# MODELLING AND COMPUTER SIMULATION STUDIES OF SUGAR BASED AMPHIPHILIC SYSTEMS

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**ABSTRACT**

Nowadays, sugar-based amphiphiles are among the most attractive class of compounds to be studied both fundamentally and application-wise. They are one of the main components in cell membranes and play important role in many biological functions. Therefore, understanding the nature of the different liquid crystal phases of these materials is important and conceivable using different experimental techniques, theory and simulation. This thesis focuses on the last two methods to investigate the properties of these highly interesting soft materials.

We begin by examining a set of novel glycolipids which has been modified to include crown ethers attached to the sugar ring which increases the size of the hydrophilic area and causes to have higher packing parameters. Higher packing parameters induced formation of nonlamellar phases and prevent formation of lamellar phases. A theoretical study of a series of five glucose based glycolipid crown ethers and their complexes with $Na^+$ and $K^+$ was performed using the density functional theory with B3LYP/6-31G*. Optimized geometrical structures of the glycolipid crown ethers with cations were obtained and their corresponding electronic properties were calculated. In general, it was found that the oxygen atoms pairs O2 and O3 (or O4 and O6) on the sugar ring are constrained from moving toward the cation, which results in a weaker O-cation coordination strength for the oxygen pair compared to the other oxygen atoms in the crown ether ring. The thermodynamic properties of the binding of the complexes and the exchange

reaction in gas phase were evaluated. The cation selectivity pattern among the five molecules was in good agreement with the experiment.

Fully atomistic molecular dynamics simulation studies of thermotropic bilayers were performed using a set of glycosides namely n-octyl-$\beta$-D-glucopyranoside ($\beta$-C8Glc), n-octyl-$\alpha$-D-glucopyranoside ($\alpha$-C8Glc), n-octyl-$\beta$-D-galactopyranoside ($\beta$-C8Gal) and n-octyl-$\alpha$-D-galactopyranoside ($\alpha$-C8Gal) to investigate the stereochemical relationships of the epimeric/anomeric quartet liner glycolipids with the same octyl chain group. The results showed that, the anomeric stereochemistry or the axial/equatorial orientation of C1-O1 ($\alpha$/$\beta$) is an important factor controlling the area and $d$-spacing of glycolipid bilayer systems in the thermotropic phase. The C4-epimeric (axial/equatorial)stereochemistry becomes dominant together with the anomeric one for the inter-molecular hydrogen bond. Thus, the trend in hydrogen bonding goes as $\beta$-C8Gal> $\alpha$-C8Glc> $\beta$-C8Glc> $\alpha$-C8Gal. The four bilayer systems showed anomalous diffusion behaviour with an observed trend for the diffusion coefficient exponent ($\alpha$-C8Gal > $\beta$-C8Glc > $\alpha$-C8Glc > $\beta$-C8Gal), and was in the reverse order to the hydrogen bonding interaction strength, but in compliance to the cis-trans effect of the C4-epimer and anomer.

We have also studied the lyotropic reverse hexagonal phase H$_{II}$ from a glycolipid, namely using the Guerbet branched-chain (2'n-octyl-n-dodecyl)-$\beta$-D-glucopyronoside(C$_8$C$_{12}\beta$-D-Glc),at 14% and 22% water concentrations. In this simulation, it is necessary for us to use the united atom force field for carbohydrate from GROMOS because this approach will overcome the ambiguity of two optical

stereoisomers arising from the chiral center at the Guerbet branched chain. Moreover, this force field will enable us to run a longer simulation. Our simulations showed that at low water concentration (14%) the sugar head group overlapped extensively and protruded into the water channel. In contrast, in the 22% concentration system, a water column free from the sugar head group was formed, as expected for the system close to the limit of maximum hydration. In both concentrations, we found anomalous water diffusion in the $xy$-plane, i.e. the two-dimensional space confined by the surface of the cylinder. On the other hand, in the $z$-axis, the water diffusion obeyed the Einstein relation for 22% system, while for the 14% system it was slightly anomalous. Generally, a higher probability of hydrogen bonding but a shorter lifetime was found for the system of 22% water compared to the system of 14% water.

# ABSTRAK

Kini, amfifilik molekul yang berasaskan karbohidrat merupakan kumpulan sebatian yang paling menarik untuk dikaji secara asas dan aplikasi. Kumpalan ini merupakan komponen utama membran sel dan memainkan peranan yang penting dalam pelbagai fungsi biologi. Oleh itu, pemahaman tabii pelbagai fasa cecair hablur sangat penting dan boleh difahami menerusi pelbagai teknik eksperimen, teori dan simulasi. Tesis ini fokus kepada penggunaan kaedah teori dan simulasi bagi mengkaji bahan lembut yang amat menarik ini.

Kami bermula dengan mengkaji satu set glikolipid baru yang telah diubahsuai dengan memasukkan mahkota eter yang terikat kepada cincin gula, yang eningkatkan saiz kawasan hidrifilik dan menyebabkan parameter pembungkusan yang lebih tinggi. Parameter pembungkusan yang tinggi telah menyebabkan pembentukan fasa bukan lamellar dan menghalang pembentukan fasalamelar. Kajian teori untuk lima siri glukosa bersandarkan glikolipid eter mahkota dan kompleksnya dengan $Na^+$ dan $K^+$ telah dilakukan menggunakan teori ketumpatan fungsi dengan B3LYP/6-31G*. Struktur geometri optimum glikolipid eter mahkota dengan kation telah diperoleh dan sifat elektroniknya dihitung. Secara umum, didapati pasangan atom oksigen O2 dan O3 (atau O4 dan O6) pada gelang gula dikekang daripada bergerak ke arah kation mengakibatkan koordinasi O-kation lemah untuk pasangan tersebut berbanding dengan atom lain dalam gelang eter mahkota. Sifat termodinamik untuk ikatan kompleks dan pertukaran tindak-balas dalam fasa gas telah dinilai. Corak

pemilihan kation dikalangan lima molekul menyokong keputusan eksperimen dengan baik.

Dalam bahagian seterusnya, simulasi dinamik molekul atom sepenuhnya ke atas dwilapisan termotropik telah dilakukan menggunakan satu set sistem glikosida iaitu n-oktil-$\beta$-D-glukopiranosida ($\beta$-C8Glc), n-oktil-$\alpha$-D-glukopiranosida ($\alpha$-C8Glc), n-oktil-$\beta$-D-galakto-piranosida ($\beta$-C8Gal) dan n-oktil-$\alpha$-D-galaktopiranosida ($\alpha$-C8Gal) bagi mengkaji hubungan stereokimia empat epimerik/anomerik glikolipid dengan kumpulan rantai oktil yang sama. Keputusan menunjukkan stereokimia anomerik atau secara paksi / khatulistiwa pada C1-O1 ($\alpha/\beta$) adalah faktor utama yang mengawal luas dan jarak-d sistem dwilapisan glikolipid dalam fasa termotropik. Sudut kecondongan kumpulan kepala dan sifat susunan rantaian juga dipengaruhi oleh kesan anomerik di mana darjah kecondongan adalah lebih kurang 25% lebih kecil untuk $\beta$-anomer ($\beta$-C8Glc/Gal) berbanding $\alpha$-anomer ($\alpha$-C8Glc/Gal) dan $\alpha$-anomer didapati lebih kurang tersusun berbanding $\beta$-anomer. Justeru itu, susunan ikatan hidrogen adalah $\beta$-C8Gal>$\alpha$-C8Glc>$\beta$-C8Glc>$\alpha$-C8Gal. Keempat-empat sistem dwilapisan menunjukkan keganjilan sifat penyebaran dengan pekali eksponen penyebaran ($\alpha$-C8Gal>$\beta$-C8Glc>$\alpha$-C8Glc>$\beta$-C8Gal), adalah bertentangan dengan kekuatan interaksi ikatan hidrogen tetapi mematuhi kesan cis-trans epimer dan anomer C4.

Dengan menggunakan GROMOS medan daya dalam simulasi dinamik molekul atomistik untuk karbohidrat, kajian tentang fasa liotropik heksagonal songsang, $H_{II}$ dari sistem glikolipid dilaksanakan. Sistem tersebut merupakan

rantaian cabang Guerbet $\beta$-D-glukosida pada 14% dan 22% kepekatan air. Simulasi kami menunjukkan bahawa pada kepekatan air yang rendah (14%), kumpulan kepala gula bertindih secara berlebihan dan menembusi ke dalam saluran air. Manakala, di dalam sistem berkepekatan 22%, satu kolum air bebas dari kumpulan kepala terbentuk seperti dijangkakan untuk sistem yang menghampiri takat maksima hidrasi. Pada kedua-dua kepekatan, kami mendapati keganjilan dalam satah $xy$ untuk penyebaran air, contohnya ruang dua dimensi yang terhad kepada permukaan silinder. Selain daripada itu, di dalam paksi-$z$, penyebaran air mematuhi hubungan Einstein untuk sistem 22%, manakala untuk sistem 14% sedikit keganjilan berlaku. Secara umumnya, kebarangkalian ikatan hidrogen adalah tinggi tetapi jangka hayat yang rendah didapati bagi sistem 22% air berbanding 14% sistem air.

# AKNOWLEDGMENTS

In the name of Him who taught the soul to think,
And kindled the heart's lamp with the light of soul

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of you very much and your love has filled my heart. Wishing all of you best wishes and happiness.

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# LIST OF SYMBOLS AND ABBREVIATIONS

| | |
|---|---|
| 1-D | One-dimentional |
| 2-D | Two-dimensional |
| 3-D | Three-dimensional |
| A | Electron affinity |
| AG | Alkyl glycoside |
| APG | Alkyl polyglycoside |
| AMBER | Assisted model building and energy refinement |
| CHARMM | Chemistry at Harvard macromolecular mechanics |
| Col | Columnar |
| COM | Center of mass |
| Cr | Crystalline |
| $C_v$ | Heat capacity |
| DFT | Density functional theory |
| e.g. | exempli gratia; for example |
| et al. | et alii (and others) |
| etc. | et cetera; and the others |
| $f$ | Fukui function |
| G | Gibbs free energy |
| Gal | Galactoside |
| GL | Glycolipid |

| | |
|---|---|
| Glc | Glucose |
| GTO | Gaussian type orbital |
| HF | Hartree-Fock |
| $H_I$ | Normal hexagonal phase |
| $H_{II}$ | Reverse hexagonal phase |
| HOMO | Highest occupied molecular orbital |
| I | Isotropic phase |
| *I* | First ionization energy |
| $I_I$ | Normal discontinuous cubic phase |
| $I_{II}$ | Inverse discontinuous cubic phase |
| IR | Infrared |
| $L_1$ | Normal micellar solution |
| $L_2$ | Inverse micellar solution |
| $L_C$ | Lamellar crystal |
| LC | Liquid crystal |
| LCAO | Linear combination of atomic orbital |
| LDP | Local density profile |
| LUMO | Lowest unoccupied molecular orbital |
| $L_\alpha$ | Fluid lamellar liquid crystal phase |
| $L_\beta$ | Gel phase |
| $L_{\beta'}$ | Tilted gel phase |
| MC | Monte Carlo |
| MD | Molecular dynamics |

| | |
|---|---|
| MM | Molecular mechanics |
| MO | Molecular orbital |
| MPn | Moller-Plesset perturbation |
| N | Neucleophilicity index |
| NMR | Nuclear magnetic resonance |
| OH | Hydroxyl group |
| PBC | Periodic boundary condition |
| PDB | Protein data bank |
| PME | Particle Mesh Ewald |
| ps | Picosecond |
| Q | Canonical ensemble |
| $Q_I$ | Normal bicontinuous cubic phase |
| $Q_{II}$ | Inverse bicontinuous cubic phase |
| $S$ | Order parameter |
| S | Entropy |
| SANS | Small-Angle Neutron-ray Scattering |
| SAXS | Small-Angle X-ray Scattering |
| SmA | Smectic A phase |
| SmC | Smectic C phase |
| STO | Slater type orbital |
| $T_c$ | Clearing temperature |
| $T_m$ | Melting temperature |
| α | Alpha |

| | |
|---|---|
| β | Beta |
| λ | Wavelength |
| τ | Lifetime |
| ψ | Wave function |
| $\widehat{H}$ | Hamiltonian operator |
| $\nabla^2$ | Laplacian operator |
| $\chi$ | Electronegativity |
| Ω | Microcanonal ensemble |
| $\Xi$ | Grand canonical ensemble |
| $\Delta$ | Isothermal-isobaric ensemble |
| μ | Chamical potential |

# LIST OF APPENDICES

# CHAPTER 1

## INTRODUCTION

## 1.1 Introduction

Exhaustive description of the phases of soft matter is conceivable through the studies of molecular motion of liquid crystals using theory and simulation. In addition, the interest in the simulation of liquid crystal system such as the lyotropic phases is to investigate those physical properties of the self-assembly structure that are of prime importance to the macroscopic function such as for those of biological systems. For example, the idea of considering lipid membrane as a two dimensional fluid where the proteins diffuse around was suggested by S. Jonathan Singer and Garth Nicolson in 1972, to be that of a fluid-mosaic model of biological membrane. Nevertheless, this model has been used for a long time to illustrate a simple view of biological membrane. It has been clarified that, the lipid molecules not only play the role as solvent for protein, but also they have a remarkable significance for the function of living systems[1]. Thus, different experimental and computational methods have been used to investigate the self-assembly systems comprise of various lipid molecules in order to understand the changes from structure to properties[2]. Nuclear magnetic resonance (NMR), infrared (IR), fluorescence spectroscopy together with neutron scattering and X-ray are some of the experimental methods that enable one to investigate the biological macromolecules at the molecular level. However, sometimes models are required in order to explain the experimental results; in this sense, the computer modelling and simulation is a very useful and powerful tool. Computer modelling is one of the dominant and impressive techniques for comprehensive understanding of the dynamics and structure of the biological systems[3, 4].Intrinsic rules like hydrogen bond controlling these systems can be interpreted by the simple computational methods. These methods treat as a bridge between theory and experiment and provide intricate structural information of the studied system. The reliability of the simulation depends on the accuracy of the input parameters such as force field; besides that, the validity of

the simulation results have to be checked and compared with the experimental results directly or indirectly.

Glycolipids (GLs) normally found at the exterior of a cell wall and they are responsible for cell recognition process[5-7]. From the chemical point of view GLs are regarded as amphiphiles because they have two parts: hydrophilic (sugar moiety with single or multiple monosaccharide units) and hydrophobic (tail contains single or branched hydrocarbon chains). The two parts of molecule with different affinity for interaction with polar molecules tend to self-assemble into different mesophases, especially in polar water, such as micelles, lamellar and vesicles depending on degree of concentration and temperature[8-10]. Additionally these molecules self-assemble into lamellar crystal $L_c$ and lamellar liquid crystal $L_\alpha$ at higher temperatures in the non-hydrated environment[11]. Natural GLs are difficult to extract in large quantity and purity that makes the synthetic GLs to be highly sought after. These glycolipids have intriguing structural diversity that gives rise to complex behaviour. Even in the simplest monosaccharide i.e. a single sugar unit, the diverse possible stereochemical arrangements of the hydroxyl groups give rise to different types of sugars, like glucose, mannose and galactose. The last two are glucose epimers, where the hydroxyl group at the 2 and 4 carbon positions within the sugar ring is axially oriented for mannose and galactose respectively instead of equatorial as for the case of glucose. The precise effect of sugar stereochemistry is very much guesswork, but how this affect the macroscopic behaviour is very profound.

This chapter describes the elementary concept of liquid crystals, their classification into both thermotropic and lyotropic phases, and a special class of liquid crystal material involving glycolipids and their applications. Following, we introduce

the crown ether system and the underlying principles of quantum mechanics and also the concept of molecular dynamics simulation.

## 1.2 Liquid crystals

In 1850, Willhelm Heintz reported the strange optical behaviour of melting stearin from a solid to a cloudy liquid, first forming an opaque and then a clear liquid. Likewise, between 1854-1860, Rudolf Virchow, Ch. Freiherr von. Mettanheimer and Gabriel Gustave Valentin, reported the same optical behaviour of a solution of nerve fiber under polarized light. These unusual melting behaviours went largely unnoticed and were insignificant. However, in 1888, an Austrian botanist by the name Friedrich Reinitzer found the unusual behaviour in the melting point of cholesteryl benzoate, and consulted a German physicist, Otto Lehmann, who was able to explain the unique crystalline properties of this material under a polarizing microscope. Lehmann called these materials by various names such as "fliessender Kristalle" (flowing crystal) or "flussige Kristalle" (fluid or liquid crystal, LC), a state of matter existing between isotropic liquid and crystalline solid caused by thermal perturbation or composition. These phases have orientational order but no or reduced positional order, and are therefore highly viscose and fluid-like [12].
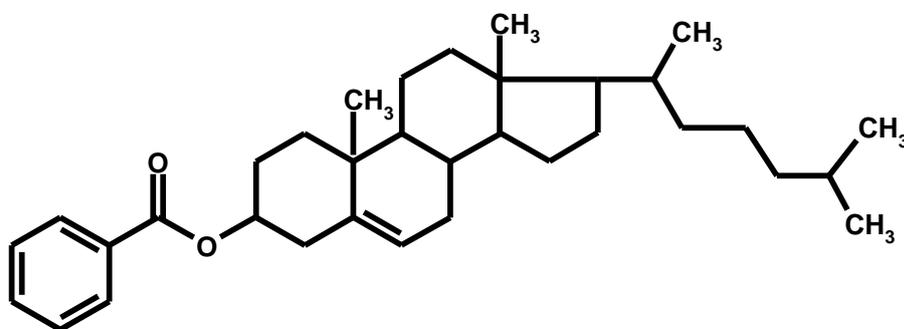


Figure1-1:Chemical structure of cholesteryl benzoate (the first liquid crystal) (Cr 145 °C $S_A$ 178.5 °C Iso)

Mesogen refers to the molecule that forms a mesophase or liquid crystal. Strong anisotropy in the shape of the substance is a minimum requirement to form a mesophase. Most mesogens are calamitic (rod shape) or discotic (disc-like). Liquid crystals can be subdivided into two major categories according to the factor controlling the formation, namely temperature, which gives the thermotropic phases including the simple ones like nematic or smectic A. Another factor is composition, which gives the lyotropic phases such as micelles, bilayers, cubic and hexagonal phases. The ability of a liquid crystal compound to form both thermotropic and lyotropic mesophases is termed amphitropic[12]although some researchers use the term "amphotropic" [13]. Therefore, both thermal perturbation and composition of the compounds may become the driving forces for the formation of these liquid crystal phases.

Melting point, $T_m$ and clearing point, $T_c$ are two temperature markers, which define the range, within which the thermotropic liquid crystalline mesophase exists.
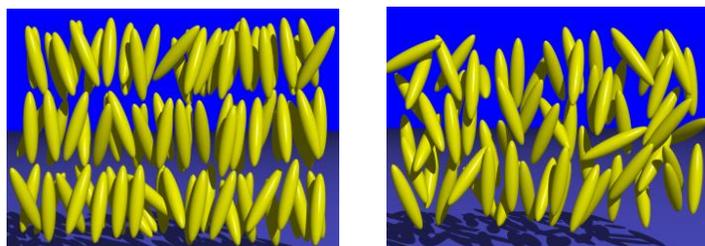


Figure 1-2:Schematic model of smectic A (left) and nematic (right)
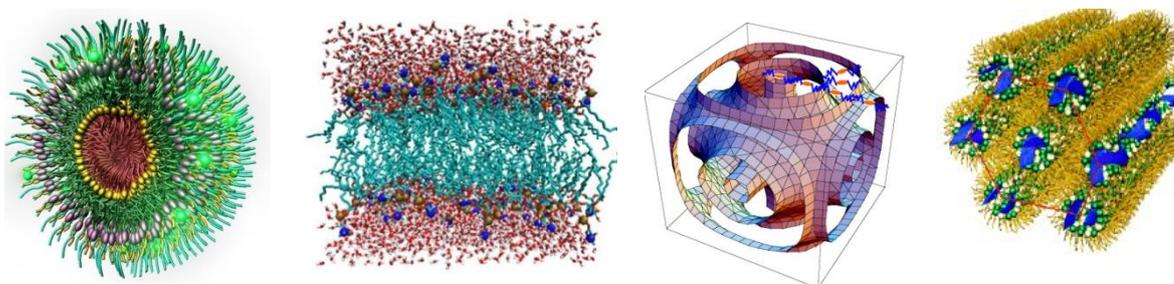


Figure 1-3: Schematic model of micelle, bilayer, cubic and hexagonal phase respectively from left to right respectively, (adopted from: http://www.pnas.org/content/106/24/9815/F1,prl.aps.org/files/ cover_image/lg89-20.jpg and,  http://today.slac.stanford.edu/ images/2006/ROW-101906.jpg) (Access to the internet page on 14/08/2013)

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$T_m$ shows the lower temperature boundary, while $T_c$ intends for the upper temperature limit of the liquid crystal phases. Within these two boundaries, there may be other phase transition temperatures, which imply polymorphism, or the ability to transform into different types of liquid crystal phases such as nematic and smectic.

