complexes that are potential candidates for molecular separator of long chain alkanes. A well-defined structure of the crystalline tunnel systems constructed from hydrogen bonding arrangement of urea molecules can be used to comprehend the fundamental aspects of processes involving ions or molecules transportation which play an important role in many physical, chemical and biological process taking place in a wide range of materials. This work endeavours to explore the diffusional behaviour of hexadecane-1,16-diol and hexadecane enclathration in urea tunnel architecture. The correlation of the diffusion mechanism with the guest's structural and conformational properties was obtained using molecular dynamics simulation approach. Three-stage of model systems have been developed in this work. In the first phase, a single urea tunnel with inclusion of only one guest molecule was constructed. In the second phase, eleven guest molecules were included inside a single tunnel of rigid and nonrigid urea host molecules to observe the influence of the existence neighbours, i.e. the guest-guest intratunnel molecular interaction. In the third phase, four urea tunnels were constructed to take into account the effect of intertunnel interaction on the guests' behavioural properties. It was found that hexadecane along the urea tunnel diffuse more rapidly than hexadecane-1,16-diol. The diffusion coefficients of hexadecane-1,16-diol in phase I, phase II of rigid and nonrigid and phase III model systems were $2.69 \times 10^{-9} \text{ m}^2\text{s}^{-1}$, $1.83 \times 10^{-10} \text{ m}^2\text{s}^{-1}$, $8.9 \times 10^{-11} \text{ m}^2\text{s}^{-1}$, and $3.2 \times 10^{-11} \text{ m}^2\text{s}^{-1}$, respectively, whilst those for hexadecane $1.96 \times 10^{-8} \text{ m}^2\text{s}^{-1}$, $2.58 \times 10^{-9} \text{ m}^2\text{s}^{-1}$, $7.15 \times 10^{-10} \text{ m}^2\text{s}^{-1}$, and $5.36 \times 10^{-10} \text{ m}^2\text{s}^{-1}$, respectively. The guests' along urea tunnel exhibited slower diffusion with the value correlated well with experimental findings, as the size of the model systems tended to mimic the real system. Elucidation on the guest rotational pattern as the molecule translated within the confinement of urea tunnel found that the guest preferred to follow the right-handed spirals of the chiral urea hydrogen-bonded structure. Besides, the translational and rotational properties of the guests are much more pronounced in the nonrigid urea systems. It was suggested that restriction imposed on the rigid urea systems constrained the molecules from being in their best conformation, thus contributed to the overall observation on the guest structural and conformational behaviour. The asymmetrical G^- and G^+ distortion along the guest's conformational energy which demonstrated the influence of urea chirality on the guest was notable on hexadecane-1,16-diol as compared to hexadecane. The variation in the diffusional and conformational properties evaluated in phase I, II and phase III model systems has highlighted the significant role of the guests' functional groups, which in turn are associated to guest-guest intratunnel and intertunnel molecular interactions as well as the host-guest interaction. Molecular dynamics method offered significant fundamental knowledge associated with the structures and dynamics of the guest molecules in a well-defined urea nanoporous model systems that have important application in molecular separation and enantiomeric discrimination area.