Lyotropic liquid crystals are controlled by some factors such as concentration, temperature and polarity of the solvent. The term 'lyo' means solvent. Therefore, the solvent type and the concentration have a strong effect on a lyotropic liquid crystal. The type of mesophase formed is highly affected by the polarity of the solvent. For instance, a thermotropic cubic phase can change into a lamellar phase after the addition of a polar solvent at room temperature, but a hexagonal phase appears when a non-polar solvent is added at the same temperature[14].Additionally, Sakya and Seddon[15]stated that the formation of the mesophases is remarkably controlled by the concentration of the solvent. For example, at room temperature a smectic A gives lamellar phase at 10% solvent, but at 30% solvent this transforms into a hexagonal phase. Shape is another controlling factor forming the type of liquid crystal phase. The packing theory, [16] expressed through a simple mathematical expression, can explain the shape factor. Equation (1.1) gives the dimensionless packing parameters,$p$:

$$p = \frac{v}{a_0 l_c}.$$ 

(1.1)

where $a_0$ is the surface area of the head group at the interface, $v$ is the hydrocarbon tail excluded volume, and $l_c$ is the hydrocarbon tail chain length. Figure 1-4 shows the $p$ value and the corresponding predicted aggregate shape [16], and Figure 1-5shows the order of the lyotropic phases for the different compositions [17].

Table 1-1: Synonyms terminology in thermotropic and lyotropic mesophases

| Terminology in thermotropic mesophases [18] | Synonyms in lyotropic mesophases [19, 20] |
|---|---|
| Smectic A, | Neat phase or lamellar phase, $L\alpha$ |
| $Col_{hd}$, columnar phase | Hexagonal phase, middle phase, $H_I$ , $H_{II}$ |
| Bicontinuous cubic phase | Bicontinuous cubic phase, $Q_I$, $Q_{II}$ |
| Discontinuous cubic phase | Discontinuous cubic phase, micellar cubic |
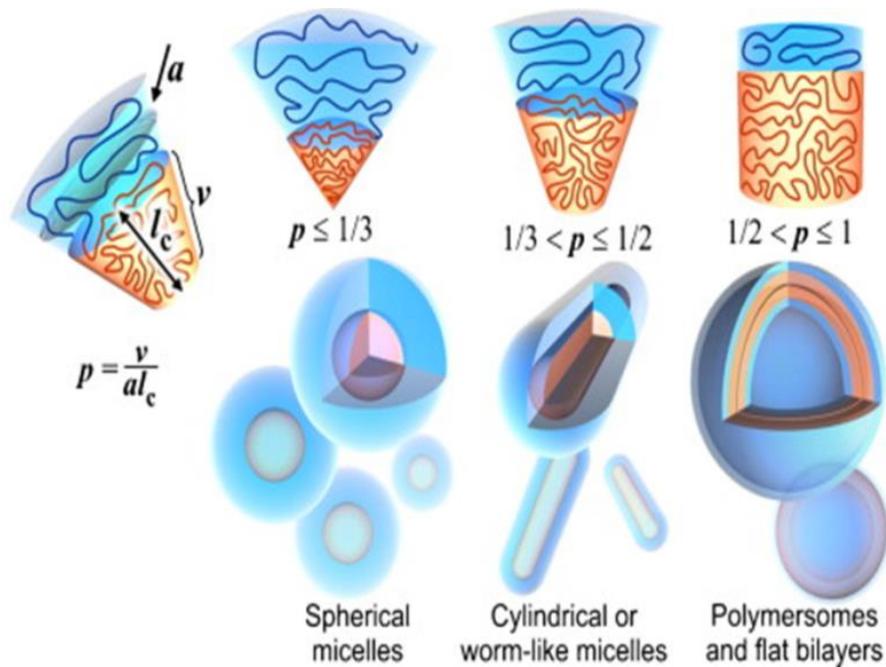


Figure 1-4:The *p*value and the aggregate shape of lipids (addopted from: http://ars.els-cdn.com/content/image/1-s2.0-S0079670009001026-gr15.jpg )
(Access to the internet page on 14/08/2013)
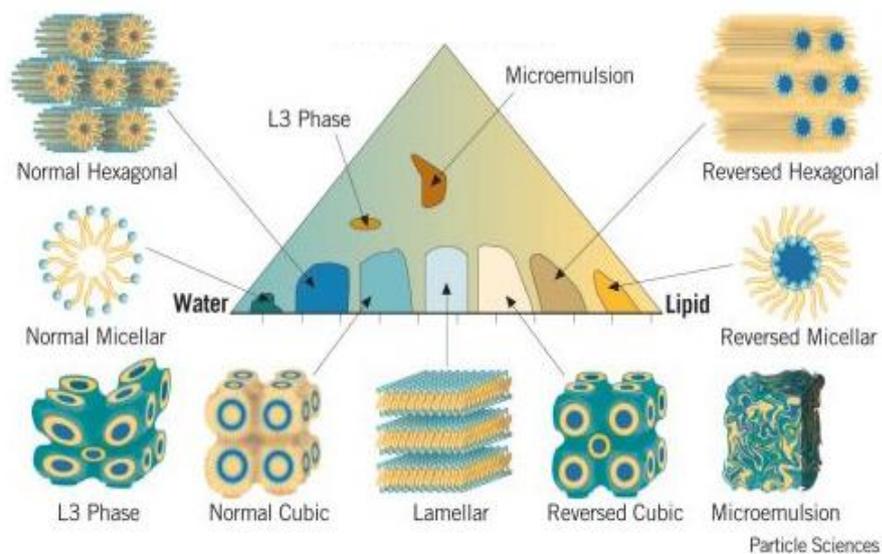


Figure 1-5:Theoretical Phase diagram of the lyotropic liquid and liquid crystalline phases (addopted from: http://www.particlesciences.com/images/tb/ lyotropic-liquid-crystalline-phases.jpg) (Access to the internet page on 14/08/2013)

Monophilic, amphiphilic and amphitropic molecules are three types of materials, which have the ability to form liquid crystals[2]. In this project we have chosen glycolipid molecules, which belong to the amphiphilic group.

Glycolipids such as glycoglycerolipids are nonionic organic compounds similar in structure to fats, but in which a short carbohydrate chain rather than a fatty acid is attached to the third carbon of the glycerol molecule (Figure 1-6) [30]; as a result, the molecule has hydrophilic "head" and a hydrophobic "tail."
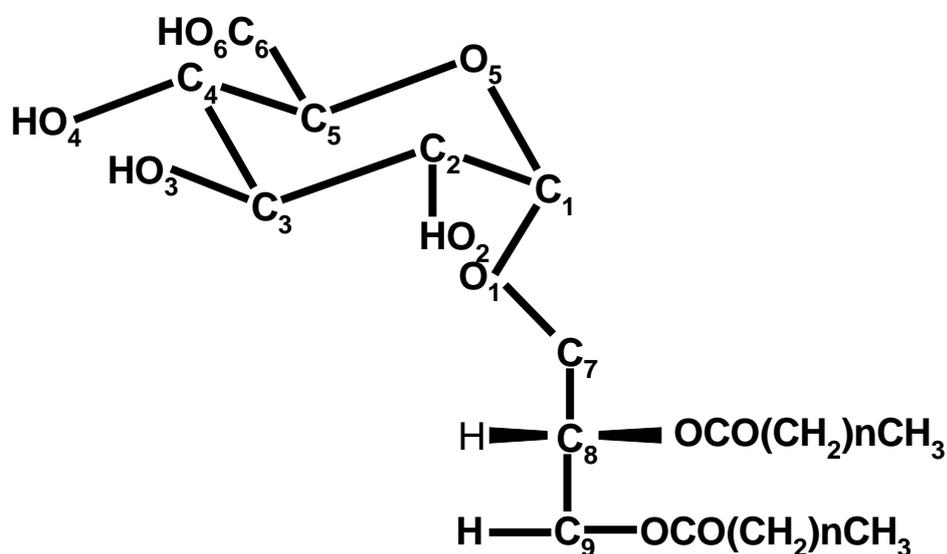


Figure 1-6: Chemical structure of a glycoglycerolipid[21]
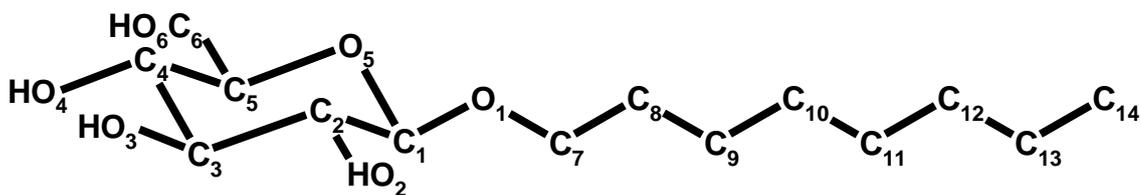


Figure 1-7: Chemical structure of n-octyl $\beta$-D-glycoside (OG)

Glycolipids are important constituents of the plasma membrane [21] and therefore, are attractive as vectors for liposomal drug delivery systems [22]. They can be extracted directly from natural sources such as palm oil and also synthesized from renewable resources such as fatty alcohols and oligosaccharides[22]. They play a major role in the isolation of membrane proteins without denaturation for physical

characterization[23] and are widespread over the surface membranes. Figure 1-8shows a typical cell membrane and the presence of glycolipids within. Natural glycolipids are classified into three categories: glycosphingolipids (GSLs),glycoglycerolipids and glycosyl phosphopolyprenols.Monogalactosyl diacylglycerol (MGDG) and digalactosyl diacylglycerol (DGDG) are two examples of glycoglycerolipids[24].
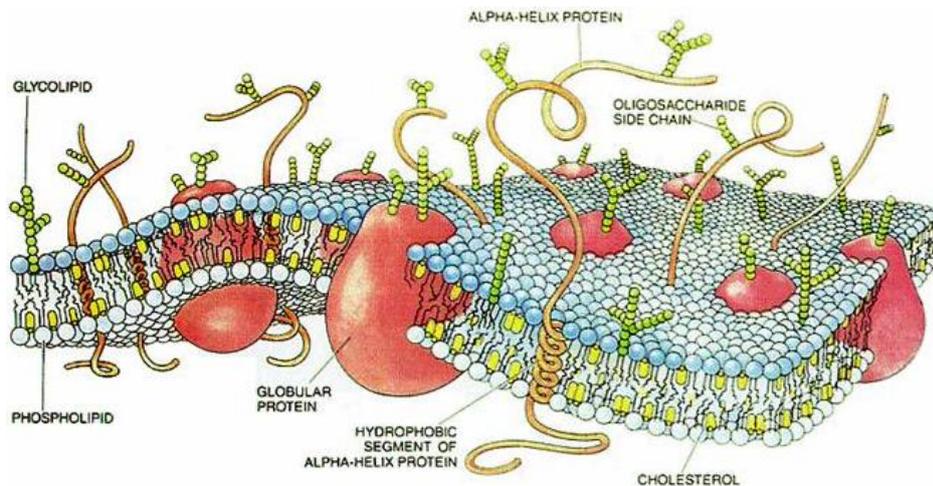


Figure 1-8: Typical cell membrane (adopted from:http://upload.wikimedia.org/wikipedia/commons/e/ee/CellMembraneDrawing.jpg) (Access to the internet page on 14/08/2013)

Glycosphingolipids (GSLs) are a class of sphingolipids that are the most common glycolipids in the cell membrane of mammals. Most of the glycosphingolipids are transported between the membranes as small vesicles maintaining a bilayer structure[25]. They also work as the modulator of signal transduction[26]. There are many references for the function of glycolipids in cell membrane[27-29].

In addition, during the last 10-15 years, there have been several investigations into the function of sugar-based surfactants to stabilize foam films. n-octyl-$\beta$-glucoside for instance can stabilize the equilibrium thickness of foam films. The long-range interactions in foam films stabilized by this nonionic surfactant are due to repulsive electrostatic double-layer forces [30].

## 1.3    Amphiphilic molecules and membrane systems

An amphiphilic molecule can exhibit liquid crystalline phasedue to the separation of the two opposing parts (e.g. hydrophilic and hydrophobic)or 'microphase separation' [11].Glycolipids are examples of these amphiphilic molecules.They have an intrinsic tendency to assemble in the water (and other solvent) environment. The assembly results from the tendency of the water molecules to avoid the hydrophobic parts of the molecules. In glycolipids, hydrophilic headgroups tend to interact with water molecules and the hydrophobic acyl and alkyl chains prefer each other together with other hydrophobic moieties in general. Usually, the specific form of glycolipid assembly is determined by their physicochemical properties.

The temperature-dependent phase behavior of glycolipids affects the properties of membranes. At low temperatures, a pure glycolipid bilayer is in a gel ($L_\beta$) phase, which is characterized by a high chain order, i.e. the chains tend to orient parallel to each other. Consequently, the lipids are closely packed, which results in a small surface area at the interface per lipid. As the temperature rises, phase transition to a lamellar ($L_\alpha$) phase occurs. The $L_\alpha$ phase is characterized by decreased chains order and increased surface area per lipid. As the temperature increases, the volume requirements of the chain region further increase and a transition to the inverted hexagonal phase takes place. Commonly, the inclination for one or both monolayer (halves of the bilayer) to curl away from a planner arrangement is the main factor driving these transitions. This arises from an unbalanced expansion in the lateral stresses such as, pressure and tension from the head group region, the polar/non-polar interface, and the hydrocarbon chain region of the bilayer [44]. In the case of single monolayer to stay flat, the lateral interactions must be in equivalence across the monolayer. Higher lateral pressure in the head group domain than that in the chain domain of the layer causes a

trend for the layer to curl towards the chain region, this is called positive curvature. On the other hand, if the pressure in the chain domain becomes dominant, we have a negative curvature and the layer bends towards the aqueous region [45]. These different contributions to the lateral stress in a monolayer are illustrated schematically in Figure 1-9.



|  |  |  |
|:---:|:---:|:---:|
| Negative | Zero | Positive |
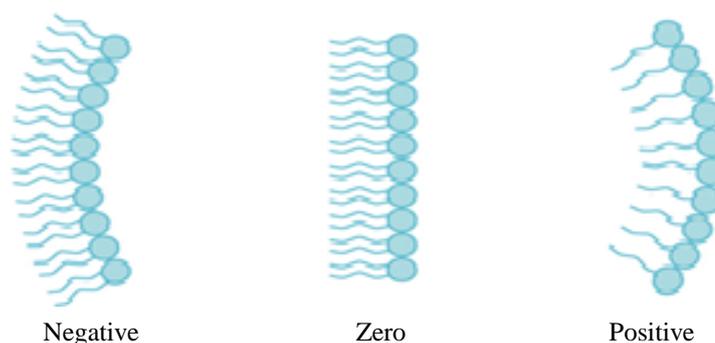
Figure 1-9: Tendency for spontaneous curvature of a lipid monolayer, due to an imbalance in the distribution of the lateral forces across the layer (Redrawn from [31])

When one monolayer tends to adopt a positive curvature and the other forms a negative curvature, the bilayer can reduce its internal stress easily by bending to form a cylindrical geometry. When these cylindrical structures assemble into a close pack arrangement, they form a hexagonal structure. It is important to understand that most lyotropic mesophases, which exist as symmetric pairs (type I) are considered as a 'normal' phase, such as oil-in-water, and a topologically 'inverted' phase (type II) water-in-oil version. The first one, i.e. the normal phase, comprises lipid aggregates in a continuous water matrix. In the second one, i.e. the reverse phase, water hydrated head group aggregates are ordered within a continuous non-polar matrix consisting of fluid hydrocarbon chains. The hexagonal phases $H_I$ and $H_{II}$ are examples of these pairs. We assume that the normal hexagonal phase has a positive curvature, $+\dfrac{1}{2}R$. In this sense, the interface bends towards the oil, or the non-polar region. On the other hand, the

inverse hexagonal phase has a negative curvature, $-\dfrac{1}{2}R$; therefore the interface bends towards the water region. $R$ is the value of the cylinder radius. A basic dysymmetry between $H_I$ and $H_{II}$ will appear as an effect of changing the water content of these phases[14]. In swelling the $H_I$phase, there are no main changes in the interfacial area per molecule, whilst in $H_{II}$ the interfacial area per lipid unavoidably increases with swelling the $H_{II}$ phase lattice. It is obvious that by the addition of the non-polar solvent, this situation will be reversed [14].
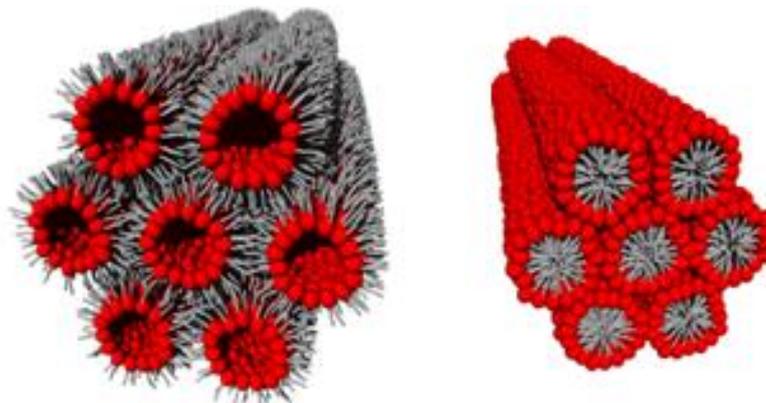


Figure 1-10: Topology of reverse $H_{II}$ (left) and normal $H_I$ (right) hexagonal phase (Adoppted from:http://www.biomedcentral.com/content/figures/1757-5036-2-3-3-l.jpg) (Access to the internet page on 14/08/2013)
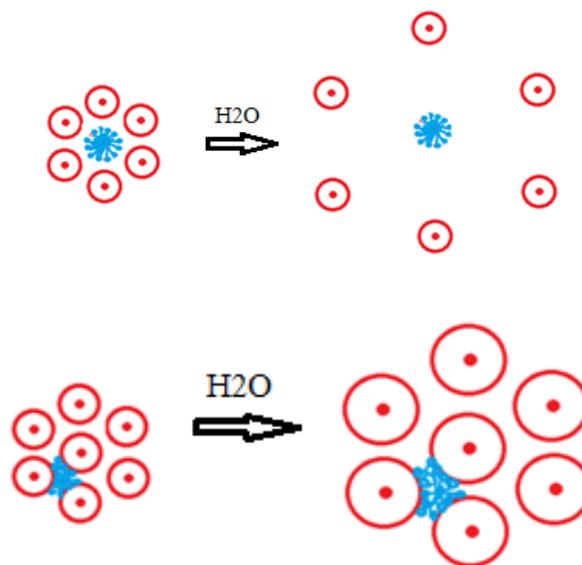


Figure 1-11: Swelling of normal $H_I$ (up) and reverse $H_{II}$ (down) hexagonal latticewith increasing water content [Redrawn from [14]]

If specified assumptions are made about the shape of the hydrated lipid aggregates and the densities of the components within the phase, substantive beneficial structural information can be easily obtained from the position of the diffraction lines, in relation with the chemical parameters such as the lipid molecular weight $M_L$, the water and lipid partial specific volumes $\bar{v}_w$ and $\bar{v}_l$ respectively, and the lipid weight concentration $c_L$ (lipid /(head + water)) [44]. The volume fraction of lipid is then:

$$\phi_L = \left[1 + \left(\overrightarrow{v_w} / \overrightarrow{v_L}\right)\left((1-c_L)/c_L\right)\right]^{-1}, \tag{1.2}$$

and the volume concentration of water is $\phi_w = 1 - \phi_L$. For the $H_{II}$ phase, the lattice spacing (Figure 1-12) is related to the $d$-spacing [32] by $a = (2/\sqrt{3})d$, and the diameter of the water cylinders is given as:

$$d_w = \left[\left(2\sqrt{3}/\pi\right)(1-\phi_L)a^2\right]^{\frac{1}{2}}. \tag{1.3}$$

The lipid layer thickness along the line connecting the cylinder axes is then $d_L = a - d_w$. The minimum length of the lipid molecule $l_{min}$ is calculated from the half thickness $d_L/2$ in the $H_{II}$ phase. Likewise, the distance from the interface to the center of the hydrophobic region corresponds to the maximum length $l_{min}$, and this is given by $a/\sqrt{3} - d_w/2$ [33].
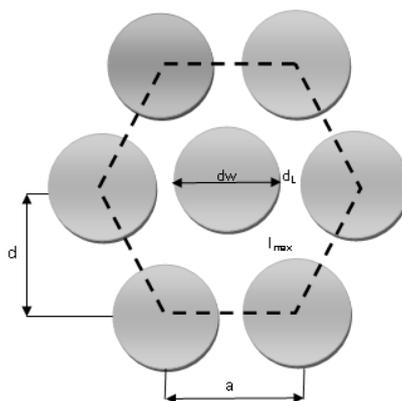
Figure 1-12: Lattice parameter and d-spacing (redrawn from http://ars.els-cdn.com/content/image/1-s2.0-S0009308497000935-gr2.gif)

## 1.4 Crown ether compounds

Crown ethers are cyclic chemical compounds that consist of a ring containing several ether groups. The term "crown" refers to the resemblance between the structure of crown ether bound to a cation, anda crown sitting on a person's head. They were first discovered by Pederson in 1967 and have long been well known for their ion selectivity[34, 35]. Crown ethers (($CH_2CH_2O$)$n$, cyclic), with the ether groups acting as hosts to trap the ionic species as a guest can  form cationic complexes. The oxygen atoms are well situated to coordinate with a cation located at the interior of the ring, whereas the exterior of the ring is hydrophobic. The resulting cations often form salts that are soluble in nonpolar solvents, and for this reason crown ethers are useful in phase transfer catalysis.  The denticity of the polyether influences the affinity of crown ethers for different cations. For example, 18-crown-6 has high affinity for potassium cation, 15-crown-5 for sodium cation, and 12-crown-4 for lithium cation. Beside this, the cavity size of the crown ether is another factor, which makes it possible for a specific entrapment of a guest particle, especially a metal cation. One can also find this kind of host-guest chemistry in Nature such as in cyclodextrins and macrocyclic polyether antibiotics[36]. Therefore, it is of special interest for researchers to understand the host-guest complex interaction, especially in view of many possible applications,

such as molecular recognition, ion sensing, heterogeneous catalysis or molecular switching [37-40].