ABSTRAK

Sebatian rangkuman urea adalah sejenis kompleks kristal organik yang mempunyai potensi sebagai pemisah alkana berantai panjang. Struktur sistem terowong hablur yang jelas dibina daripada susunan ikatan hidrogen molekul urea boleh digunakan untuk memahami aspek asas proses yang melibatkan pengangkutan ion atau molekul, yang memainkan peranan penting dalam banyak proses fizik, kimia dan biologi yang berlaku di dalam pelbagai bahan. Kajian ini berusaha untuk meneroka sifat pembauran heksadekana-1,16-diol dan pemerangkapan heksadekana di dalam kerangka terowong urea. Korelasi mekanisme pembauran dengan ciri-ciri struktur dan konformasi molekul-molekul tetamu telah diperolehi dengan menggunakan pendekatan simulasi molekul dinamik. Tiga peringkat sistem model telah dibangunkan dalam kajian ini. Dalam fasa pertama, terowong urea dengan rangkuman hanya satu molekul tetamu telah dibina. Dalam fasa kedua, sebelas molekul tetamu telah dimasukkan ke dalam terowong tunggal terdiri daripada molekul-molekul hos urea tegar dan tidak tegar untuk melihat pengaruh kewujudan molekul jiran, iaitu interaksi molekul tetamu-tetamu di dalam terowong. Dalam fasa ketiga, empat terowong urea dibina untuk mengambil kira kesan interaksi di antara terowong terhadap sifat perilaku molekul tetamu. Didapati, heksadekana di sepanjang terowong urea membaaur dengan lebih cepat berbanding heksadekana-1,16-diol. Pekali difusi bagi heksadekana-1,16-diol dalam model sistem fasa I, fasa II dengan sistem tegar dan tidak tegar serta fasa III masing-masing adalah $2.69 \times 10^{-9} \text{ m}^2\text{s}^{-1}$, $1.83 \times 10^{-10} \text{ m}^2\text{s}^{-1}$, $8.9 \times 10^{-11} \text{ m}^2\text{s}^{-1}$, dan $3.2 \times 10^{-11} \text{ m}^2\text{s}^{-1}$ manakala nilai bagi heksadekana adalah $1.96 \times 10^{-8} \text{ m}^2\text{s}^{-1}$, $2.58 \times 10^{-9} \text{ m}^2\text{s}^{-1}$, $7.15 \times 10^{-10} \text{ m}^2\text{s}^{-1}$, dan $5.36 \times 10^{-10} \text{ m}^2\text{s}^{-1}$. Molekul tetamu di sepanjang terowong urea memperlihatkan pembauran yang lebih perlahan dengan nilai pembauran berkorelasi baik dengan dapatan eksperimen, apabila saiz model sistem cenderung untuk mengikut sistem yang sebenar. Pencerahan terhadap corak putaran molekul tetamu apabila bergerak dalam rangka kurungan terowong urea mendapati bahawa molekul tetamu lebih memilih untuk mengikuti spiral tangan-kanan struktur ikatan hidrogen urea kiral. Selain itu, sifat translasi dan putaran molekul tetamu adalah lebih menyerlah dalam sistem urea tidak tegar. Dicadangkan, sekatan pada sistem urea tegar telah menghalang molekul-molekul daripada berada dalam konformasi terbaik, justeru menyumbang kepada pemerhatian keseluruhan terhadap tingkah laku struktur dan konformasi tetamu. Herotan G^- dan G^+ yang asimetri pada sepanjang tenaga konformasi tetamu menunjukkan bahawa pengaruh kekiralan urea pada tetamu adalah ketara pada heksadekana-1,16-diol berbanding dengan heksadekana. Variasi sifat pembauran dan konformasi yang dinilai dalam model sistem fasa I, II dan fasa III menjelaskan peranan penting kumpulan berfungsi tetamu, yang mana mempunyai kaitan dengan interaksi tetamu-tetamu dalam terowong dan antara terowong serta interaksi hos-tetamu. Kaedah molekul dinamik menawarkan pengetahuan asas yang signifikan berkaitan dengan struktur dan dinamik molekul tetamu dalam model sistem urea berliang nano yang mempunyai aplikasi penting dalam bidang pemisahan molekul dan diskriminasi enantiomer.

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LIST OF ABBREVIATIONS

ABNR	-	Adopted-basis Newton Raphson
ACE	-	Angiotensin-converting enzyme
Ag	-	Silver
AMBER	-	Assisted model building with energy refinement
Au	-	Gold
¹³ C CPMAS	-	Carbon-13 cross-polarisation magic-angle-spinning
C	-	Carbon
CH ₄	-	Methane
CHARMM	-	Chemistry at Harvard macromolecular mechanics
CICT	-	Centre of communication and information technology
CNT	-	Carbon nanotubes
CO	-	Carbon monoxide
CO ₂	-	Carbon dioxide
COMPASS	-	Condensed-phase optimised molecular potentials for atomistic simulation studies
CPU	-	Central processing unit
DA	-	Decanoic acid
DDA	-	Dodecanoic acid
DFT	-	Density functional theory
DIBD	-	(E,E)-1,4-diiodo-1,3-butadiene
DSC	-	Differential scanning calorimetry
EPR	-	Electron paramagnetic resonance
EXAFS	-	X-ray absorption fine structure
FTIR	-	Fourier-transform infrared spectroscopy
GO	-	Grapheme oxide
GROMOS	-	Groningen molecular simulation