The combination of the self-assembly behavior with a special functionality of some supramolecules has provided a way to design specific function from molecular level to the nanoscale, offering new functionality to the self-assembly system [41].For example, incorporating cation selectivity of crown ether attached to the system of self-organization, create a cation channel, which mimics the natural protein ion-channel for bio-membranes[42-44].

Recently, a series of new compounds was prepared by Sabah *et al*.[45] which combined the self-organizing property of sugar-based glycolipids with the crown ethers (Figure 1-13). These compounds are a combination of glycolipid dodecyl-*β*-D-glucoside with crown ethers. The compounds 15-crown-5, 18-crown-6 and 21-crown-7 have their crown ethers attached to hydroxyl groups at O2 and O3 positions on the sugar ring of the dodecyl-*β*-D-glucoside to give G15C5, G18C6 and G21C7, (Figure 1-13, a-c) respectively. Meanwhile different positions of the hydroxyl groups (O4 and O6) of the dodecyl-*β*-D-glucoside are chosen to attach the crown ethers of the 16-crown-5 and 19-crown-6 for G16C5 and G19C6 (Figure 1-13, d-e). These new functionalized glycolipids have significantly increased size of hydrophilic heads due to the crown ethers. In terms of self-assembly packing, increase in the size of head group would result in higher packing parameters,[16] which could prevent the formation of lamellar phase and induce the formation of non-lamellar curve phases such as micellar, hexagonal and even cubic phases. In this work, we studied the properties of these compounds from a theoretical point of view. The electronic structure, molecular conformation and the thermodynamic properties of these compounds and their

complexes with cations Na$^+$ and K$^+$ were obtained from the quantum chemistry calculation using Gaussian 09W program. Through this study we can understand the possible effect of molecules on their self-assembly structure.



a) G15C5                    b) G18C6

c) G21C7

d) G16C5                    e) G19C6
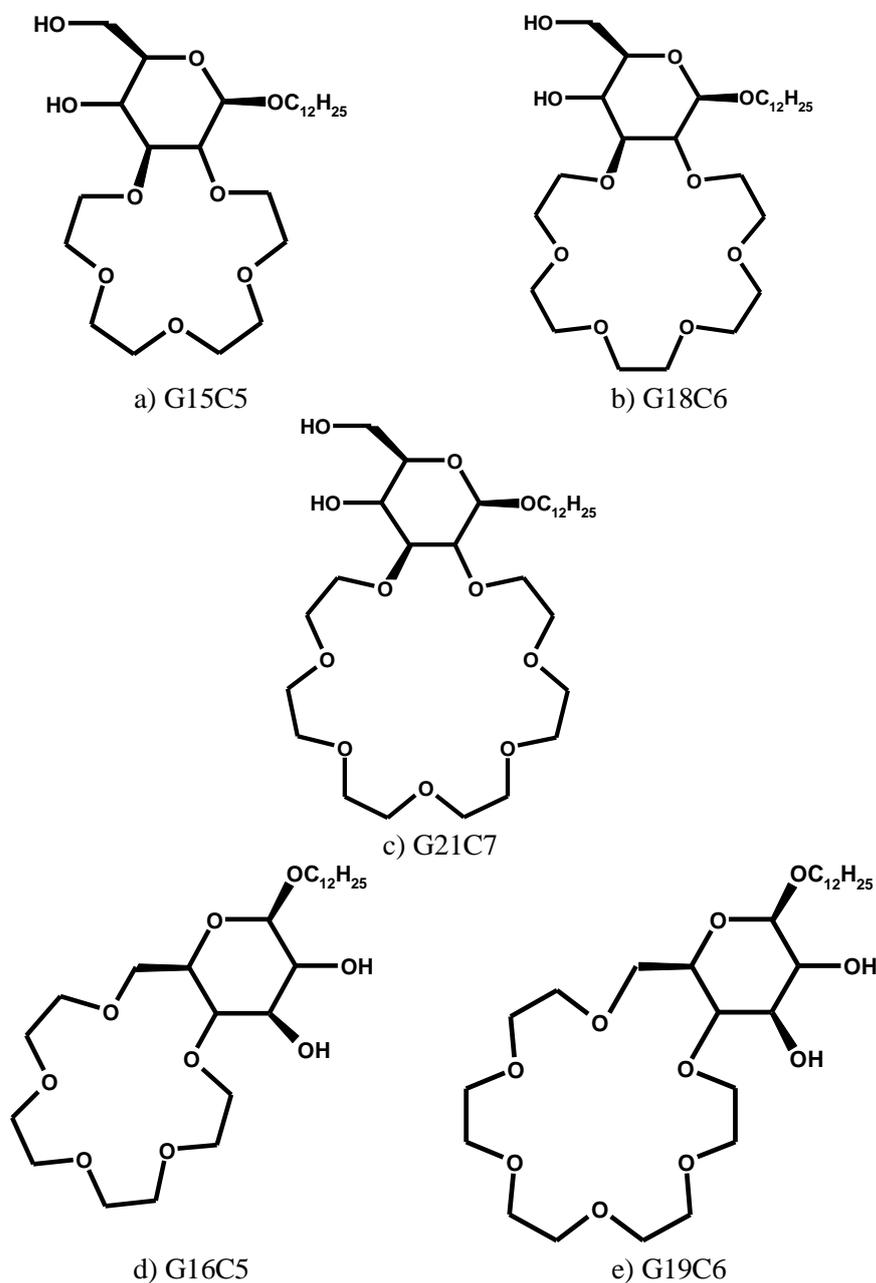
Figure 1-13: Schematic drawing of the molecular structures of glycolipids crown ethers

## 1.5    Molecular Dynamics Simulation

Traditionally, chemistry is an experimental science, no molecule could be investigated without prior being synthesized or found in Nature. In contrast, nowadays

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with the advent of modern computers and advances in simulation technique, the dynamics and structure of molecular systems can be studied theoretically without them being synthesized nor have to be naturally occurring [46-48]. Thus, the real beauty of this technique lies in its capability to predict the properties of a well-defined model of a chemical system based on a set of rules governing them. Compatibility between the simulation results and the experimental data has encouraged scientists to apply this method widely. In modern chemistry, there are two types of modelling approaches widely used, namely molecular mechanics and quantum mechanics.Monte-Carlo (MC) [49]and molecular dynamics[50] (MD) are two simulation techniques that are commonly applied for the force field obtained from molecular mechanics [51, 52]. The Metropolis MCuses a random number to evaluate the multi-dimension integration needed to evaluate statistical averages, which define the properties of a system. In contrast to the random MC method, molecular dynamics simulation follows step wisely real time dynamics of the particles using the Newton's equations of motion. The first MD was carried out for a system of hard spheres by Alder and Wainwright [4]. Compared to MC, the implementation of MD simulation codes is more complicated, but the underlying physics is relatively simple and involves setting the equation of motion for N-particle system and solving these numerically. Of course, MD has added advantage since dynamical properties such as diffusion coefficients and viscosities may be calculated in addition to the usual thermodynamic behaviour. Here, we outline only two simple numerical solutions to these equations of motion to illustrate the technique.

Consider, $\boldsymbol{F}_i = m_i \boldsymbol{a}_i$, where $\boldsymbol{F}_i$ is the resultant force exerted on particle $i$, $m_i$ and $a_i$ are its mass and acceleration respectively. Expressing the force as the gradient of the potential energy, $\boldsymbol{F}_i = -\nabla_i U_N$ modifies the equation of motion and relates this to the derivative of the potential energy with respect to position, $\boldsymbol{r}_i$, as a function of time;

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$$-\frac{dU_N}{d\mathbf{r}_i} = m_i \frac{d^2\mathbf{r}_i}{dt^2} \ . \tag{1.4}$$

By assuming that the acceleration is constant for linear velocity in one dimension, classical mechanics gives the following relationships:

$$\mathbf{F} = m\mathbf{a} = m\frac{d^2x}{dt^2} \ ,$$

$$a = \frac{d\mathbf{v}}{dt} \ , \quad \mathbf{v} = \mathbf{a}t + \mathbf{v}_0 \ , \quad x = \mathbf{v}t + x_0 \quad . \tag{1.5}$$

A combination of these equations then gives the position, $x$ as a function of $t$, at a given acceleration ($\mathbf{a}$), the initial position ($x_0$) and velocity ($\mathbf{v}_0$). Thus,

$$x = \frac{1}{2}\mathbf{a}t^2 + \mathbf{v}_0 t + x_0. \tag{1.6}$$

Although the solution to this equation for $x$ is deterministic, a few issues remain to be addressed due to the microscopic nature of the problem. First, the method must ensure the conservation of energy and momentum which means the initial distribution of velocities, selected randomly must have magnitudes which conform to the required temperature and ensures the overall momentum, $P$ sums to zero or $\mathbf{P} = \sum_{i=1}^{N} m_i \mathbf{v}_i = 0$.

Secondly, from these selected velocities, the probability $P_i$ that a particle $i$ has a velocity $v_{ix}$ in the $x$ direction may be calculated and consequently, the temperature determined, hence,

$$p_i(v_{ix}) = \left(\frac{m_i}{2\pi kT}\right)^{1/2} exp\left(-\frac{1}{2}\frac{m_i v_{ix}^2}{kT}\right) \quad and \quad T = \frac{1}{3N}\sum_{i=1}^{N}\frac{|p_i|}{2m} \ . \tag{1.7}$$

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Applying these to a set of N-particle system of defined interaction, $U_N$,

$$U_N = \frac{1}{2}\sum_{i \neq j} U(X_i, X_j), \qquad i, j = 1,...,N. \tag{1.8}$$

would similarly give the trajectories of N-particles if the initial particles' positions, velocities and accelerations are known. These become a system of coupled ordinary differential equations with no analytical solution, but several algorithms have been proposed to solve them numerically. Choosing an appropriate one, depends on some criteria, such as the algorithm must conserve energy and momentum, be computationally efficient and should allow for a long time-step for integration. Usually these algorithms use Taylor series expansion, equation(1.9), to express the positions, velocities (v) and accelerations (a);

$$r(t+\delta t) = r(t) + v(t)\delta t + \frac{1}{2}a(t)\delta t^2 + ...$$
$$v(t+\delta t) = v(t) + a(t)\delta t + \frac{1}{2}b(t)\delta t^2 + ... \tag{1.9}$$
$$a(t+\delta t) = a(t) + b(t)\delta t + ...$$

One of the earliest and easiest to implement but not necessarily the optimum is the Verlet algorithm [53], which initially calculates the position and acceleration at time $t$ and $(t-\delta t)$ and uses these to calculate $r(t+\delta t)$ as follows;

$$r(t+\delta t) = r(t) + v(t)\delta t + \frac{1}{2}a(t)\delta t^2,$$
$$r(t-\delta t) = r(t) - v(t)\delta t + \frac{1}{2}a(t)\delta t^2. \tag{1.10}$$

Summing these two equations therefore gives the new position,

$$r(t+\delta t) = 2r(t) - r(t-\delta t) + a(t)\delta t^2 \ . \tag{1.11}$$

Since the Verlet algorithm uses no explicit velocities, it is straightforward and requires low storage, but against this, the algorithm is of a moderate precision.

Another common approach used in MD is the leap-frog algorithm [54], where both the position and velocity are evaluated from;

$$r(t+\delta t) = r(t) + v\left(t+\frac{1}{2}\delta t\right)\delta t,$$
$$v\left(t+\frac{1}{2}\delta t\right) = v\left(t-\frac{1}{2}\delta t\right) + a(t)\delta t. \tag{1.12}$$

The velocities are first calculated at a half advanced time step, $t+1/2\delta t$ and these are used to calculate the positions, $r$, at a time $t+\delta t$. In this way, the velocities leap over or are calculated first before the new positions, then the positions leap over the velocities and so on. Although the velocities are calculated explicitly, the positions are not obtained at the same time. The velocities at time t may be approximated by:

$$v(t) = \frac{1}{2}\left[v\left(t-\frac{1}{2}\delta t\right) + v\left(t+\frac{1}{2}\delta t\right)\right] \ . \tag{1.13}$$

### 1.5.1 Force field development for carbohydrates

Atomistic simulations have different aims and challenges and one of these must be to obtain the exact properties of a real molecular system since it uses the most exact 'realistic' (*an initio*) model. One major problem in atomistic based molecular modeling is unfortunately, the system for realistic simulation is too large to be considered by quantum mechanical methods. Under such circumstances, molecular mechanics is

capable of performing calculations on a very large system containing thousands of atoms [55] by using some approximations such as united atom approach. A simple molecular mechanics force field contains terms of a relatively simple five component representations of the intra- and inter-molecular forces within the system such as bonds, angles, rotation (dihedral) and non-bonded interactions which contain both electrostatic and van der Waals. More sophisticated force field may have additional terms, for example polarization but invariably contain these five components. In general, the total potential energy for a molecule or assemblies of atoms and/or molecules is given as:

$$U_{total} = U_{bond}(d) + U_{angle}(\theta) + U_{dihedral}(\varphi) + U_{vdw}(r_{ij}) + U_{elec}(r_{ij})$$ (1.14)

This equation can be illustrated by the schematic model for the five key contributions to a molecular mechanics force field as shown in

Figure 1-14. To simulate carbohydrate related compounds, the Assisted Model Building and Energy Refinement (AMBER) *ff99* force field augmented with the more specific force field called Glycoprotein and Carbohydrate Parameters for AMBER (GLYCAM)[56] were used. GLYCAM was developed to determine the structures of oligosaccharides and also to study oligosaccharide-protein interactions. It is so important to parameterize the correct force field because the ultimate aim in molecular modeling is to explain experimental observations and to act in a predictive capacity, e.g. drug design.

Bond stretching

Angle bending

Non-bonded interactions (electrostatic)

Bond rotation (torsion)

Non-bonded interactions (van der Waals)
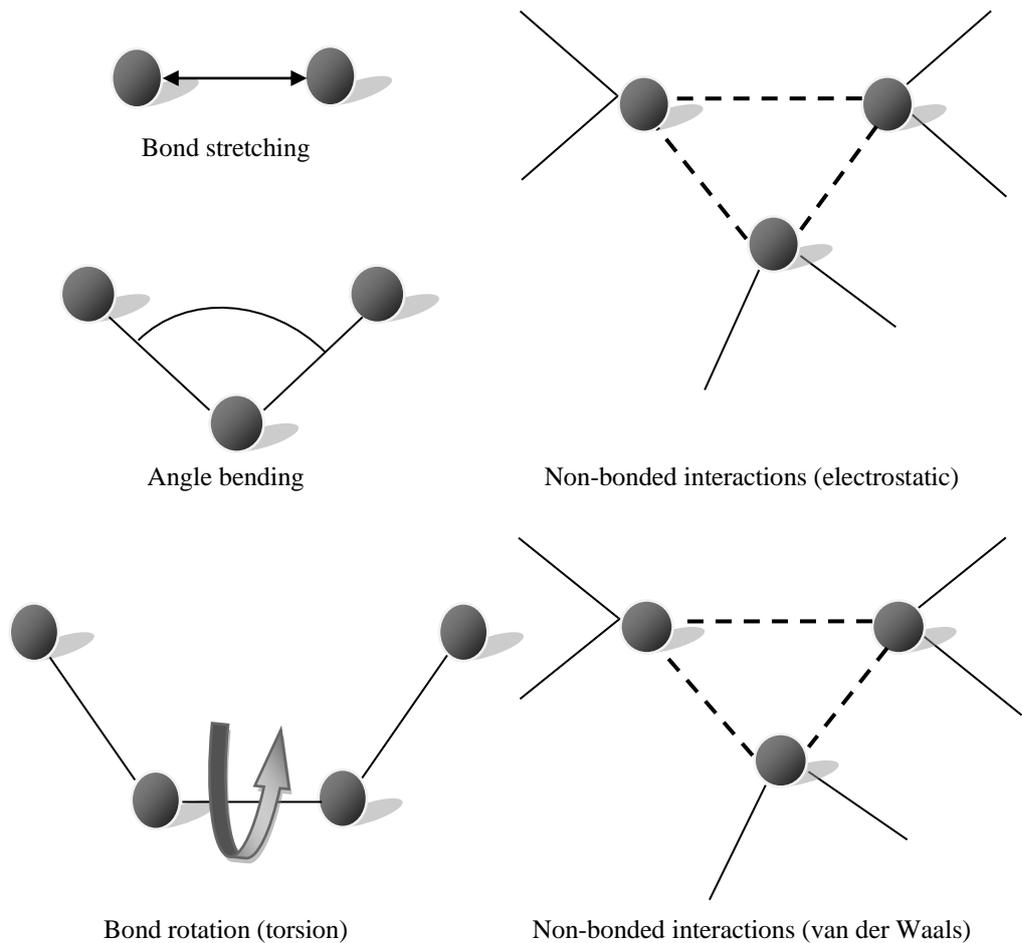
Figure 1-14: Schematic representation of bond stretching, angle bending, torsional terms and non-bonded interactions (adapted from[55])

## 1.5.2 System size and periodic boundary condition

Computer simulation method is a useful tool for investigating the properties of a model system. Limited by computational resources, only a small number of particles are used in simulation. In a small size system, the contribution of surface molecules to the property of the system becomes significant. However, in a real system, the number of surface molecules is very insignificant, and the contribution to the properties of the system is negligible, which means the property of the system is largely determined by the bulk molecules. Therefore, in many simulation studies, surface molecules are ignored completely and only focus on the bulk molecules by introducing the periodic

boundary condition (PBC) [57]. In periodic boundary conditions, the cubical simulation box is replicated throughout space to form an infinite lattice. During the simulation, when a molecule moves in the central box, its periodic image in each of the other boxes moves in exactly the same orientation and exactly the same way. Thus, as a molecule leaves the central box, one of its images will enter through the opposite face. Though there are no walls at the boundary of the central box, and the system has no surface, the momentum and position of the particles in the imaginary boxes are always relevant to the atoms in the original cell. Long-range electrostatic energy of each cell in a macroscopic lattice of repeating images will be calculated with the Particle Mesh Ewald (PME) summation method. Figure 1-15shows a two-dimensional example of such a periodic system [58].
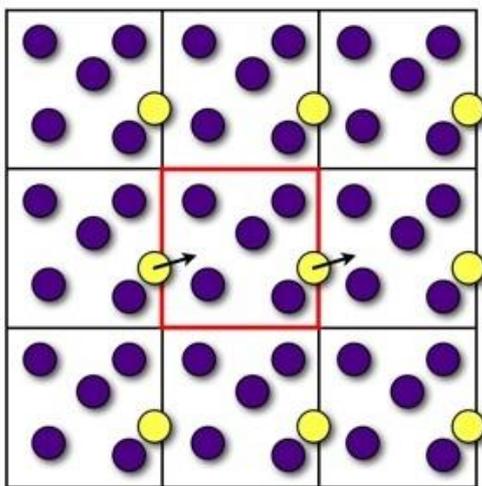


Figure 1-15: Two dimensional periodic boundary conditions (addopted from: http://matdl.org/repository/eserv/matdl:857/web_wiki2fez2465.jpg)

### 1.5.3  Ensembles and time averages from the MD simulations

Molecular dynamics simulations can describe the thermodynamic states of a system which contains a constant number of atoms ($N$), temperature ($T$), pressure ($P$), energy ($E$), and volume ($V$) [59]. Besides these, atomic positions r (in 3 dimensions),

and momenta p, are two parameters used for defining the macroscopic state of a system. These are considered as coordinates in a multidimensional space called phase space. Therefore there are $6N$ coordinates for a system with $N$ atoms [60]. Every individual point in the phase space determines the microscopic state of the system and a collection of these points is called the ensemble, which refers a specific macroscopic state. During a molecular dynamics simulation a sequence of points as a function of time will be generated in the phase space. Each point represents one configuration of the system, but all of them belong to the same ensemble. Table (1.3) shows different types of ensemble which are used in the molecular dynamics simulation. Each ensemble has an equilibrium state as follows:

Canonical ensemble (Q): minimum Helmholtz free energy (A), $A = -k_B T \ln Q$

Microcanonical ensemble $(\Omega)$ : maximum entropy $(S)$, $S = k_B \ln \Omega$

Grand canonical ensemble $(\Xi)$:maximum pressure and volume $(PV)$, $PV = k_B T \ln \Xi$

Isothermal-isobaric ensemble $(\Delta)$: minimum Gibbs function (G), $G = -k_B T \ln \Delta$

Table 1-2: Terminology in thermotropic mesophases and Synonyms in lyotropic mesophases

| Ensemble type | Constant parameters |
| --- | --- |
| Microcanonical $(\Omega)$ | N, V, E |
| Canonical $(Q)$ | N, V, T |
| Isobaric-Isothermal $(\Delta)$ | N, p, T |
| Grand canonical $(\Xi)$ | μ, V, T |

For a macroscopic sample the statistical average is calculated by equation(1.15)

$$\langle A \rangle_{ens} = \iint dp^N dr^N A(\, \boldsymbol{p}^N , \boldsymbol{r}^N \,) \rho(\, \boldsymbol{p}^N , \boldsymbol{r}^N \,),$$ 
(1.15)

where $A(p^N, r^N)$ is a function of coordinates and momenta and $\rho(p^N, r^N)$ is the probability density function. The probability density function is defined as:

$$\rho(p^N, r^N) = \frac{1}{Q} exp\left[-H(p^N, r^N)\Big/{k_B T}\right],$$
(1.16)

where $H$ is Hamiltonian, $k_B$ is the Boltzmann's constant, T is the temperature and $Q$ is the partition function of the system,

$$Q = \int ...dr^N \int ...dp^N \left[-H(p^N, r^N)\Big/{k_B T}\right].$$
(1.17)

Calculating thermodynamic properties such as energy $(E)$, entropy $(S)$ and heat capacity $(C_v)$ according to the partition function is difficult because of multi-integrations, which calculate for all accessible states of the system. Thus a molecular dynamics simulation is a good substitute for calculating the time average properties of the system from the thermodynamics ensemble [60].