H ₂	-	Hydrogen
He	-	Helium
ICU	-	Intensive care unit
IQNS	-	Incoherent quasielastic neutron scattering
LAF	-	Lafutidine
MA	-	Malathion
MD	-	Molecular dynamics
MDE	-	Methyldecanoate ester
MM	-	Molecular mechanics
MNP	-	Metal nanoparticle
MSD	-	Mean square displacement
N ₂	-	Nitrogen
NDO	-	Nonadecanone
NMR	-	Nuclear magnetic resonance
O ₂	-	Oxygen
OPLS	-	Optimised potentials for liquid simulations
PBC	-	Periodic boundary conditions
PCFF	-	Polymer consistent force field
PCL	-	Poly(ϵ -caprolactone)
PEU	-	Poly(ester urethane)
RAE	-	Rapidly adductible endocyte
RAM	-	Random-access memory
RCG	-	Readily complexing guest
RDF	-	Radial distribution function
SASS	-	Switching-angle sample spinning
SMV	-	Simvastatin
UFF	-	Universal force field
UIC	-	Urea inclusion compound
UTM	-	Universiti Teknologi Malaysia
VMD	-	Visual molecular dynamics
XRD	-	X-ray diffraction

LIST OF SYMBOLS

a	-	Acceleration
c_h	-	Periodicities of the host
c_g	-	Periodicities of the guest
D	-	Diffusion coefficient
E	-	Energy
F	-	Force
fs	-	Femtosecond
H	-	Enthalpy
kJ	-	Kilojoules
K	-	Kelvin
m	-	Mass
m	-	Metre
m^2s^{-1}	-	Metre squared per second
N	-	number of particles
N_A	-	Avogadro number
ns	-	Nanosecond
P	-	Pressure
ps	-	Picosecond
Q	-	Atomic charges
R	-	Gas constant
s	-	Second
T	-	Temperature
V	-	Volume
\AA	-	Angstrom
θ	-	angle
φ	-	Torsion angle
ε	-	Dielectric constant

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CHAPTER 1

INTRODUCTION

1.1 Background of Study

Inclusion compounds, in a general sense, can be defined as systems in which one species which is the “guest” is spatially confined within another species, known as the “host” [1]. They can be formed from diverse types of organic and inorganic host components such as urea, thiourea, cyclophosphazenes, cyclodextrin [2], aluminosilicates (zeolites and clay minerals), aluminophosphates, graphite, layered metal chalcogenides, and layered metal phosphonates [3].

Over the years, many studies have been done in great detail on inclusion compound for it can be applied on industrial scale. Cyclodextrin, for example, is used in stabilisation of food flavours and fragrance [4] while urea inclusion compounds work in separation of components in mixture [5], particularly within petrochemical industry [1]. The selective separation of substances incurred by the formation of inclusion compounds have led the materials to be utilised at various stages of chromatography process due to their capability to provide solutions for specific analytical problems and one of the many materials to be used is urea inclusion compounds [6].

Urea inclusion compounds, the early representative of the host-guest molecular systems, are nanoporous solid materials which belong to the family of supramolecular compounds. These materials have been successfully applied in the laboratory and separation industry of linear and branched compounds in solution. The host structure

was reported to form an extensively hydrogen-bonded arrangement containing linear, parallel tunnels with an effective “diameter” of the tunnels ranging between approximately 5.5 and 5.8 Å [1, 6]. Since the selection for enclathration of guest molecules is essentially governed by the size of available tunnels, urea preferentially forms inclusion compounds with straight chain hydrocarbons. Compounds with larger substituents such as benzene and side chains remain excluded [5, 6]. In other words, the tunnel diameter serves as the “discriminator” for the incorporated guest molecules [7]. Thus, the selective character infatuated by the size of the urea tunnels has been the subject as why urea inclusion compounds can be used in separation technique. Indeed, this was one of the motivations for many of the early studies concerning urea inclusion compounds. Another example is the study conducted by Holman and Ener [8] on the use of urea inclusion compounds containing essential fatty acid for an experimental diet. In the report, they stated the danger that always exists when fat has been included in the experimental diet containing essential fatty acids was the occurrence of unwanted rancidity and destruction of vital nutrients, at least partially, by oxidation with atmospheric oxygen. Since the formation of inclusion compounds between urea and essential fatty acids or esters are not subject to autoxidation, urea became the preferred material to be used in their laboratory.