### 1.5.4  Long-range interactions

In a molecular dynamics simulation the most time-consuming step is the calculation of the pair-wise non-bonded interaction since this changes quadratically with the number of atoms in the system. During the last 20 years several attempts have been made and different approximations have been used to decrease the computation effort needed [61]. One of these approximations is to use the cut-off that specifies the maximum distance between pairs of atoms before computing their energy of interaction. In this case, the forces between the atoms can be omitted when they are sufficiently far

from one another. Such a cut-off distance is suitable to model the contribution of the short-range force within the Lenard-Jones potential [62]. In the last few years, long-range interaction behaviour has been investigated [63, 64] and the most useful method for truncation is the Particle Mesh Ewald summation [65].The method of Ewald summation can be implemented on a grid. Essentially, the charges on the nuclei are mapped onto grid points, and the electrostatic problem is solved in two parts. The difference is that outside the "cut-off" the potential is not set to zero, but is solved using an approximate method. Inside the cut-off the potential energy is calculated using the Poisson equation. The grid method made the Particle Mesh Ewald (PME) approach tractable. This method is particularly important for nucleic acids, since they have polyanionic backbones. In this project the typical cut-off distance used is 9.

## 1.6    Schrodinger equation

A quantum mechanical model predicts the behaviour  of electrons [66]. There are some properties (reactivity, electronic, magnetic and optical) that can only be calculated using a QM model because these are determined from the electronic states that cannot be approximated well using other modelsincluding the atomistic force field models [67]. The Schrödinger equation is the fundamental equation of quantum mechanics. In order to use this equation to describe the interaction of electromagnetic radiation with matter the wavefunctions of the system must first be specified. Each wavefunction describes a particular quantum state of the molecule. In order to simplify the solution of the Schrödinger equation the states of the molecule are treated as time-independent stationary states in the "zero-order approximation". The Schrodinger equation is a partial differential equation (PDE) that can be written as:

$$\hat{H}\,\psi = E\psi,$$

<div align="right">(1.18)</div>

where $\hat{H}$ is the Hamiltonian operator, $\psi$ is the wave function and $E$ is the total energy of the system. The wave function contains all the information about the system which is of interest to chemists and physicists. The probability density of finding a particle in a given space at a given time is $|\psi|^2$. The Hamiltonian in Schrodinger's equation is:

$$\hat{H} = \hat{T} + \hat{V} \tag{1.19}$$

where $\hat{T}$ and $\hat{V}$ are kinetic and potential energy operators respectively. For a single electron system such as hydrogen atom these operators are:

$$\hat{T} = -\frac{h}{8\pi^2 m}\nabla^2, \tag{1.20}$$

and

$$\hat{V} = -\frac{Ze^2}{r}. \tag{1.21}$$

where, m is the mass of electron, r is the distance between electron and nucleus, $Z$ is the atomic number, e is the unit of the electronic charge and $\nabla^2$ is the Laplacian operator, $\nabla^2 = \left(\frac{\partial^2}{\partial x^2} + \frac{\partial^2}{\partial y^2} + \frac{\partial^2}{\partial z^2}\right)$, in the Cartesian coordinate system. Solving the Schrodinger equation for any system with more than one electron is difficult. Fortunately, there are different approximations that help to solve this equation for complex systems, even though they need a long computing time. In the generalized Schrödinger equation for a multinuclear, multielectron system, $\psi$ is a many-electron wave function and $H$ is the Hamiltonian operator which is equal to [68]:

$$\hat{H} = -\frac{1}{2}\sum_{i}^{electrons}\nabla_i^2 - \frac{1}{2}\sum_{A}^{nuclei}\frac{1}{M_A}\nabla_A^2 - \sum_{i}^{electrons}\sum_{A}^{nuclei}\frac{Z_A}{r_{iA}} +$$
$$\sum_{i}^{electrons}\sum_{j>i}^{nuclei}\frac{1}{r_{ij}} + \sum_{A}^{nuclei}\sum_{A<B}^{nuclei}\frac{Z_A Z_B}{R_{AB}}.$$

(1.22)

$Z$ is the nuclear charge, $M_A$ is the ratio of mass of nucleus $A$ to the mass of an electron, $R_{AB}$ is the distance between nuclei $A$ and $B$, $r_{ij}$ is the distance between electrons $i$ and $j$, and $r_{iA}$ is the distance between electron $i$ and nucleus $A$. Some coupling terms appear in this Hamiltonian that makes it difficult to solve this equation without applying certain approximations.

## 1.6.1 Born-Oppenheimer approximation

Max Born and J. Robert Oppenheimer suggested that to simplify the Schrodinger equation, one could consider the nuclear positions as fixed and the electrons as moving around the nucleus, because of the enormous difference in mass between electrons and nuclei. Accordingly, under the Born-Oppenheimer approximation the electronic wave function depends explicitly on the electron coordinates and parametrically on the nuclear coordinates. The Born-Oppenheimer approximation gives the electronic Schrodinger equation as follows[68]:

$$\hat{H}^{el}\psi^{el} = E^{el}\psi^{el},$$

(1.23)

where,

$$\hat{H}^{el} = -\frac{1}{2}\sum_{i}^{electrons}\nabla_i^2 - \sum_{i}^{electrons}\sum_{A}^{nuclei}\frac{Z_A}{r_{iA}} + \sum_{i}^{electrons}\sum_{i<j}^{electron}\frac{1}{r_{ij}}.$$

(1.24)

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In this equation the term describing the nuclear kinetic energy is zero, and the nuclear-nuclear Coulomb term is constant. The latter needs to be added to the electronic energy, $E_{el}$, to yield the total energy, $E$, for the system.

$$E = E^{el} + \sum_{A}^{nuclei} \sum_{A<B}^{nuclei} \frac{Z_A Z_B}{R_{AB}}. \tag{1.25}$$

### 1.6.2   Hartree-Fock approximation

The electronic Schrödinger equation (1.23) is still unsolvable and further approximations are required. At first glance, the electrons may be considered to move independently of one another. Practically, individual electrons are confined to functions called molecular orbitals, which are defined by assuming that the electron is moving within an average field of all the other electrons. The total wave function $\psi$, is written in the form of a single determinant (Slater determinant) which is given as:

$$\psi(x_1, x_2, ....x_N) = det \begin{bmatrix} \psi_1(x_1) & \psi_1(x_2) & ... & \psi_1(x_n) \\ \psi_2(x_1) & \psi_2(x_2) & ... & \psi_2(x_n) \\ . & . & . & . \\ . & . & . & . \\ \psi_n(x_1) & \psi_n(x_2) & ... & \psi_n(x_n) \end{bmatrix}, \tag{1.26}$$

$(\psi_n, n=1,2,....n)$ is the wave function of each particle. This approximation reduces a wave function in the 3N dimensional space to N wave functions in the 3-dimensional space, which are computationally solvable. The assumption that the electrons in the systeminteract with one another only through a mean field is equivalent to the approximation of the electronic wave function by a Slater determinant, thus effectively ignoring completely the electron correlation. The Hartree-Fock (HF) method provides

the ground-state energy of the system, which is slightly higher than itsreal ground-state energy. With regard to this, the Hartree-Fock method has a useful variational structure associated with it. Exploiting this variational structure, the Hartree-Fock method has been extended to obtain a more refined electronic structure, which is described by the multi-configuration method. A multi-configuration methodis a natural generalization of the Hartree-Fock method, where a linear combination of a number of Slater determinants is used to approximate the wave function, against a single Slater determinant in the case of Hartree-Fock approximation. It can be shown that as the basis of the single electron wave function is increased to span the complete Hilbert space, the multi-configuration equations reproduce the exact quantum mechanical equations[69, 70]. The Hartree-Fock approach has been used quite extensively, over the course of last few decades. The major drawback of HF method is the exclusion of electron correlation. Moller-Plesset perturbation models start with an HF caluculation and then correct for electron repulsion. Moller-Plesset perturbation theory are denoted as MPn (n=2,...,6). In practice, MP2 and MP4 are the only methods used, since the other n's are either too computationally expensive or do not improved the results significantly compared to those obtained from a method with less complexity (i.e. lower level approximation). In another approach to overcome the lack of electron-electron correlation in the HF method, Hohenberg, Kohn, and Sham introduce the density-functional theory (DFT), which uses the electron density to represent the ground-state energy of the system. DFT has become very popular for its accuracy, reliability, and feasibility of electronic structure calculations on a wide range of materials[71]. In this research we used the DFT method to calculate the energy of the new class of glycolipid crown ether and these contain cations such as $K^+$ and $Na^+$.

### 1.6.3 Density functional theory

The density functional theory(DFT) is based on a variationl formulation, which reduces the problem of solving the Schrodinger equation of an N-electron system to evaluating the wave functions and energies of an effective single-electron system.Although, it is suitable for ground state calculation, the technique may be used to calculate the excited state [72]. DFT is based on the hypothesis that "describing the properties of a material system in its ground state is possible only with the electron density is a "principle variable" [73, 74]. This is a significant and powerful expression, to reduce the problem of solving a quantity (electronic wave-function) in the 3N-dimensional space to solving a quantity (electron-density) in the 3-dimensional space. Accordingly, [74]DFT is based on the fact that the sum of the exchange and correlation energies of a uniform electron gas can be calculated exactly when its density is known.In the Kohn-Sham formalism, the ground state electronic energy, $E$, is written as a sum of the kinetic energy, $E_T$, the electron nuclear-interaction energy, $E_V$, the Coulomb energy, $E_J$, and the exchange/correlation energy, $E_{xc}$.

$$E = E_V + E_J + E_T + E_{xc}. \tag{1.27}$$

Except for $E_T$, all components depend on the total electron density, $\rho(r)$:

$$\rho(r) = 2 \sum_{i}^{orbitals} \left| \psi_i(r) \right|^2. \tag{1.28}$$

Here, $\psi_i(r)$ are the so-called Kohn-Sham orbitals and the summation is carried out over pairs of electrons. Within a finite basis set (see next section), the energy components may be written as follows:

$$E_T = \sum_{\mu}^{basis} \sum_{V}^{functions} \int \phi_\mu(r)\left[-\frac{1}{2}\nabla^2\right]\phi_V(r)dr, \tag{1.29}$$

$$E_V = \sum_{\mu}^{basis} \sum_{E_T}^{functions} \rho_{\mu V} \sum_{A}^{nuclei} \int \phi_\mu(r)\left|\frac{Z_A}{\|r-R_A\|}\right|\phi_V(r)dr, \tag{1.30}$$

$$E_J = \frac{1}{2}\sum_{\mu}^{basis}\sum_{V}\sum_{\lambda}^{functions}\sum_{\sigma}\rho_{\mu V}\rho_{\lambda\sigma}\left(\mu V/\lambda\sigma\right), \tag{1.31}$$

$$E_{xc} = \int f\left(\rho(r),\nabla\rho(r),...\right)dr. \tag{1.32}$$

$Z$ is the nuclear charge, $r-R_A$ is the distance between the nucleus and the electron, $\rho$ is the density matrix, $\left(\mu V/\lambda\sigma\right)$ is two-electron integrals, and $f$ is an exchange/correlation function, which depends on the electron density and perhaps as well as on the gradient of the density. Minimizing $E$ with respect to the unknown orbital coefficients yields a set of matrix equations.

### 1.6.4   Molecular orbital theory

The molecular orbital theory is an alternative approach to studying the electronic structure of molecules[75]. This theory uses the concept of the orbital to understand the electronic structure of atoms and molecules. The advantage of using an orbital is that it reduces a many-body problem to the same number of one-body problems in the study of electrons in atoms or molecules. Generally, an orbital is the quantum mechanical description (wave function) of the motion of a single electron moving in the average potential field of the nuclei and of the other electrons present in the system[75]. The difficulty in determining the average potential field of the other electrons makes it hard to obtain an accurate description of an orbital. For example, the 2$s$ orbital in the lithium

atom is a function, which determines the motion of an electron in the potential field of the nucleus and in the average field of the two electrons in the 1s orbital. However, the 1s orbital is itself determined by the nuclear potential field and the average potential field exerted by the electron in the 2s orbital. In a system, all orbitals are relevant to one another and to know the form of one orbital we need to know the forms of all of them[75]. There is a mathematical solution to overcome this problem. The difference between molecular and atomic orbitals is that, in the former the orbital must demonstrate the motion of an electron in the field of more than one nucleus, as well as in the average field of the other electrons[75]. A molecular orbital generallyencompasses all the nuclei in the molecule, rather than being centered on a single nucleus as in the atomic case. After defining the forms and properties of molecular orbitals, we can use the Pauli'sexclusion principle to assign electrons to the molecular orbitals, in the order of increasing energy, to specify the electronic configuration and properties of the molecule[75]. According to the valence bond theory, a covalent bond is formed between two atoms by the overlap of half-filled valence atomic orbitals of each atom containing one unpaired electron (or mathematically formulation of the theory, the product of atomic orbitals). In contrast, in the molecular orbital theory the electrons are not assigned to individual bonds between atoms, but are treated as moving under the influence of the nuclei in the whole molecule.

### 1.6.5   The basis set approximation

In the Hartree-Fock method, theequations for small highly symmetric systems may be solved by mapping the orbitals on a set of gridpoints. Nevertheless, to express the unknownMOs (molecular orbitals) in terms of a set of known functions, all calculations use a basis set expansion. A basis set in theoretical and computational

chemistry is a set of functions (called basis functions) which are combined in linear combinations to create MOs.[76] Different types of basis functions such as exponential, Gaussian, polynomial, cube and plane wave can be used [77]. We can choose the basis function according to two different recipes. In the first recipe, the basis functions should have a behaviour, which agrees with the physics of the problem. In this case, the convergence is reasonablyrapid as more basis functions are added.For bound atomic and molecular systems, the functionsshould go towards zero as the distance between the nucleus and the electronsbecomes large[77]. In the second recipe, the chosen functions shouldmake it easy to calculate all the required integrals.Slater type orbitals(STO) and Gaussian type orbitals (GTO) are two different types of basis functions, which are generally used in electronic structure calculations. GTO gives less accurate results but it uses a simple calculation process, making it more favorable [78].  Slater type orbital has the functional form:

$$X_{\xi,n,l,m}(\,r,\theta,\phi\,)=NY_{l,m}(\,\theta,\phi\,)r^{n-1}e^{-\xi r}.$$

(1.33)

where $N$ is a normalization constant and $Y_{l,m}$ are the usual spherical harmonic functions.STOs are primarily used foratomic and diatomic systems, where high accuracy is required[78]. We can use polar or Cartesian coordinates to write Gaussian type orbitals:

$$X_{\xi,n,l,m}(\,r,\theta,\phi\,)=NY_{l,m}(\,\theta,\phi\,)r^{(\,2n-2-1\,)}e^{-\xi r^2 r},$$

(1.34)

$$X_{\xi,l_x,l_y,l_z}(\,x,y,z\,)=Nx^{l_x}y^{l_y}z^{l_z}e^{-\xi r^2}.$$

(1.35)

where the sum of $l_x$, $l_y$ and $l_z$ determines the type of orbital (for example $l_x+l_y+l_z=1$ is a p-orbital). There is a precise difference between the two sets of GTO coordinates. A d-

type GTO is written in terms of the spherical function which has five components $(Y_{2,2}, Y_{2,1}, Y_{2,0}, Y_{2,-1}, Y_{2,-2})$, but there appears to be six components in the Cartesian coordinates $(x^2, y^2, z^2, xy, xz, yz)$. The latter six functions, however, may be understood as five spherical d-functions and one additional s-function $(x^2 + y^2 + z^2)$. Similarly, there are 10 Cartesian "f-functions" which may be modified into seven spherical f-functionsand one set of spherical p-functions. Having decided on the type of function (STO or GTO) and the location (nuclei), the most important factor is the number of functions to be used. In the minimum basis set we have the least number of possible functions. For example for hydrogen and helium only a single s-function is necessary, while for the first row elements in the periodic table two s-functions ($1s$ and $2s$) and one set of p-functions ($2p_x, 2p_y$ and $2p_z$) are required.Lithium and beryllium formally only require two s-functions, but a set of p-functionsis usually also added. For the second row elements, three s-functions(1s, 2s and 3s) and two sets of p-functions (2p and 3p) are used[78]. Abriefdescription of some common basis sets(generallycalled Pople Style Basis Sets) are mentioned by Jensen (1998)[78]as follows:

**a)STO-nG basis sets:** There are Slater type orbitals that have n PGTOs (primitive Gaussian type orbitals). This is aminimum type basis, where the exponents of the PGTO are determined by fittingto the STO, rather than optimizing them by a variational procedure. Althoughbasis sets with n = 2, 3…6 have been derived, it has been found that using more thanthree PGTOs to represent the STOs gives little improvement, and the STO-3Gbasis is a widely-used minimum basis [76].

**b)3-21G:**This is a split va1ence basis, where the core orbitals are a contractionof three PGTOs, the inner part of the valence orbitals is a contraction of twoPGTOs and the outer part of the valence is represented by one PGTO. Notethat the 3-21G basis

contains the same number of primitive GTOs as the STO-3G. However, it is much more flexible as there are twice as many valence functions, which can combine freely to make MOs [76].

c)**6-31G:**This is also a split valence basis, where the core orbitals are acontraction of six PGTOs, the inner part of the valence orbitals is a contractionof three PGTOs and the outer part of the valence is represented by one PGTO. Interms of contracted basis functions it contains the same number as 3-21G, but therepresentation of each function is better since more PGTOs are used[76].

d)**6-311G:**This is a triple split valence basis function, where the core orbitals are acontractionof six PGTOs and the valence orbital splits into three functions, representedby three, one and one PGTOs, respectively.To each of these basis sets, diffuse and/or polarization functions can be added.Diffuse functions are normally s- and p-functions and consequently written beforethe G, denoted by + or ++, with the first + indicating one set of diffuses- and p-functions on heavy atoms, and the second + indicating that a diffuse s-functionis also added to hydrogen. Polarization functions are indicated after the G,with a separate designation for heavy atoms and hydrogen atoms. The 6-31+G(d) is asplit valence basis with one set of diffuse sp-functions on heavy atoms only and a single d-type polarization function on heavy atoms[78]. Similarly 6-311++Gis a triple split valence with additional diffuse sp-functions, and two d- andone f-functions on heavy atoms and diffuse s- and two p- and one d-functionson hydrogen. The largest standard Pople style basis set is 6-311++G. These types of basis sets have been derived for hydrogen and the first row elements, and some of the basis sets have also been derived forsecond and higher row elements[78]. If only one set of polarization functions is used, an alternative notation in termsof * is also widely used. The 6-31G*

basis is identical to 6-31G(d), and 6-31G**is identical to 6-31G(d,p). A special note should be made for the 3-21G* basis.The 3-21G basis is basically too small to support polarization functions (itbecomes unbalanced). However, the 3-21G basis by itself performs poorly forhypervalent molecules, such as sulfoxides and sulfones. This can besubstantially improved by adding a set of d-functions. The 3-21G* basis hasonly d-functions on second row elements (it is sometimes denoted as 3-21G(*) toindicate this), and should not be considered a polarized basis[78].

## 1.7    Objectives and outline of the chapters in this thesis

Glycolipids are one of the principle components in the cell membrane, and play important roles in many cellular processes; therefore, there is a need to understand them at the molecular levelto relate their structuresto the properties of their assemblies. The combination of self-assembly with the special functionality of some supra-molecular structure provides a way to scale up this specific function from molecular level to the nano scale, offering improved performance to the self-assembly system. For example, macrocyclic ligands, like crown ethers which can bind with sugar based surfactant has the ability to increase the solubility of selected ions. Additionally, their spherical structure with metal complexation implies a large surface area for the polar head group of a crown ether-sugar based surfactant.

According to the packing theory, an increase in the surface areas of the macrocyclic head group compare to the hydrophobic chain, limits the ability of the surfactant to form a lamellar phase, but instead promotes the formation of non-lamellar phases. In this thesis, we investigate the electronic properties of synthesized sugar based crown ether molecules and proceed with the study of the self-assembly behaviour of

glycolipids in two different phases namely, two-dimensional bilayer and three-dimensional hexagonal phase.

The thesis is divided into seven chapters. The first chapter includes a general introduction on glycolipid and crown ether systems, the underlying the principles of quantum mechanics and the review of some basic concepts of molecular dynamics simulation.

In the second chapter we have a brief overview of the past experimental and computational research on crown ether systems and also the investigations of the self-assembly of glycolipids in hexagonal, bilayer and micellar phases.

Methodology and technical parts of the DFT calculation of crown ether systems and their complexes with cation, the techniques used for modeling and the simulation of a reverse hexagonal ($H_{II}$) phase and bilayer systems are explained in Chapter 3.

Chapter 4 presents the results of the density functional theory (DFT) investigation of glucose-based glycolipid crown ethers and their complexes with alkali metal cations $Na^+$ and $K^+$. This probe helps to have a deeper understanding of the electronic properties, molecular conformation, thermodynamic behaviour of crown ethers and their complexes with cations $Na^+$ and $K^+$ and determine the selectivity of different crown ether sugar-based surfactants toward $Na^+$ and $K^+$.

The results from the simulation of the bilayer (thermotropic) and hexagonal (lyotropic) phases are given in chapter 5 and 6 respectively. From the simulation of the anhydrous bilayer we expected to gain knowledge on the molecular interactions within the hydrophilic region of bilayer, considers the effect of detailed stereochemistry of

sugar without any solvent and find the molecular substantiation on the likely relationship between two pairs of liner glycolipids, namely, $\alpha/\beta$-octyl-galactosides ($\alpha/\beta$-C$_8$Gal) and $\alpha/\beta$-octyl-glucosides ($\alpha/\beta$-C$_8$Glc) in thermotropic bilayer system. The interactions between the sugar head and water molecules in H$_{II}$ phase and examine the extension and compression of the alkyl chain by calculating the distribution of average radial distance of CH$_3$ group over the angle around a cylinder is another achievement of this project.

Finally, in Chapter 7 we discuss the overall conclusion of the three different works in this thesis and future research undertakings as a result.

# CHAPTER 2

## LITERATURRE REVIEWON CROWN ETHER, BILAYER AND REVERSED HEXAGONAL SYSTEMS

## 2.1    Literature review of quantum study on crown ether system

Since the fortuitous discovery of macrocyclic polyethers by Pedersen in 1967 [34], there has been huge interest in these compounds as complexing agents, primarily for metal ions and also for some neutral and anionic species [79]. They exhibit strong affinity and high selectivity for alkali and alkaline earth metal ions because of a hydrophilic cavity consisting of heteroatoms, demarcated by a lipophilic envelop of ethylene units [80, 81]. Researchers use them as a model for biologically significant host-guest interactions [79]. Their specific efficiency can be found in the areas of chromatography separation, molecular transport, catalysis, selective transport and separation of metals, phase-transfer catalysis, solvation of ions in nonpolar solvents, stabilization of proton action sites in biological molecules, and isolation of radioactive components of nuclear wastes [82-84]. Apart from this, crown ethers and their behaviours in different environments are interesting for theoretical scientists. In 1990 Dang and Kollman [85] performed a molecular dynamics simulation study on the free energy of association of 18-crown-6: $K^+$ complex in water. They investigated the cation-crown association process in aqueous solution using thermodynamic perturbation theory and molecular dynamics simulations. They found that, when the $K^+$ was in thecenter of the crown ether, the structure with $D_{3d}$ symmetry was the stable structure. A hybrid of quantum mechanics and molecular mechanics calculation of the nature of $K^+$/crown ether interactions was published by Mark A. Thompson [86]. Their results for the simulation of $K^+$/18C6 in $H_2O$ show that the most probable $K^+$/18C6 center of mass displacement is 0.25 Å. A density functional theory with B3LYP/6–31G* method has been used by Hou to explore the  molecular and electronic structures for 12- to 16-crown-4 (named 12C4, 13C4, 14C4, 15C4, 16C4, respectively) and their complexes with alkali metal cations $Li^+$ and $Na^+$[87]. Their selectivity tendency shows that among all crown ethers, the highest cation selectivity for $Li^+$ over $Na^+$ belong to the 14-crown-

4. Their finding also shows that $Li^+$/crown-4 series are more stable than $Na^+$/crown-4 series in the gas phase. There are many other experimental and theoretical studies in the different compounds of crown ethers to understand their nature and function of crown ethers [88-91]. The result of an *ab initio* study of 18-crown-6 and its interaction with the alkali metal cations $Li^+$, $Na^+$, $K^+$, $Rb^+$, and $Cs^+$ was published by Glendening*et al*. [92]. They used the Restricted Hartree-Fock (RHF) method with 3-21G and 6-31+G* basis sets to calculate the geometries, binding energies, and binding enthalpies. MP2 method was used to estimate the electron correlation effect and the wave function analysis was performed by the natural bond orbitals (NBOs) and associated methods. The result of the research showed that the strong affinity of alkali metal cations (50-100 kcal $mol^{-1}$, depending on cation type) was due to the electrostatic (ionic) interaction of the cation with the nucleophilic ether backbone. Also, the charge transfer (covalent bonding) has less effect on the affinity of alkali metal cations. They found that in the gas-phase and in aqueous environments, 18-crown-6 preferentially bound to $Li^+$, not $K^+$[92].

Martínez-Haya*et al*. [93] applied infrared spectroscopy and quantum mechanical calculation to investigate the emergence of symmetry and chirality in gas-phase complexes formed by the 18-crown-6 ether with the alkali metal cations employed. The results showed that chirality and symmetry have a dominant role in the conformational landscape of the 18-crown-6-alkali system. $C_{3V}$ is the dominant symmetry for 18-crown-6-$M^+$ conformers, while $C_2$ for $Cs^+$, $D_{3d}$ for $K^+$, $C_1$ and $D_{3d}$ for $Na^+$, and $D_2$ for $Li^+$.

In 1994 Kowall *et al*. [94]  applied molecular dynamics simulations on crown ether 18-crown-6 and $K^+$ (18-crown-6/$K^+$ ) in aqueous solution to investigate the structure and dynamics of the hydration shell.  They found that on both sides of the

crown's plane a distinct water molecule was translationally fixed by two H-bonds. From the structural and dynamical properties of the hydration shell there was a clear distinction between the hydrophilic and hydrophobic regions. A complexed $K^+$ ion stayed about 1 Å outside the crown's center and could be regarded as replacing one of the two "complexed" water molecules. A molecular dynamics study on the mechanism of ion selectivity in aqueous solutions of 18-Crown-6 ether was performed by Dand [95] using the potential of mean force approach to the evaluation of crown ether selectivity in an aqueous solution. The free energy profiles and the corresponding binding free energies for $M^+$:18-crown-6 ($M^+ = K^+$, $Na^+$, $Rb^+$, $Cs^+$) indicated that minimum free energy surfaces for $K^+$ and $Na^+$ were located at the crown ether center of mass. At the same time, a second minimum for $Na^+$ was also observed in the potential of mean force. In their investigation they also considered the relevance between the size of cation and the crown ether cavity. The calculated binding free energies were less than the experimental values, but the trend ($K^+ > Rb^+ > Cs^+ > Na^+$) in both experimental and theoretical cases was the same.

## 2.2    Literature review of simulation studies on micellar, bilayer and hexagonal systems

Although, lamellar being the most studied lyotropic liquid crystalline phase and useful for drug delivery and biomembranes [96], other self-assembly structures such as hexagonal, micellar etc… have also drawn research interest in both experiments and simulations. The materials forming these phases are usually amphiphilic in nature such as phospholipids and glycolipids. Since this thesis concerns glycolipids that can form various phases for example micelles, bilayers and hexagonal phases, hence this section surveys a selection of literatures related to the present studies using mainly the pre-constructed computer atomistic models.

The simplest form of self-assembly system, the micellar phase has been studied by many groups using full atomistic models of real surfactants such as sodium dodecyl sulfate (SDS). Bogusz*et al.* performed probably the earliest molecular dynamics simulation on a pre-constructed model to the structural properties of glycolipid micelle of n-octyl-$\beta$-D-glycopyranoside to explore the effect of aggregate size on the structural properties of octyl glucoside (OG) micelles [97]. They have selected micelle systems containing 1, 5, 10, 20, 27, 34, 50, and 75 surfactant molecules in water, as well as an OG bilayer, and neat octane. The results showed that micelles with aggregation containing at least 10 remained intact during the 4 ns simulations. In addition, some properties such as aggregate shape and internal properties (tail length, dihedral angle distributions, and isomerization rates) did not change much during the simulation time, while the changes in surface properties (hydrophobic accessible surface area and head group cluster size) were reasonable. Following this, there was another MD investigation for the micelle size of n-octyl-$\beta$-D-glucopyranoside, n-octyl-$\beta$-D-maltopyranoside and n-octyl-$\beta$-D-galactopyranoside[98]. This work showed that the n-octyl-$\beta$-D-galactopyranoside micelle was bigger in size than the n-octyl-$\beta$-D-glucopyranoside system, a result comparable with the experimental data of small-angle neutron scattering method[99]. In another study of the micellar phase using a galactose head group, an MD simulation of n-octyl-$\beta$-D-galactopyranoside with two different initial coordinates and velocities in explicit solvent was performed by Konidala *et al*. to determine the characteristic of n-octyl-$\beta$-D-galactopyranoside aggregate[100]. They calculated geometric packing parameters and distinguished the prolate ellipsoid for the average micelle structure.Iin addition they calculated the radial distribution functions for the hydroxyl oxygen atoms of the n-octyl-$\beta$-D-galactopyranoside. The results showed that at a minimum van der Waals contact distance sharper peaks were observed for the

hydroxyl oxygen atoms than those for the acetal oxygen, ring oxygen and aromatic carbon atoms [100].

Recently, there has been increasing interest in the more complicated self-assembly in 2-D and 3-D ordered structures of the lyotropic liquid crystalline phases, such as reverse hexagonal ($H_{II}$) and reverse biontinuous cubic phases ($V_2$)[101]. These phases can be stable in excess water as in the case of lamellar phase, which simplifies the preparation of nanoparticle dispersions and makes them suitable for encapsulation and controlled release of drugs. Water channel diameter and lipid bilayer thickness are two important factors in the application of reverse phases for encapsulation and controlled release[101].The result of a 10 ns MD simulation of hydrogen bonding structure and dynamics of water at the dimyristoylphosphatidylcholine (DMPC) lipid bilayer surface was presented by Lopez[102].The average of hydrogen bonds per lipid's oxygen atom was varied depending on its position within the lipid. The hydrogen bonding dynamics of water at the lipid surface investigation revealed that the life of a single-bonded lipid oxygen atom was shorter than that between the water and the double-bonded lipid oxygen atoms. Moreover, hydrogen bonds between water and the head group oxygen atoms were shorter than those between water and the tail lipid oxygen atoms[102]. Shinoda *et al*. [103] performed an MD simulation on straight- and branched-chain dipalmitoylpho-sphatidylcholine (DPPC) and diphytanoylphosphatid-ylcholine (DPhPC) respectively to understand the effect of branching on bilayer properties. A comparison between the results of these compounds showed that the higher structural stability of the branched DPhPC bilayer was attributable to the slower conformational motion of the hydrophobic chain. Also, the characteristic conformation of the branched-chain decreased the probability of parallel chains in lipid. On the other hand, to date, detailed simulation studies on glycolipids self-assembly [104-108] are

relatively rare compared to studies conducted for phospholipids bilayer systems[109, 110].

An MD simulation on 200 n-octyl-$\beta$-D-glycopyranosides solvated in 584 water molecules was performed for 1 ns, and some different parameters such as the tilt angle and the chain length to investigate the bilayer structure were calculated [111].They found thatin the case of alkyl monosaccharide glycolipids, only branched-chain compounds gave a thermotropic fluid lamellar ($L_\alpha$)phase at roomtemperature, and that this phase occurred atmuch higher temperaturesfor the monoalkylated systems. At room temperature, only the gel phase ($L_\beta$) or lamellar crystal ($L_C$) phase could be observed for monoalkylated systems[112]. Recently, Manickam Achari*et al.*[108] explored the effect of sugar head group and tail branching of four anhydrous bilayers of dodecyl $\beta$-maltoside, dodecyl $\beta$-cellobioside, dodecyl $\beta$-isomaltoside and a branched-chain maltoside ($\beta$BCMal-$C_{12}C_{10}$) in lamellar phase. They found that glycolipid chain branching had a remarkable effect on the dimensions and interactions of the lamellar assembly but this effect was rather less than in the substitution of the maltosyl head group with an isomaltosyl moiety. This investigation also showed that the microscopic properties of the glycolipid assemblies were highly affected by the sugar head group stereochemistry.

Simulation interest in non-lamellar curved phases such as the hexagonal phase appeared in the literature very recently. These phases have interesting structural and dynamic roles in biological systems[17, 113]. They can be stable in excess water as in the case of the lamellar phase. They are characterized by densely-packed, straight water-filled cylinders and exhibit a 2-D ordering[114]. These systems are considered to be active as transient intermediates in biological phenomena that require topological

rearrangement of the lipid bilayers such as in membrane fusion[115]. The first normal hexagonal phase $H_I$ was distinguished in aqueous solution of tobacco mosaic virus by Bernal[116]. This type of hexagonal phase is widespread in biological systems, especially in DNA solutions, polysaccharides and polypeptides. After that, Mc Bain found the first normal hexagonal phase $H_I$ of lipid/water in hydrated dodecyl sulfonic acid in 23-70% in water[117]. Consequently, Luzzati *et al*. elucidated its structure [118], and also distinguished the $H_{II}$ phase of phospholipids in the human brain lipid at below 22 wt% water contents and 37 ℃[119, 120]. The same structure was characterized by Ekwall *et al*. in the ternary surfactant system of sodium caprylate-/decanol/water[121]. In 1992, Takada *et al*.performed X-ray diffraction studies on a series of cellobios octa-alkanoates with alkyl chain lengths from 7 to 14. They observed that all components form enantiotropic discotic columnar phases, and all these formed columns were in a two-dimensional lattice. Temperature and the member of the homologous were two important factors in this kind of phases. So hexagonal ordered columnar (Colho) phases would form with n=9-14 while rectangular ordered columnar (Colro) phase would form with n=7[122]. Francescangeli reported the evidence of an inverted hexagonal phase $H_{II}$ of phospholipid-DNA-metal complexes that self-assembled in an aqueous mixture of neutral lipid dioleoylphosphatidy-lethanolamine, DNA and divalent metal cations (Fe, Co, Mg, Mn). X-ray diffraction showed cylindrical DNA strands that arranged on a two-dimensional hexagonal lattice and covered by a lipid monolayer[123]. Recently, Zahid *et al*. showed the stable hexagonal phase of *β*-D-maltoside (comprised 65% (w/w)), using fluorescent probes[124]. A molecular dynamics study of the hexagonal mesophase of sodium dodecylsulphate (SDS) in aqueous solution has been carried out by Sanjoy[125]. The simulation system consisted of two cylindrical aggregates, each containing 128 SDS and 4350 water molecules plus 256 sodium counterions. The simulation production time was 260ps and it was

conducted at T= 333K. The result showeda small distortion from the ideal hexagonal symmetry. Meanwhile, Vesselin Kolev and coworkers [126] used molecular dynamics simulation to investigate the structure of water inside the cylinder of the inverse hexagonal mesophase (H$_{II}$) of glyceryl monooleate. They used an NVT ensemble and the simulation time was 10 ns with GROMACS software[126]. Radial distribution function, distribution of hydrogen bonds and density of a water molecule across the water cylinder showed the presence of water structure deep in the cylinder. A computer simulation of a hexagonal assembly for a Guerbet-type maltoside involving a long symmetrically branched-chain alcohol was performed by Chong [127]. This model consisted of 224 glycolipids and 560 water molecules. The simulation time was 5 ns at 300 °K using Amber package[128]. They found stable hexagonal structures and classified water as bond water.

There are several experimental investigations on the transition from lamellar to an inverted hexagonal phase and also on the behaviour of the hexagonal structure for a variety of systems[129-132].To study such phenomena, a fully atomistic simulation model is unsuitable. Therefore, many coarse-grain simulation models have been proposed. For example, Corsi*et al*. reported a coarse-grained molecular dynamics simulation of H$_{II}$ phase formation in a dsDNA-HL system as a function of hydration, and a change from L$_{\alpha}$ to H$_{II}$[133]. They showed that a coarse-grained MD simulation is a powerful tool to understand and design novel lipoplex systems. Marrink and Mark also used coarse-grained (CG) molecular dynamics simulation to study the transition pathway from a multilamellar to an inverted hexagonal. They used the Lennard-Jones potential and considered every 4-6 heavy atoms as a single coarse-grained interaction center. On a nanosecond timescale, they saw spontaneous stalks formation from

multilamellar configuration, and finally, these stalks elongated to form the inverted hexagonal phase[134].

In the next chapter we demonstrate the methodology and quantuthe calculation of glycolipid crown ether system with GAUSSIAN 09 and also the initial configuration, model building procedures and molecular dynamics simulation with AMBER and GROMACS which are used for the simulation of bilayer systems (thermotropic phase) and also the simulation of hexagonal phase respectively.

# CHAPTER 3


# RESEARCH METHODOLOGY

## 3.1 System description and quantum calculations of sugar-based glycolipids with the crown ether

In this part of the project we used the Avogadro software package [135] for preparing the primary structures of five compounds which are combination of glyclipid dodecyl-$\beta$-D-glucoside with the crown ether attached to hydroxyl groups at O2 and O3 namely 15-crown-5 (G15C5), 18-crown-6 (G18C6) and 21-crown-7 (G21C7) and also16-crown-5 (G16C5) and 19-crown-6 (G19C6) with the crown ethers attached to the hydroxyl groups at O4 and O6. The Molecular mechanics of Merk Molecular force field (MMFF94) available within the software was used to minimize the conformational energies for these models (Figure 3-1). Using these optimized conformations, glycolipid crown ether complexes with cations $Na^+$ or $K^+$ were prepared by bringing the cation close to the crown ether ring (Figure 3-2 and Figure 3-3). FurtherMMFF94 minimizations were performed to obtain the optimizedcomplexes so that all oxygen atoms on the crown ether ringwere as close as possible to the cations. These optimizes structures and their complexes were studied using the density functional theory (DFT) at B3LYP/6–31 G* level. All the calculation was carried out using the Gaussian 09 program package[136]. The DFT method is an efficient method in the study of large molecules and has been widely used since it is capable of giving sufficiently accurate conformational analyses and thermodynamics properties. Meanwhile the B3LYP (Becke-Lee-Yang-Parr) version of DFT is the combination of Becke's three-parameter nonlocal hybrid functional of exchange terms [137] with the Lee, Yang and Parr correlation functional[138].The basis set able to reproduce experimental data[139, 140].