Urea inclusion compounds have also been found to increase the guest compounds performance, such as increasing the bioavailability of drugs [9–11], storing nanoparticles without aggregation in the solid state, and preventing the loss of products due to decomposition process [12]. Recently, with the ability to form co-inclusion complex with substituted compounds such as Malathion (MA), a highly toxic organophosphate insecticide that was being used widely to control insect pests, urea, due to its low cost and high solubility of water in place of cyclodextrin, has been employed as a host compound in Dhall and Madan studies [10]. The co-inclusion of MA in urea host lattice showed a steep reduction in the toxicity and was found to improve the handling characteristics.

Studies concerning urea inclusion compounds are still a subject of continuing interest, covering a wide range of scientific area [12–19], including this supramolecular compound’s physicochemical characteristics. The reported studies

include molecular transport [20–22], structural and molecular recognition [20, 23], host–guest chiral recognition [20, 24, 25], and dynamical properties [20–23] that are predominantly related to the molecular motion of the guest molecules.

Molecular transport phenomena have wide applications in a broad range of scientific disciplines, for example, in solid state [26, 27], biomedical engineering [28, 29], and chemical engineering [30, 31]. Studies concerning transport phenomena through nanoporous systems, where diffusion is one of its fundamental characterisations [32], have a very significant role in understanding the separation process which functions as a crucial technological phase in extensive industrial processes [33]. On the other hand, knowledge involving interactions between atoms and molecules, constituents of structural and conformational features at the molecular level with specific functional properties, is essential in designation and advance of constantly developing materials and chemicals [34]. Aside from that, understanding the structure of materials is also crucial for the determination of transport properties as it serves as the key to understanding many practical applications including separation process in porous materials [35]. Moreover, utilisation of computational approach such as molecular dynamics (MD) simulations in assessing the dynamics of a substance's diffusional and structural behaviour at the molecular level could assist in discovering irregular properties that could not possibly be identified by physical experiments [33], where in many situations are associated with high cost. In addition, the ability to design materials at the molecular level to enhance system performance with desired functional properties makes computational analysis a powerful approach that could be exploited in exploring and understanding a variety of systems [34].

1.2. Problem Statement

Since their discovery in the 1940s by Bengen [36], considerable experimental and theoretical works [1, 20] on urea inclusion compounds with different types of guest such as n-alkanes, α,ω -dihalogenoalkanes, carboxylic acids, α,ω -alkane dicarboxylic acids, anhydrides, diacyl peroxides, alcohols, alkanones [37, 38], and various other types [12, 13, 16, 39] of guest compounds have been explored. However, to the best

of our knowledge, no study has been reported yet concerning α,ω -dihydroxyalkanes type of guest family in urea inclusions by means of theoretical approach; only experimental studies have been reported so far on this type of guest family [40, 41]. Thus, our research highlighted and extended the theoretical studies of urea inclusion compounds with hexadecane-1,16-diol, a member of the α,ω -dihydroxyalkanes family, as guest molecules. The α,ω -dihydroxyalkanes have many potential applications of industrial and biological importance such as the use in polyesters production [42] and serve as initiators in biomaterials area [43].

There has been a variation of scale in modelling the urea inclusion systems in molecular dynamics studies. Some researchers model the system as a single tunnel [23, 44] whilst others build larger systems which consist of a few tunnels [20, 21] with insertion of at least one guest molecule or more. Large model systems were preferred [20, 21] in order to achieve a result that can accurately and reliably correlate with experimental findings. Regardless of some limitations, studies that used small urea model systems [23, 44] were still able to address significant findings related to their extent of problems. Compared to the previous works, both the small and large systems were included in the construction of urea model in this work, in which the model systems were not limited to a single urea tunnel or a number of urea tunnels but encompassed a series of urea tunnel systems. As this investigation was initially conducted from a small system, a single urea tunnel with one guest, understanding on the behavioural properties of guest molecules was hoped to be achieved from the ground level and to be gradually extended as the systems develops.

1.3. Objectives of Study

This study focused on probing the movement of guest molecules of interest along the urea tunnel and their behavioural properties by inspecting their reactions along the tunnel structure. The main objectives in this study are:

- 1) to explore the diffusion of hexadecane-1,16-diol and hexadecane guests along urea host tunnel for three different stages of systems,
- 2) to determine the structural and conformational properties of hexadecane-1,16-diol and hexadecane guests as they translated and rotated along urea host tunnel for three different stages of systems, and
- 3) to compare the behavioural properties of hexadecane-1,16-diol and hexadecane guests inside urea host tunnel for three different stages of systems.

The three stages of the systems are (i) single guest inside a single urea tunnel, (ii) eleven guests inside a single urea tunnel and (iii) eleven guests inside each of the four urea tunnels.

1.4 Scope of Study

In this work, we studied the transport and structural properties of hexadecane-1,16-diol guest molecules by means of molecular dynamics simulation. The guest compounds come from the α,ω -dihydroxyalkanes family, a type of molecule that consists of a hydroxyl group attached at each end of the long alkane chain. In order to assess the effect of these hydroxyl groups towards the guests' behavioural properties in urea inclusion compounds, another molecular dynamics simulation was run for hexadecane. This way, observation on the differences between guest representatives of different functional groups in the hydrocarbon chain could be carried out. The model systems were initially built as a single tunnel with introduction of one single guest within the framework of the urea tunnel. Development of the model system continued with construction of a single tunnel with introduction of eleven guests within the tunnel structure. At this phase, two parameters were imposed. One of the urea host molecules was held rigid whilst the other one was held nonrigid. In the third phase, the system was modelled by constructing four urea tunnels with insertion of eleven guests in each tunnel.

Hexadecane-1,16-diol guest compound was selected to represent the α,ω -dihydroxyalkane family in this work. Martí-Rujas *et al.* [41] mentioned that two types of crystal system, α,ω -dihydroxyalkane/urea co-crystals and α,ω -dihydroxyalkane/urea inclusion compounds could exist using the mixture of the same compounds. The molar ratio of urea to α,ω -dihydroxyalkane co-crystals are stoichiometric but in the urea inclusion compounds, they are not stoichiometric as a result of an incommensurate relationship between the host-guest periodicities. Their research work emphasised on the investigation of structural properties for a series of α,ω -dihydroxyalkane/urea co-crystals: hexane-1,6-diol, octane-1,18-diol, decane-1,10-diol, dodecane-1,12-diol, tetradecane-1,14-diol, and hexadecane-1,16-diol.

However, they revealed that in some of the crystallisation experiments which involved α,ω -dihydroxyalkanes as guest, the formation of urea inclusion compounds, rather than the urea co-crystals, was obtained and interestingly prevalent, particularly with α,ω -dihydroxyalkanes that exhibit longer chain length. Their attempts to produce a hexadecane-1,16-diol/urea co-crystal were only successful in their early studies. All the subsequent attempts using that particular guest molecule resulted in the formation of urea inclusion compounds. This information essentially gave us a basis for selection and designation of hexadecane-1,16-diol as the representative guest molecule in urea inclusion model systems of our work. There was another class of guest molecule that has been mentioned to form inclusion compounds with urea, hexane-1,6-diol. However, with limited computational resources and high computational cost, our work was restricted and focused only on hexadecane-1,16-diol as the guest molecule.

1.5 Significance of Study

Diffusion is an important molecular transport phenomena. Understanding the process of molecule or ion transportation at the atomic or molecular level is the basis for many physical, chemical, and biological processes of materials [32]. In this regard, studies of appropriate model systems such as urea inclusion compounds could play an important role in establishing fundamental knowledge of such transport processes, i.e.

in the field of molecular separation. Moreover, with the ever-changing needs for improvement and designation of new chemicals and materials, researchers and engineers are becoming increasingly engaged in using the knowledge about interactions [34].