G15C5

G18C6

G21C7

G16C5

G19C6
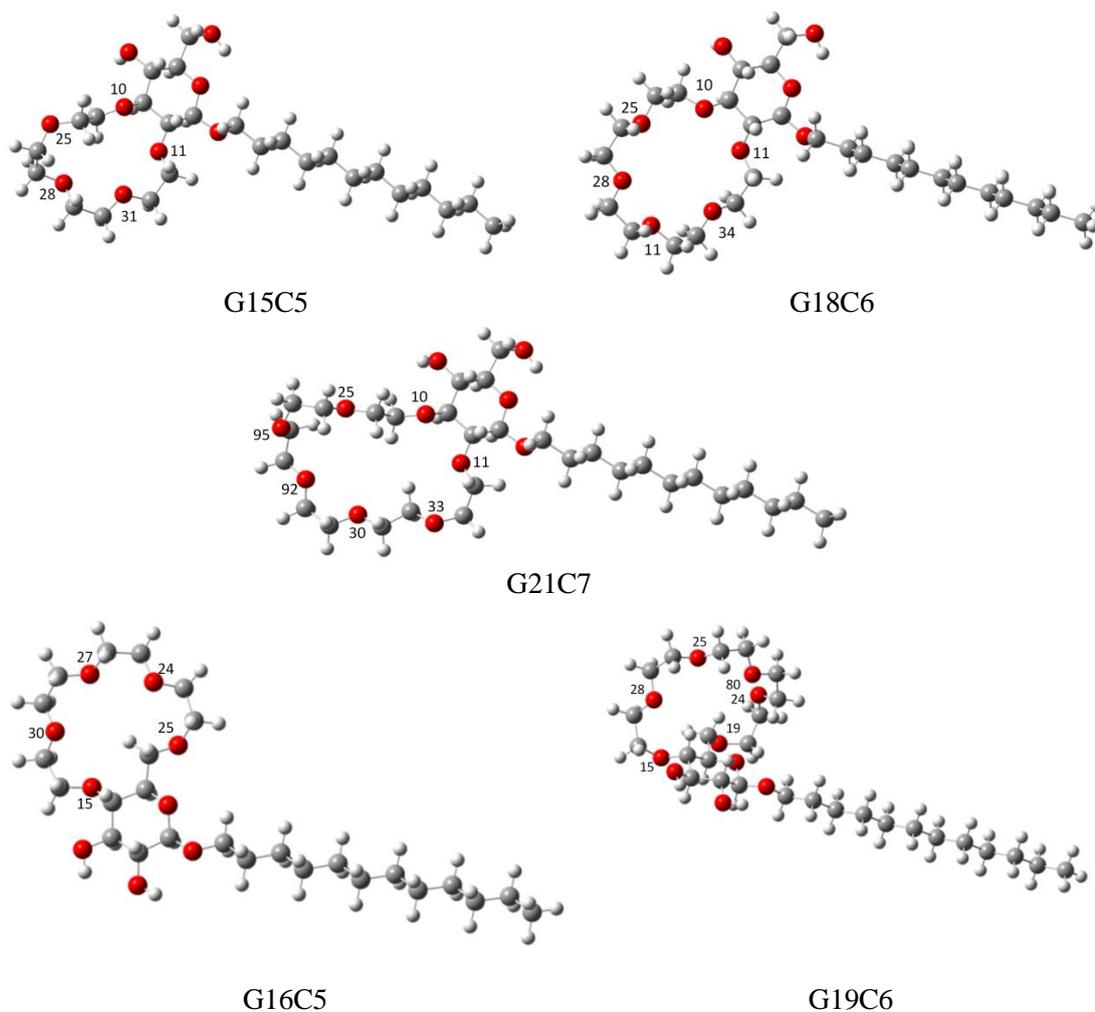
Figure 3-1:The optimized structures of the series of glycolipid crown ethers with the level of theory B3LYP/6-31G*.

Using the DFT method, the best minimum energy conformations were achieved by full geometry optimization of each crown ether glycolipid. In order to prove that each conformation is located at a stable minimum point of the potential energy surface, frequency calculations were carried out based on these optimized structuresto subsequentlyobtain their vibrational frequencies. Furthermore, using the results obtained from the calculation,electron affinity ( $A$ ) and condensedFukui functions

Na⁺/G15C5
(Top view)

Na⁺/G15C5
(Side view)

K⁺/G15C5
(Top view)

K⁺/G15C5
(Side view)

Na⁺/G18C6
(Topview)

Na⁺/G18C6
(Side view)

K⁺/G18C6
(Top view)

K⁺/G18C6
(Side view)

Na⁺/G21C7
(Top view)

Na⁺/G21C7
(Side view)

K⁺/G21C7
(Top view)

K⁺/G21C7
(Side view)
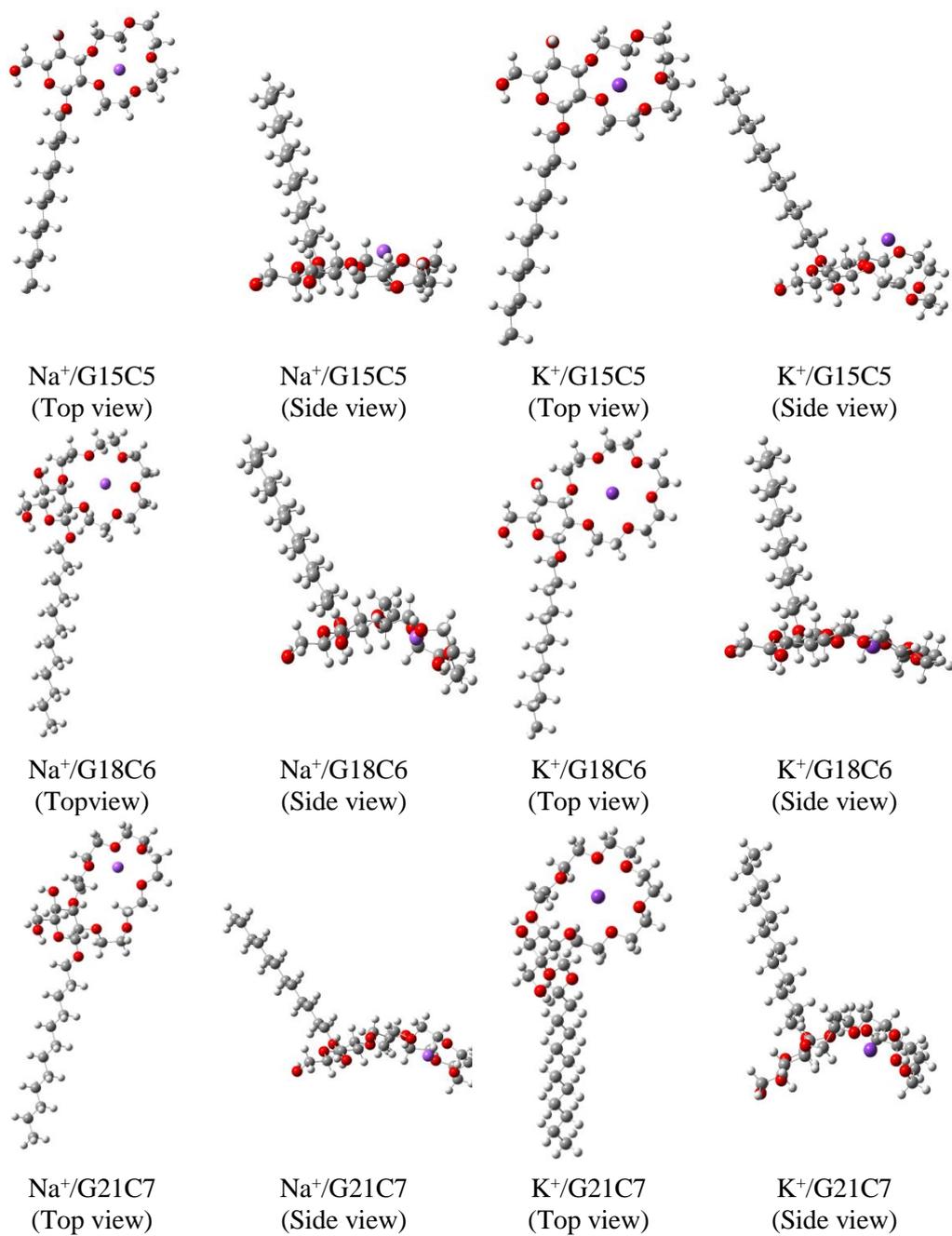
Figure 3-2:The optimizedstructures of complexes M⁺/G15C5, M⁺/ G18C5 and M⁺/G21C5 at the level of theory B3LYP/6-31 G* where M⁺represent the cations Na⁺and K⁺

Na⁺/G16C5
(Top view)

Na⁺/G16C5
(Side view)

K⁺/G16C5
(Top view)

K⁺/G16C5
(Side view)

Na⁺/G19C6
(Top view)

Na⁺/G19C6
(Side view)

K⁺/G19C6
(Top view)

K⁺/G19C6
(Side view)
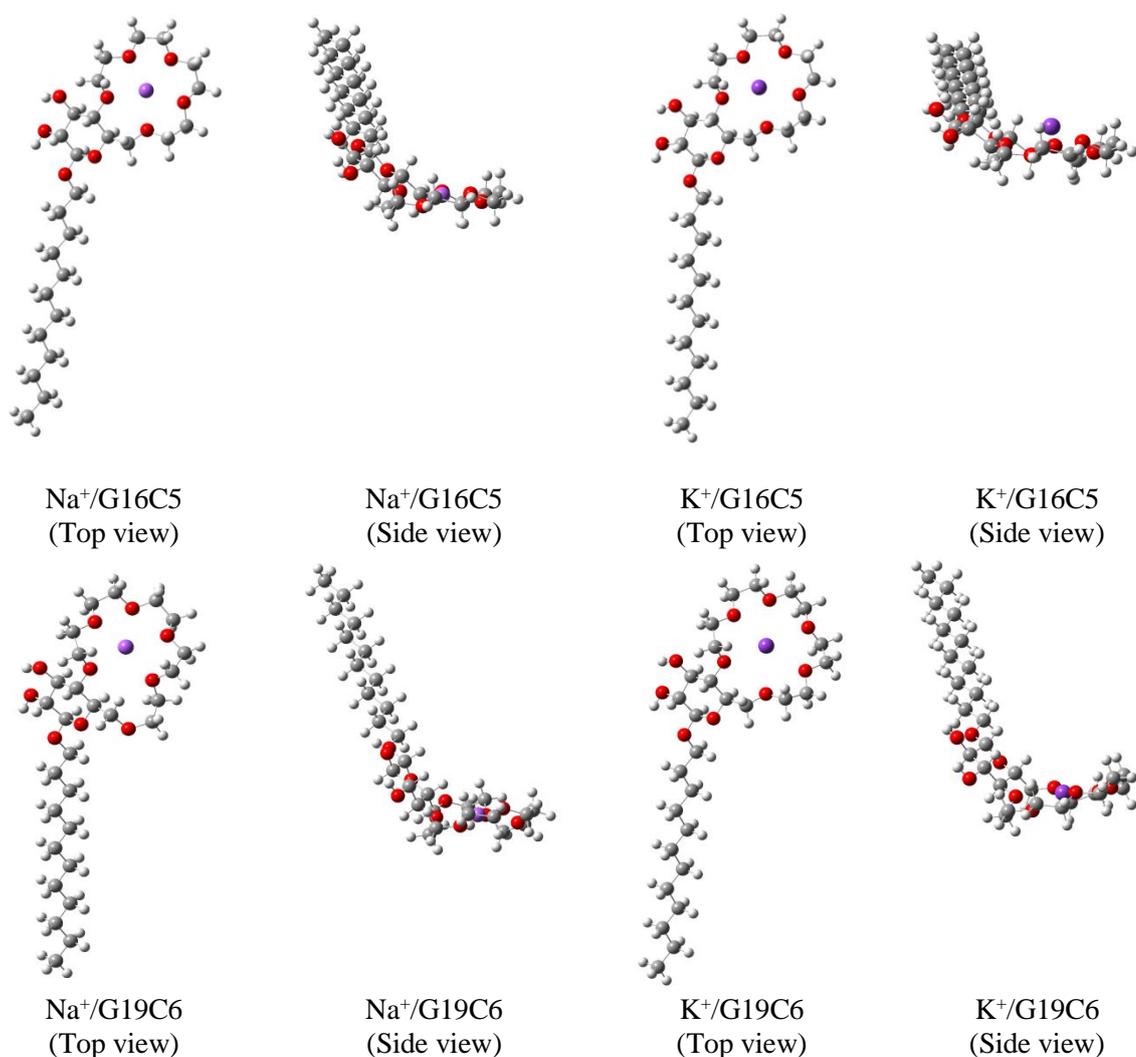
Figure 3-3: The optimized structures of complexes M⁺/G16C5 and M⁺/G18C5 at the level of theory B3LYP/6-31G* when M⁺ represents the cations Na⁺ and K⁺

($f^+$) were investigated.The thermodynamic properties such as binding energy ($\Delta E^b$), binding enthalpy ($\Delta H^b$) and Gibbs free energies ($\Delta G^b$) in gas phase of the complexes, formed by the combination of the glycolipids crown ethers with cation Na⁺ and K⁺,were also studied. The calculations were based on the reaction scheme 1 as follows:

M⁺ + glycolipids crown ether $\longrightarrow$ M⁺/glycolipids crown ether.

In addition, the exchange enthalpies ($\Delta H$) and the Gibbs free energies ($\Delta G$) were also calculated for the reaction scheme 2 as follow:

Na⁺/glycolipids crown ether + K⁺ $\longrightarrow$ K⁺/glycolipids crown ether + Na⁺
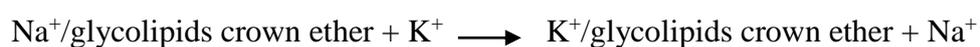
It was known that a finite basis set such as 6-31 G*, can give rise to the basis set superposition error (BSSE) in the DFT calculation involving interaction of two different fragments, which in our case is between a glycolipid crown ether and a cation. To remove this error, the counterpoise method was applied in the DFT calculation of the complexes. The Simon and Boys[141, 142] counterpoise correction is a prescription for removing BSSE. In this method the interaction energies between two atoms or molecules A and B are typically calculated as the energy difference between the product complex AB and its components A and B:

$$E_{int} = E(AB, r_c) - E(A, r_e) - E(B, r_e). \tag{3.1}$$

$r_c$ indicates the geometry of the product complex AB while $r_e$ indicates the geometry of the separate reactants.

## 3.2 Calculated parameters

### 3.2.1 Electronic chemical potential and electronegativity: Bridging computational and conceptual DFT

Base on the excellent work of Parr *et al.*[143, 144] most of the frontier-electron theory of chemical reactivity can be rationalized from the density functional theory of the electronic structure of molecules [45]. For a system of *N* electrons with ground-state energy *E(N,v)*, where *v* is the potential energy acting on an electron due to the presence of all nuclei, several quantities of fundamental importance can be defined. The chemical potential *μ* could be written as a partial derivative of the system's energy *E* with respect to the number of electrons *N* at a fixed external potential *v(r)*,

$$\mu = \left( \frac{\partial E}{\partial N} \right)_{v(r)}, \qquad (3.2)$$

In the early 1960s, Iczkowski and Margrave [145] explained that the energy $E$ of an atom could be reasonably well represented by a polynomial in the order of $n$ (where nequals the number of electrons ($N$) minus the nuclear charge ($Z$) ) around $n=0$, on the basis of experimental atomic ionization energies and electron affinities:

$$E = E( N ) = an^4 + bn^3 + cn^2 + dn; \qquad n = N - Z \qquad (3.3)$$

By considering the continuity and differentiability of $E$, the slope $-\left( \frac{\partial E}{\partial N} \right)_{N=0}$ , at $n \to 0$ was simply seen as a measure of the electronegativity, $\chi$[146]. Iczkowski and Margrave suggested defining the electronegativity as this derivative for fixed nuclear charge, so that:

$$\chi = -\left( \frac{\partial E}{\partial N} \right), \qquad (3.4)$$

Since the cubic and quadratic terms in equation (3.3) were negligible, Mulliken's definition, [147]

$$\chi = \frac{1}{2}(I + A), \qquad (3.5)$$

where $I$ and $A$ were the first ionization energy and electron affinity, respectively was calculated from:

$$I = E( N - 1 ) - E( N ), \qquad (3.6)$$

$$A = E(N) - E(N+1),$$  (3.7)

where $E(N)$, $E(N-1)$ and $E(N+1)$ were the calculated total energies for the neutral, cationic and anionic states[148].

The linking of the chemical potential concept to the fundamental equation of density functional theory, bridging conceptual and computational DFT is a remarkable development [146]. The sharp definition of $\chi$ (electronegativity) and moreover, its form afford its calculation via electronic structure method [146]. The analogy with the thermodynamic chemical potential $\mu_i$, of a component $i$ in a macroscopic system at temperature $T$ and pressure $P$ [149]:

$$\mu_i = \left( \frac{\partial G}{\partial n_i} \right)_{P,T,n_j(j \neq i)},$$  (3.8)

where $n_j$ and $\mu_j$ refer to all species other than species $i$. Gibbs energy $G$ is the chemical potential that is minimized when a system reaches equilibrium at constant pressure and temperature. Its derivative with respect to the reaction coordinate of the system vanishes at the equilibrium point. As such, it is a convenient criterion of spontaneity for processes with constant pressure and temperature [150]. If $\Delta G$ of a certain reaction is negative, this reaction is a spontaneous reaction and thermody-namically it is a useful reaction [93].

## 3.2.2   HOMO and LUMO

From the molecular orbital (MO) theory a linear combination of atomic orbitals (LCAO) forms bonding and antibonding molecular orbitals. The bonding orbital is at a lower energy than the corresponding antibonding orbital, so the bonding orbital is the first to be occupied. To understand molecular reactivity, it is important to identify the highest occupied molecular orbital (HOMO) and the lowest unoccupied molecular (LUMO) [151]. They are also called the frontier orbitals. The energy difference between the LUMO and HOMO (i.e. the energy gap) ($\Delta\varepsilon_{LUMO-HOMO} = \varepsilon_{LUMO} - \varepsilon_{HOMO}$) is the key parameter for understanding the electronic structures. The energy gap is related to the polarizability and chemical hardness of the molecules, where a higher energy gap means lower molecular polarizability and higher chemical hardness [148]. In fact according to the Koopman theorem [152] chemical hardness $\eta$ is equal to the energy gap.

Table 3-1:Comparison between HOMO and LUMO orbitals



| | **LUMO** lowest unoccupied molecular orbital | * LUMO receives electrons, * Lowest energy orbital available, * Characteristic for electrophilic component. |
| --- | --- | --- |
| $\Delta\varepsilon_{LUMO-HOMO}$ $= \varepsilon_{LUMO} - \varepsilon_{HOMO}$ | **HOMO** highest occupied molecular orbital | * Electrons from the HOMO are donated * Most available for bonding * Most weakly held electrons * Characteristic for nucleophilic component |

### 3.2.3 Fukui Function

The local nucleophilicity and electrophilicity refer to the capability of a site in a particular molecule to donate or attract electron, respectively. Fukui function is used to describe this local reactivity toward an electron donor or acceptor. Parr and Yang [143] defined Fukui function $f(\bar{r})$, as follows:

$$f(\vec{r}) = \left( \frac{\partial \rho(\vec{r})}{\partial N} \right)_{v(\vec{r})}, \tag{3.9}$$

where $\rho(\vec{r})$ is the electron density and

$$N = \int \rho(r) dr, \tag{3.10}$$

is the total number of electrons, and $v(\vec{r})$ denotes the external potential of the system. In chemistry, one is seldom interested at which ''point'' in a molecule is most reactive; rather one wishes to identify which atom in a molecule that is most likely to react with an attacking electrophile or nucleophiles [153]. To achieve this, Yang and Mortier [144] proposed the condensed Fukui function. The condensed Fukui function calculation is based on the finite difference approximation and the electron density $\rho(\vec{r})$ between atoms in a molecular system. With the approximation, the Fukui function at the atom $k$, is denoted as $f_k^+$ and $f_k^-$, and can be estimated by using an atomic charge partitioning scheme, such as Mulliken population analysis [144]. Here, for a nucleophilic attack,

$$f_k^+ = q_{N+1} - q_N, \tag{3.11}$$

and for an electrophilic attack,

$$f_k^- = q_N - q_{N-1}, \tag{3.12}$$

$q_N$, $q_{N-1}$ and $q_{N+1}$ denote the charges for atom $k$ on the neutral, cation and anions species respectively. While the condensed Fukui function gives the nucleophilicity locally at each atom, the overall or global nucleophilicity or electrophilicity [154] of the

systems can be measured according to their ionization potential *I* equation (3.6)and electron affinity *A* (3.7). Using the estimated *I* and *A,* we analyzed the global nucleophilocity according to the nucleophilocity index *N* defined as:

$$N = \left( \frac{(I+A)^2}{8(I-A)} \right)^{-1}. \tag{3.13}$$

### 3.3 System description and molecular dynamics simulation details of thermotropicbilayer phase

Each starting glycoside molecule ($\alpha/\beta$-C8Gal and $\alpha/\beta$-C8Glc) was built and geometry optimized using the HyperChem package [29]. The initial structure of each single bilayer of $\alpha/\beta$-C8Gal and $\alpha/\beta$-C8Glc was obtained by arranging a $10 \times 10$ array of 100 optimized lipids in the x and y plane, which constituted the first monolayer leaflet. The bilayer with the tail groups pointing to its center and the head groups facing the opposite direction was obtained using packmol [30]. GLYCAM_06d [25] and the *ff99* [31] force fields were used to assign the atom types, bond length, bond angle, dihedral angle and partial charges for the carbohydrate head group and the tail group, respectively. The GLYCAM_06 contains all the parameters for sugar and lipids [25]. For carbohydrates, it has a single parameter set applicable to both $\alpha$- and $\beta$-anomers and to all monosaccharide ring sizes and conformations [25]. The *ff99* force field is a derivative of the original Cornell *et al. ff94* force field [32], where improvements have been made in many torsional parameters. Such parameterization supports both additive and non-additive (polarizable) force fields [32]. The *ff99* force field has been extensively used for MD simulation of the biomolecular systems [26,33,34]. Additionally, alkyl chain carbon atoms on $\alpha/\beta$-C8Gal and $\alpha/\beta$-C8Glc were assigned a charge of zero implying non-ionic surfactant nature. The molecular dynamics (MD) simulation was performed on each system using AMBER12 software package [23,24]. Prior to the actual molecular dynamics run, the energy minimization using first the steepest descent(SD) algorithm followed by applying the adopted basis Newton-Raphson method, was performed to eliminate any unfavorable contacts and overlapping of atoms resulting from the model building procedure [23]. Pre-equilibration under the constant number of particles N, volume, V and temperature, T, (NVT-ensemble) of the energy minimized structures was performed for 2 ns by increasing the temperature from

0 to 90°C using the Andersen thermostat ($\tau_P$ = 0.5 ps) [35] with a 1 fs time step. Subsequently, the molecular dynamics simulation of the glycolipid lamellar system was carried out under the condition of constant number of particles N, pressure, p and temperature, T (NpT-ensemble). Periodic boundary conditions were applied to the simulation box in all three coordinate directions (with *x*, *y* in the bilayer plane and *z* normal to the bilayer) in cubic lattice geometry. The Berendsen pressure coupling method is normally used to simulate the bilayer system either anisotropically or semi-isotropically [36]. In the anisotropic case, the three unit-cell dimensions fluctuate independently, and the total pressure p remains constant 1 bar, corresponding to an $Np_xp_yp_zT$ ensemble, unlike the semi-isotropic case, which gives an $Np_Np_LT$ ensemble, where $p_N$ and $p_L$ are pressures along the normal and lateral to the bilayer respectively. In general, the two pressure coupling methods produce equilibrium properties, which cannot be differentiated statistically [14]. However the advantage of the semi-isotropic case is, the interface maintains a square, while in the anisotropic case the simulation box fluctuates independently in x and y directions [37]. Therefore, in our simulation we have used the semi-isotropic pressure coupling method, with a time constant 1ps and a compressibility of $4.5 \times 10^{-5}$/bar. The simulation temperature was set at 363 K for all the four glucosides. At this temperature, $L_\alpha$ phase is stable for three of these systems, namely *α/β*-C8Glc and *α*-C8Gal, while for *β*-C8Gal, it is at the border of $L_\alpha$ and $L_C$ phases.

Non-bonded interactions were truncated with a cut-off range of 9.0 Å and long-range electrostatic interactions were treated using the particle mesh Ewald summation method [38,39]. The SHAKE algorithm was used to constrain covalent bonds involving hydrogen atoms [40]. The time step was 1 fs and the simulation's trajectories were saved once every 5 ps. The simulation was performed for a total duration of 200 ns dynamics. In order to monitor the equilibrium condition of the bilayer, we monitored

two parameters: area per lipid and the local density profiles (LDPs). Block averages of the local density profiles (LDPs) over 20 ns were calculated for the entire 200 ns simulation. The LDPs show small fluctuation in the interface, but does not change significantly after 40 ns, so we assume 40 ns is sufficient for the system to reach its equilibrium and the bilayer properties are calculated from the last 160 ns. The area per lipid is very sensitive to the simulation details and is generally considered to be a reliable criterion for comparing and validating the simulation results [14]. Incidentally, these simulations were performed using the GPU-accelerated version of the *pmemd* simulation engine on NVIDIA Tesla graphic card. A typical simulation performance for these systems on a normal PC-hardware is 18ns/day, which is more than an order of magnitude higher than that of a typical CPU-based simulation [41].



Figure 3-4: Schematic structure of  *n*-octyl-*β*-D-glucopyranoside (*β*-C$_8$Glc) in HyperChem
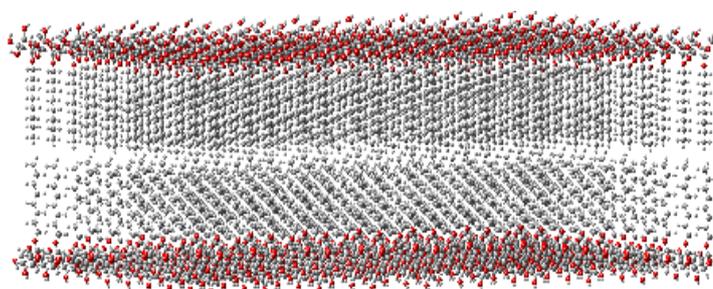


Figure 3-5: Schematic structure of bilayer system in thermotropic phase in packmole
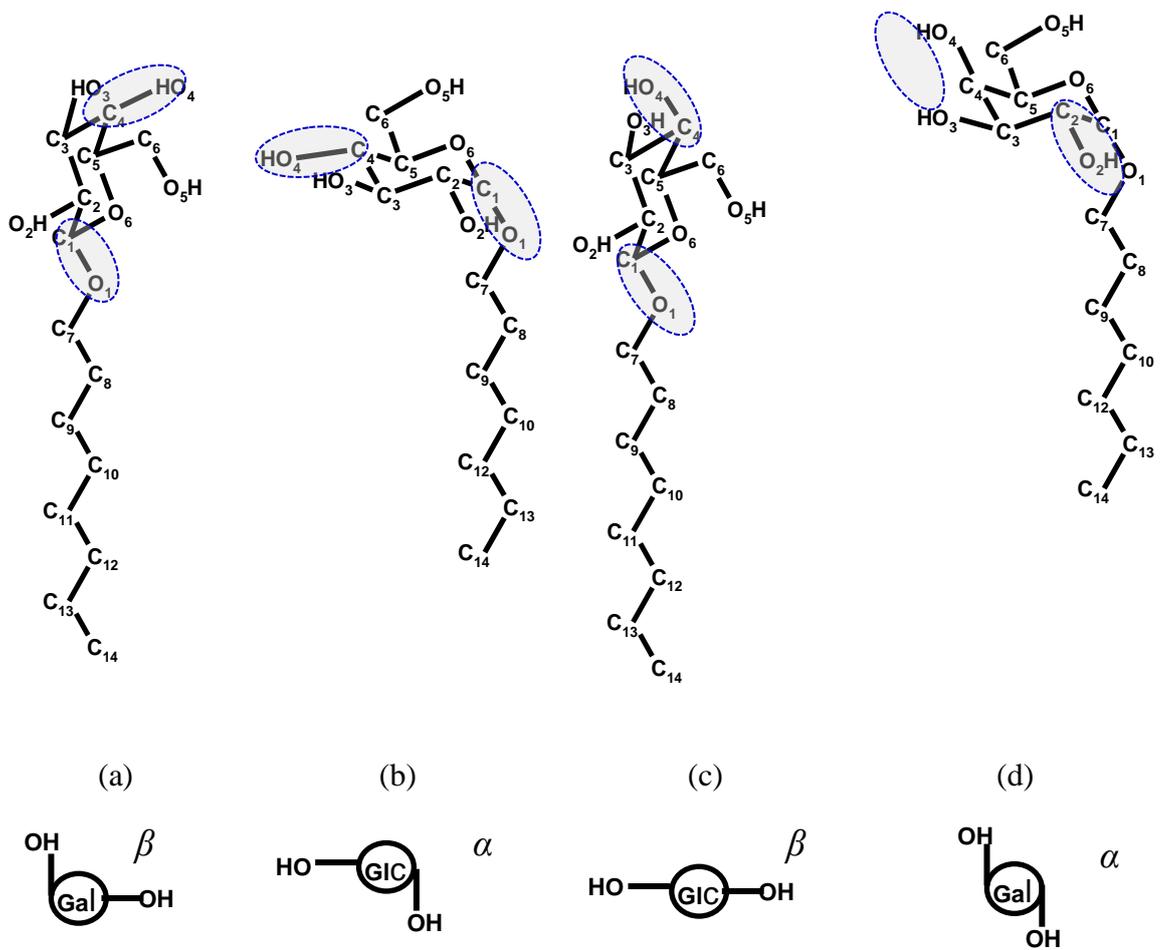
Figure 3-6: Chemical structures for glycolipids, a) *n*-octyl-*β*-Dgalactopyranoside (*β*-C$_8$Gal), b) *n*-octyl-*α*-D-glucopyranoside (*α*-C$_8$Glc),c) *n*-octyl-*β*-D-glucopyranoside (*β*-C$_8$Glc) and d) *n*-octyl-*α*-D-galactopyranoside (*α*-C$_8$Gal)

### 3.4 System description and molecular dynamics simulation details of the reverse hexagonal phase

We began by constructing a full atomistic model of $C_8C_{12}\beta$-D-Glc (see Figure 3-7 a) using the modelling software package of Avogadro,[155] followed by a brief energy minimization using the molecular mechanics with MMFF94 forcefield [156]. Subsequently, in the pre-constructed atomistic model of $C_8C_{12}\beta$-D-Glc, all hydrogen atoms were removed except the four hydrogen atoms from the hydroxyl groups within the sugar unit. Hence, a united atom model was built (see Figure 3-7, b), whose carbohydrate force field was obtained from GROMOS [157].



(a) (b)
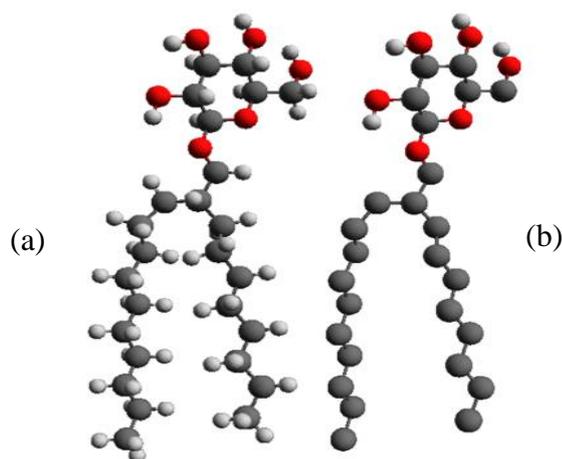
Figure 3-7: Full atomistic model of (2'n-octyl-n-dodecyl)-$\beta$-D- glucopyronoside (C8C12$\beta$-D-Glc), (b) United atom model of C8C12$\beta$-D-Glc.

In order to construct the initial configuration of the reverse hexagonal phase using the united atom model of $C_8C_{12}\beta$-D-Glc, the following steps were applied. Firstly, the $C_8C_{12}\beta$-D-Glc was replicated into a number of copies. These were arranged into a disc with a hole in the middle. Ten of these disc aggregates were stacked to form a column. The column was replicated and arranged into a hexagonal lattice (see Figure 3-8 (a)). Separately, a configuration of randomly distributed water molecules residing in a rectangular box was generated using the *genbox* utilities software in the GROMACS MD simulation package [158, 159].The length of the rectangular box along

its long axis was set according to the length of the column. In addition, the surface area perpendicular to its long axis was made small enough for the box to be inserted into the hollow space of the column. The water box was later replicated six times and each of these was inserted into the hollow space of the column. Subsequently, this configuration was used as the initial structure of the H$_{II}$ phase in the simulation as shown in Figure 3-8 (b), where the yellow dotted lines indicate the boundaries of the periodic box.



| (a) | (b) |
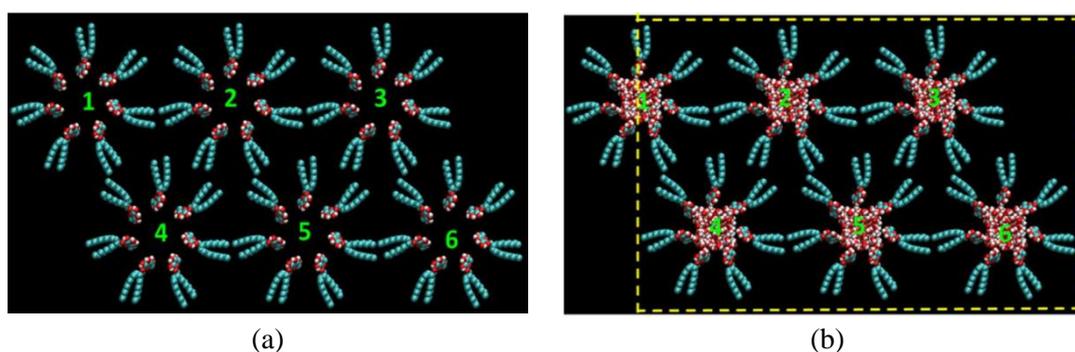
Figure 3-8: (a) Six columnar of C$_8$C$_{12}\beta$-D-Glc arrange in a hexagonal lattice. (b) The initial configuration for MD simulation, where the yellow lines indicate the periodic boundary.

Our approach in setting the periodic boundary condition is similar to the one used by Bandyopadhyay *et al*. [160].Each column was assigned to a number in order to keep track of any changes during the simulation. In the construction of a single column, the size of the hole depends on how close the nearby C$_8$C$_{12}\beta$-D-Glc molecules are toeach other, when arranged into a column structure. It should be made large enough to accommodate the targeted number of watermolecules, i.e. 1746 and 3023 water molecules, making a total number of 20,358 and 24,189 atoms for the 14% and 22% systems, respectively. These two concentrations were chosen since small angle X-ray measurements have been reported and corresponds a reverse hexagonal phase. In addition, at the 22% water concentration, the phase exists in an excess water condition which is more biologically relevant.

In the simulation, the starting structure can affect thetime the simulation takes to achieve the equilibrium. The closerthe initial hexagonal structure is to the experimental one, thefaster the simulation will reach the equilibrium state that agreeswith the real system. However, compare to the flat membrane like bilayer model system, it is relatively hard to construct theinitial structure of a $H_{II}$ phase that is close to the equilibriumstate. Therefore, we tested on a number of different initialstructures, each of which differed in terms of the radius andlength of the hollow space, hence the size of the rectangular boxof water molecules. These initial structures were first energyminimized using the steepest descent method to remove the badcontact between molecules; subsequently followed by MDsimulations with constant pressure (NPT) performed for 5 ns attemperature T = 298K. From this series of simulations, the system whose result that gave the average lattice parameter closest to theexperimentally measured value after 5 ns simulation was chosen.Amongst the configurations generated from the chosensimulation system, we further selected the frame, which matchedclosely the experimentally measured lattice parameter. The selected frame became the starting configuration for a further MDsimulation of 50 ns. In this work we focused on two systems of$H_{II}$ formed by $C_8C_{12}\beta$-D-Glc at different water contents of 14%and 22%, respectively. Here, water molecules were modeled as the simple point charge (SPC)[161].

Energy minimization was performed to each of the initial configuration of the two systems, followed by  50 ns constant pressure simulation, where the first 10 ns was taken as the equilibration stage, while the last 40 ns was considered as the production stage. All the simulations applied the period boundary condition and leap-frog algorithm for the integration of the Newtonian equations of motion with a time-step of 2 fs. In addition, LINCS algorithm was used to fix the bond length involving the hydrogen atom.

The particle mesh Ewald (PME) approach was employed to calculate the electrostatic interactions with a cutoff of 12 Å. The cutoff of 12 Å was applied for the non-bonded interaction. The temperature was controlled by the Nose-Hoover thermostat, while the isotropic pressure was applied using the Parrinello-Rahman pressure coupling.

## 3.5 Calculated parameters

### 3.5.1 Lipid tail and order parameter

In order to monitor the stability of the bilayers, 20 ns block averages[108] of the local density profiles(LDP) were calculated up to 200 ns. Generally, the LDP was calculated along the bilayer normal, taking the centre of the bilayer as the origin. This distribution function $g(Z)$ was calculated from the number density, $\rho(x, y, z)$, given as:

$$N = \iiint \rho(x, y, z) dx dy dz, \tag{3.14}$$

where $N$ is the total number of atoms. Along the z-direction, we defined $g(Z)$ as:

$$N = \iiint \rho(x, y, z) dx dy dz, \tag{3.15}$$

$$g(z) = \rho(z) / \rho = (N(z)V) / (NA\Delta z). \tag{3.16}$$

where $A$ is the bilayer area, $\Delta Z$ is the bin size along the z-axis, and $V$ is the volume.

### 3.5.2 Area at the interface per sugar head

the convergence of the simulated system to its equilibrium state may be monitored through the time evolution of the area per lipid calculated by dividing the total area in the x and y directions of the bilayer by the total number of glycolipids (100) in a single bilayer leaflet[162]. Area per lipid is one of the parameters that can be used to determine how well equilibrated the simulated system is[163] because among the bulk quantities it gives a more detailed convergence perspective[164]. It was found that from the total 200 ns simulation run, the first 40 ns dynamics could be regarded as the equilibrium phase. Subsequently, for the analysis purpose, every 5 ps frame was archived from the last 160 ns dynamics.

### 3.5.3   Lipid tail and order parameter

The conformational disorder of the hydrophobic chain is related to the bilayer stability under the mechanical stress and it is more disordered in a liquid-crystal state than in a gel or a crystal state[164].Therefore the chain order parameter $S_{CH}$ has been used to estimate the degree of ordering in the chain region. This is derived from the general $3 \times 3$ Saupe ordering tensor, $S$ whose element, $S_{ij}$ is given as:

$$S_{ij} = \frac{1}{2}(\overline{3cos\,\theta_i\,cos\,\theta_j} - \delta_{ij}),$$

(3.17)

where $\theta_i$ is the angle between the $i^{th}$ molecular axis and the bilayer normal, and the bar represents the time or ensemble averaged quantity [165]. The alkyl chain order parameter was defined according to van der Ploeg and Brendsen[166], where the molecular axes for the $n$th methylene group are defined by the H-H vector (x-axis), the bisectrix of the H-$C_n$-H angle (y-axis), and the vector $C_{n-1}$ to $C_{n+1}$(z-axis). From the symmetry argument, the tensor $S$ is diagonal and $S_{ZZ}$ illustrates the chain order

parameter. $S_{ZZ}$ takes a value of unity if the average orientation is parallel to the bilayer normal (i.e., fully ordered), $-\dfrac{1}{2}$ if it is perpendicular to the normal, and zero if the system is completely disordered. $S_{CH}$ is related to $S_{CD}$ determine by the deuterium NMR experiment, where:

$$S_{CH} = S_{CD} = \frac{2}{3}S_{xx} + \frac{1}{3}S_{yy},$$

(3.18)

where $S_{xx}$ and $S_{yy}$ are the order parameters in the $x$ and $y$ directions, respectively. In the case of a bilayer system, reduction of the length of the lipid chains correspond to decreasing density and increasing free volume fraction towards the middle bilayer[167]. The order parameter is indirectly related to the chain's tilt angle and trans-gauche distribution of chain dihedral. Simulations show that the number of gauche defects in membranes above the phase transition is smaller than in liquid alkanes. The fraction of gauche dihedrals decreases with decreasing temperature or increasing chain length[168].

### 3.5.4    Hydrogen bonding interaction

From the biological relevance, one of the main characteristic of sugars is the ability to participate in hydrogen bonds as both acceptor and donor.Each sugar has hydrophilic and hydrophobic region; the detailed interaction of hydrophilic part is under the control of the carbohydrate head group which can involve in hydrogen bonding, whereas the hydrophobic interaction is due to the branching of the alkyl chains. There is also a close relationship between the properties of biological membrane and the self-assembly of glycolipid dominated by this network of hydrogen bonds [104]. Thus, to determine quantitatively the hydrogen bonds is necessary to gain deep understanding on

the self-assembly behaviour. According to the classical chemical theory hydrogen has a valance of one but sometimes in some special cases it can behaves as bivalent[169]. That may be so, is the basis of the concept of hydrogen bonding: that between molecule A-H and a second atom, or a molecule, B, a particular force of attraction may operates Figure 3-9 shows a typical hydrogen bond. Although the bonding represented by the broken line is much weaker than the covalent bond A-H, such a formation does amount to assign some degree of bivalency to the hydrogen atom. Significant bonding will happen only when atoms A and B are sufficiently electronegative. Hydrogen bonding is probably favored when it is stereochemically possible for a lone-pair of electrons on B to point towards H. Ideally bonding is favored when the angle $\psi$ is near to $180°$. For weak bonds considerable deviations from $180°$ are often found [170]. Inter-molecular and intra-molecular hydrogen bond analysis was performed in each layer using the *ptraj* module in AMBER 12, and CARNAL (from AMBER7) respectively, by defining the O-O distance to be $\leq 3.5 \text{Å}$ and $4 \text{Å}$ and thecut-off angle of $120°$ from linearity. Since the results of both O-O distances are almost similar we show only the results of O-O distance $\leq 3.5 \text{Å}$ here.
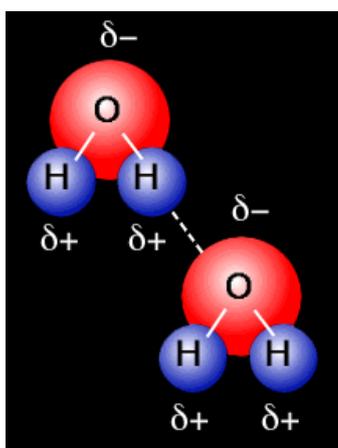


Figure 3-9:Typical hydrogem bonding in water molecule

### 3.5.5 Tilt angle and head group orientation

The tilt angle for the headgroup orientation was calculated based on the definition used by Tomasz[104]. The vector representing sugar headgroup is defined from C9-O4 (see Figure 3-6) and the orientation of the head group is defined by the angle between this vector and bilayer normal (along $z$axis). In this study we chose the above vector definition for the sugar headgroup to compare the results obtained by others and subsequently discernthe effect of chain length[171] and branching[104] on the sugar head stereochemistry.