This study investigated guest molecule transportation as well as interactions in urea host compounds. The significant insights on the structures and dynamics of the host and guest elements could provide an opportunity to understand properties at the molecular level, which in several cases cannot be retrieved by investigations by means of experimental approach. In addition, execution of considerable scientific works to understand in details, particularly of that physicochemical characteristics, of urea inclusion compounds [20–25] reflected on the relevance of studies related to the transport and structural properties of these compounds at the atomic or molecular level. Our work thus contributed in enriching and extending the knowledge at the fundamental level on these physicochemical areas of urea inclusion compound studies with hexadecane-1,16-diol (and hexadecane for comparison) as guest molecules. Since this investigation used a series of urea inclusion model systems starting from small to large, an insight towards the structural and dynamics characterisation which reflects the behavioural properties of the guest molecules could be observed and comprehended as a whole, i.e. the effect of urea confinement could be observed towards not only the guest molecules that have the nature of guest-guest interaction within the tunnel (guest-guest intratunnel interaction) but also towards the single guest molecule that have no guest-guest interaction as well as the guest-guest interaction between different tunnels (guest-guest intertunnel interaction).

1.6 Outline of the Thesis

This thesis consists of seven chapters. Chapter 1 gives a brief overview on the research background. It includes the problem statement, objectives, scope, and significance of the present study.

Chapter 2 compiles the literature review of the present study. The literature was divided into four main categories: (i) introduction to the inclusion compounds, the host-guest complex; (ii) discussion on urea inclusion compounds, i.e. urea as the host molecule, hexadecane-1,16-diol and hexadecane as the guest molecules, the application of urea inclusion compounds in various fields which demonstrates the relevance and continuous use of urea as a promising host molecule, and also theoretical studies on the physicochemical characteristics of this supramolecular compounds; (iii) reviews on the importance of diffusion and structure studies in nanoporous host-guest complex by molecular dynamics simulation approach; and (iv) brief overview on the basic principle used in molecular dynamics simulation.

Chapter 3 gives the details of the theoretical works. It includes the description about the construction of urea model systems, the computational method of molecular dynamics simulation, and the basic concepts used in the structural and dynamical analysis.

Chapter 4 provides the discussion on the results obtained from simulation of phase I model system, a single urea tunnel in which only one guest molecule resided. The highlight on this system is to perceive the rotational patterns of hexadecane-1,16-diol and hexadecane guest molecules as they translate along the urea tunnel and to probe if they have a certain recognisable preferential orientation. Diffusional behaviour of the single guest molecule was described through measurement of the diffusion coefficient. This chapter also includes the discussion on the translational and rotational properties of the guest molecules. The translational and rotational mode of the guest molecules along the tunnel was evaluated by measuring the travelling distance and torsion angle of the guest molecules.

Chapter 5 continues the discussion on the diffusional behaviour as well as the translational and rotational properties of hexadecane-1,16-diol and hexadecane, now in phase II model system where a single urea tunnel was filled with eleven guest molecules. The inclusion of additional guest molecules enabled analysis on the guest-guest interactions within the tunnel to be carried out. Two types of model system were

constructed at phase II, the urea molecule was held rigid on one tunnel and the other was held nonrigid. With implementation of these parameters, this chapter focuses more on describing the interplay between the diffusion of the guest molecules and their structural and conformational properties when a rigid and nonrigid urea host molecules were imposed.

Chapter 6 presents a study of a more profound property, i.e. the induced effect of urea chirality on the guest molecules and examination on factors that contribute to the behavioural properties of the guest molecules in a system that consists of four urea tunnels with the inclusion of eleven guest molecules in each tunnel. The findings were then compared to that of phase I and phase II model systems. This chapter also discusses the variations found on the diffusional behaviour of the guest molecules in all model systems. With the presence of neighbouring tunnels in the phase III model system, the influence of guests-guests intertunnel interaction was also addressed towards several of the discussed properties in this chapter.

Chapter 7 gives a summary of this study and concluded on the results obtained throughout the study with some suggestions presented for future work.

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