### 3.5.6   Lipid Dynamics in Anhydrous Bilayer

To examine the dynamic behaviour of sugar molecules in the bilayer system, we computed the mean square displacement (MSD) of the translational diffusion for the sugars at the lipid surface using the *ptraj* module in AMBER.   Generally, the translational mobility of lipids in the bilayer membrane model is considered to be two-dimensional. The lateral diffusion of the molecules was evaluated from the mean square displacement (MSD) of their centre of mass in two-dimension i.e. $\langle \Delta r_{xy}(t) \rangle$, as a function of time.

$$\langle \Delta r_{xy}^2(t) \rangle = \left( \frac{1}{N} \sum_{i=1}^{N} \left[ (\Delta x_i(t))^2 + (\Delta y_i(t))^2 \right] \right). \tag{3.19}$$

where $\Delta x_i$ and $\Delta y_i$ represent the differences of the centre of mass (COM) for the ith molecule between a time t and $t_0$.

# CHAPTER 4

# RESULT AND DISCUSSION    DFT STUDY OF GLUCOSE BASED GLYCOLIPID CROWN ETHERS AND THEIR COMPLEXES WITH ALKALI METAL CATIONS NA $Na^+$ AND $K^+$

This chapter contains the results of the DFT study of glucose based glycolipid crown ethers and their complexes with alkali metal cataions $Na^+$ and $K^+$. We shall explain about the structures and coordination of these complexes. Meanwhile, there is the result of the investigation of the electronic structures, molecular conformations and the thermodynamic properties of glucose based glycolipid crown ethers and also their complexes with cations $Na^+$ and $K^+$.

## 4.1    Structure of glycolipid crown ethers and their nucleuleophilicity

Figure 4-1shows the optimized structures of different glycolipids crown ethers calculated at B3LYP/6-31G* level of DFT in ground state. From these structures we can see that the shape of crown ethers in G18C6 and the G16C5 is less deformed compared to the rest.The reactivity of the oxygen atoms around the crown ethers of the five molecules described using condensed Fukui function are given in Table 4.1. Positive values of the condensed Fukui function $f_k^+$ at site $k$ mean that the particular atom is especially reactive to nucleophilic attacks.The higher the values of the $f_k^+$ on the site, the more reactive the particular site. From Table 4.1.we can see that not all the oxygen atoms in the crown ethers are reactive sites for neucleophilic attacks and the most reactive site of each molecule is located further away from the sugar ring, i.e., O31 in G15C5 and G18C6, O92 in G21C7, O24 in G16C5 and O80 in G19C6.

G15C5

G18C6

G21C7

G16C5

G19C6
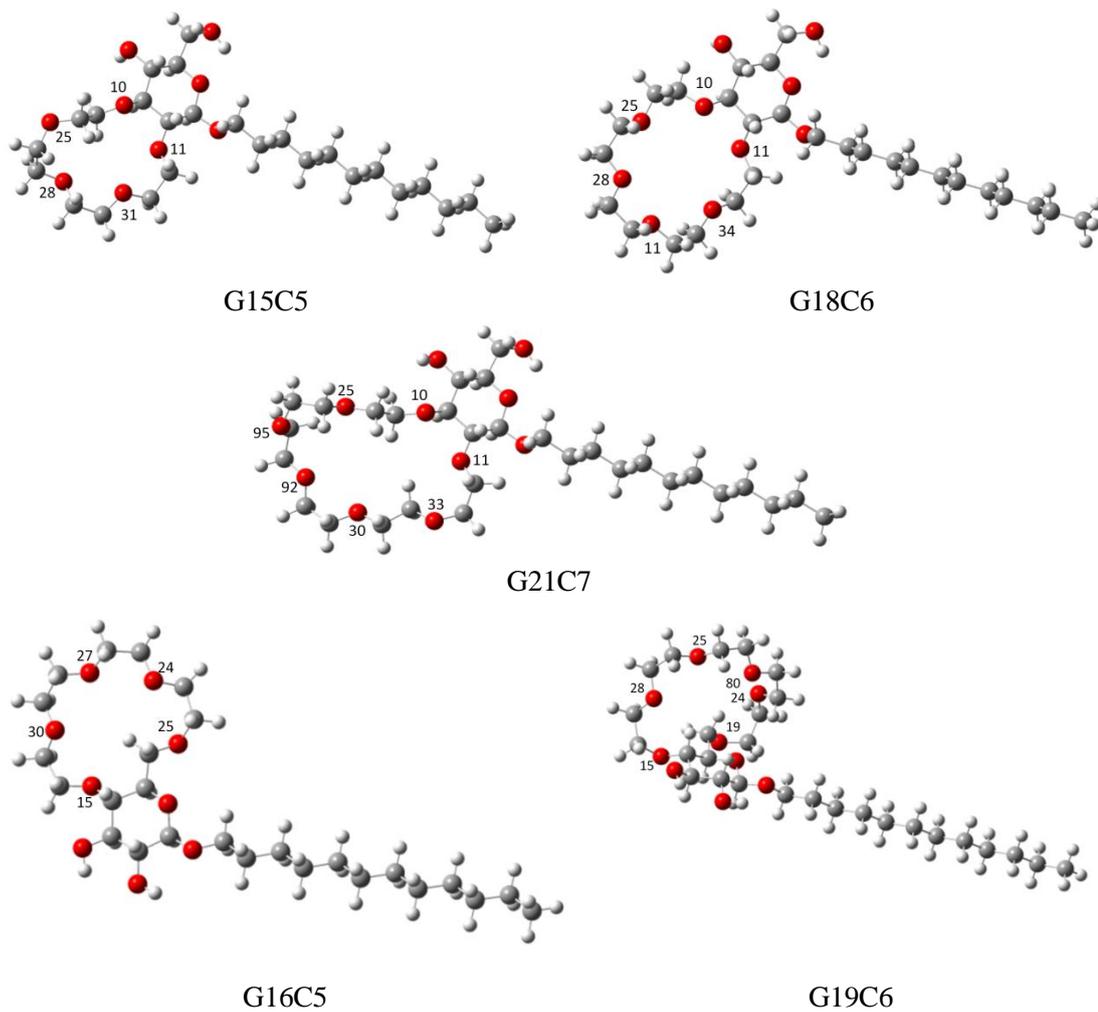
Figure 4-1: The optimized structures of the series of glycolipids crown ethers with the level of theory B3LYP/6-31G*. The oxygen atoms on the crown ethers are labelled

Table 4-1: Fukui function values for a nucleophilic for the different crown ethers

| G15C5 Atom | $f_k^+$ | G18C6 Atom | $f_k^+$ | G21C7 Atom | $f_k^+$ | G16C5 Atom | $f_k^+$ | G19C6 | $f_k^+$ |
|---|---|---|---|---|---|---|---|---|---|
| O3 | -0.0073 | O3 | -0.0266 | O3 | 0.0022 | O4 | -0.0122 | O4 | 0.0008 |
| O25 | -0.0033 | O25 | 0.0027 | O25 | -0.0096 | O30 | 0.0061 | O28 | -0.0025 |
| O28 | 0.0041 | O28 | 0.0055 | O95 | -0.0116 | O27 | 0.0055 | O25 | 0.0041 |
| O31 | 0.0121 | O31 | 0.0060 | O92 | 0.0128 | O24 | 0.0079 | O80 | 0.0124 |
| O2 | -0.0008 | O34 | 0.0011 | O30 | 0.0064 | O6 | 0.0047 | O24 | -0.0011 |
| | | O2 | -0.0041 | O33 | -0.0138 | | | O6 | -0.0070 |
| | | | | O2 | 0.0037 | | | | |

Table 4-2, gives the overall electronic properties of the optimized structures in terms of HOMO-LUMO energies, energy gaps, ionization energies, electron affinity and nucleophilicity index. The energy gaps $\Delta\varepsilon_{LUMO}-\varepsilon_{HOMO}$ calculated show that they are more or less the same for the five glycocolipids crown ethers. However, among them G16C5 has the highest energy gap, suggesting that G16C5 is chemically the hardest. The ionization potential of the five molecules gives values that are also rather close to one another, while their electron affinities are more sensitive to the difference in size of crown ethers. Relatively, the largest glycolipids crown ether G21C7 has the highest ionization potential and electron affinity. However, G19C6 is the lowest in both quantities although it is not the smallest molecule. This is probably due to the optimized structure of the G19C6 being deformed in such a way that its cavity became as small as that of G15C5 (see Figure 4-1). In terms of global nucleophilicity, the relative nucleophilicity index $N$ is G19C6 > G15C5 > G16C5 > G18C6 > G21C7.

Table 4-2: HOMO and LUMO energies $\varepsilon_{HOMO}$ and, $\varepsilon_{LUMO}$ , energy gap $\Delta\varepsilon_{LUMO\text{-}HOMO}$, ionization potential $I$, electron affinity $A$ and nucleophilicity index $N$ for the glycolipids crown ethers

| Molecule | $\varepsilon_{HOMO}$ (eV) | $\varepsilon_{LUMO}$(eV) | $\Delta\varepsilon_{LUMO\text{-}HOMO}$(eV) | $I$ (eV) | $A$ (eV) | $N$ (eV) |
|----------|---------|---------|---------|---------|---------|---------|
| G15C5 | -6.372 | 1.559 | 7.889 | 7.385 | -2.226 | 2.890 |
| G18C6 | -6.395 | 1.534 | 7.932 | 7.412 | -1.713 | 2.247 |
| G21C7 | -6.565 | 1.397 | 7.962 | 7.534 | -1.629 | 2.102 |
| G16C5 | -6.326 | 1.957 | 8.283 | 7.465 | -1.906 | 2.425 |
| G19C6 | -6.032 | 1.881 | 7.913 | 7.346 | -2.611 | 3.552 |

## 4.2    Geometrical structure of the complexes

The optimized structures of the complexes formed by the glycolipids crown ethers with the cations ae given in Figure 4-2andFigure 4-3. For each complex, the distances in Angstrom between the binding sites of oxygen atoms in the crown ethers to the cation Na$^+$ and K$^+$ have been worked out and presented inTable 4-2.FromFigure 4-2, the optimized structure of complexes Na$^+$/G15C5 and K$^+$/G15C5 shows that the cations are located on the mean planes formed by the crown ethers, where K$^+$ is slightly further away from its crown ethers mean plane. This suggests that the cavity size for G15C5 is fit to accommodate Na$^+$but too small for K$^+$. For bigger sized crown ethers such as G18C6 and G21C7, the crown ethers cavity is big enoughto encapsulate cation Na$^+$ by distorting their structure from being planar to form Na$^+$/G18C6 and Na$^+$/G21C7 complexes. The cavity size of G18C6 matches the size of cation K$^+$, such that the cation is located on the mean plane of the crown ethers in the K$^+$/G18C6 complex.
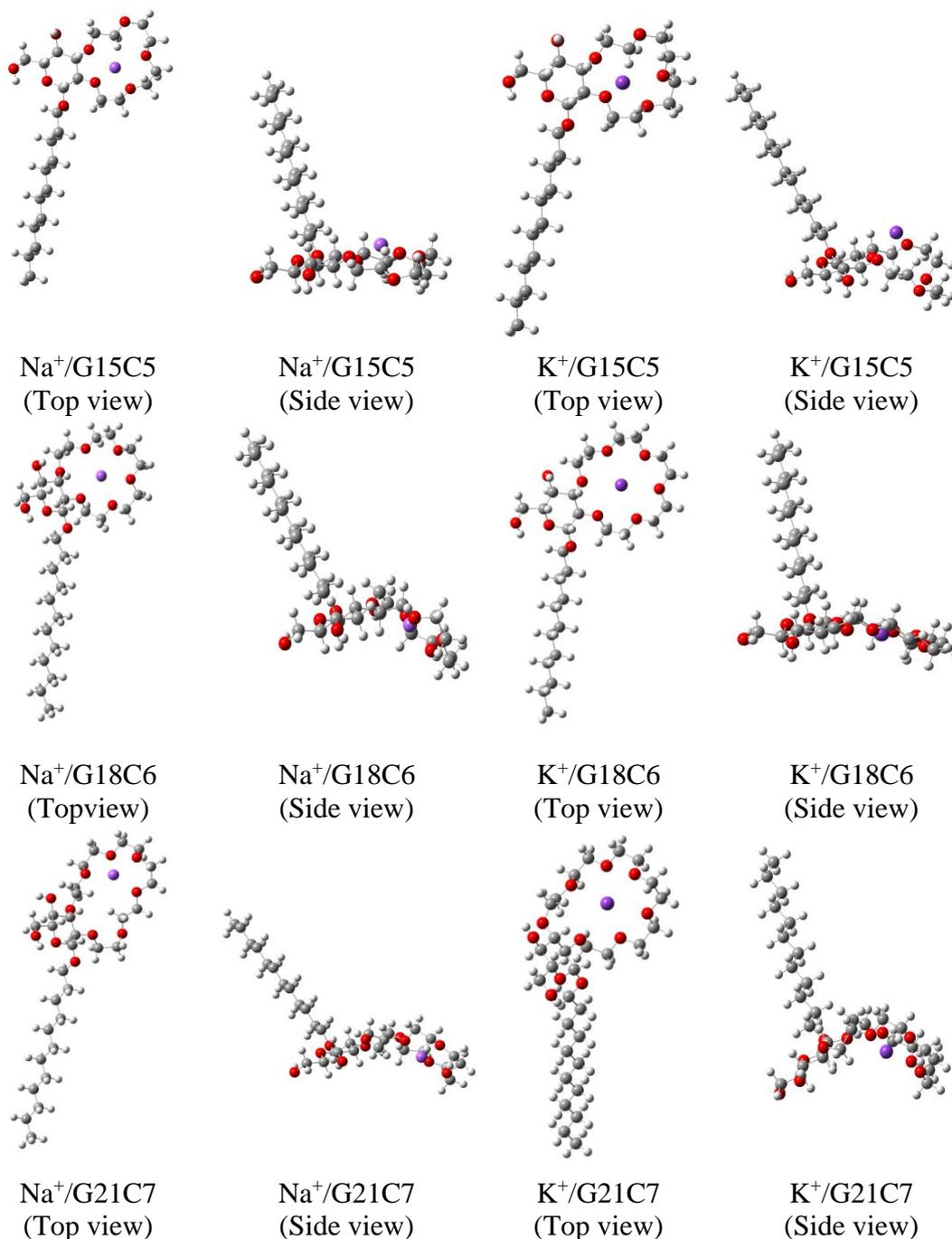
Na⁺/G15C5
(Top view)

Na⁺/G15C5
(Side view)

K⁺/G15C5
(Top view)

K⁺/G15C5
(Side view)

Na⁺/G18C6
(Topview)

Na⁺/G18C6
(Side view)

K⁺/G18C6
(Top view)

K⁺/G18C6
(Side view)

Na⁺/G21C7
(Top view)

Na⁺/G21C7
(Side view)

K⁺/G21C7
(Top view)

K⁺/G21C7
(Side view)

Figure 4-2: The optimized structures of complexes M⁺/G15C5, M⁺/ G18C5 and M⁺/G21C5 at the level of theory B3LYP/6-31 G* where M⁺ represent the cations Na⁺and K⁺

Na+/G16C5
(Top view)

Na+/G16C5
(Side view)

K+/G16C5
(Top view)

K+/G16C5
(Side view)

Na+/G19C6
(Top view)

Na+/G19C6
(Side view)

K+/G19C6
(Top view)

K+/G19C6
(Side view)
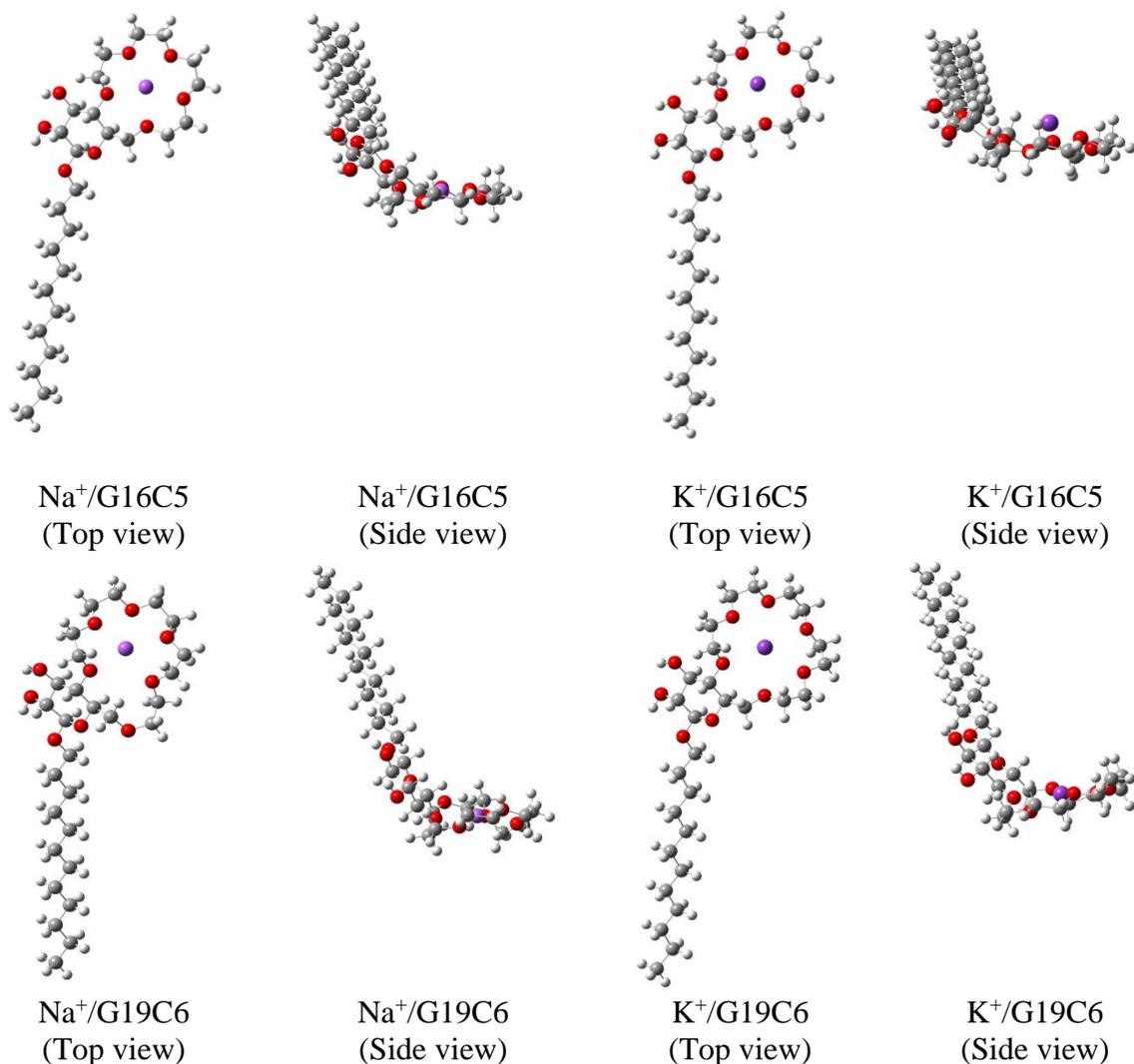
Figure 4-3: The optimized structures of complexes M+/G16C5 and M+/G18C5 at the level of theory B3LYP/6-31G* when M+ represents the cations Na+ and K+

Nevertheless, the cavity size of G21C7 is still bigger than that of cation $K^+$. Therefore the crown ether of the structure of the complex $K^+$/G21C7 is distorted from planar.

On the other hand, glycolipid crown ethers G16C5 and G19C6, which have a different linkage to the sugar ring from the other three, form complexes with the two cations $Na^+$ and $K^+$ with their crown ethers in planar structure (seeFigure 4-3). G16C5 is shown to have the cavity size that matches well the size of the $Na^+$ since its optimized structure in Figure 4-3shows that the cation $Na^+$is located at the mean planeformed by

the crown ether.Meanwhile the cation $K^+$in the $K^+$/G16C5 complexis located at slightly above the mean plane of its crown ethers. The crown ether of G19C6 is expected to have a bigger cavity size than the crown ether in G15C5, G16C5 and G18C6.Surprisingly the optimized structure of the $Na^+$/G19C6 complex inFigure 4-3shows that the crown ether of G19C6 still forms a plane with its cation $Na^+$ in the middle of the plane.Comparing thetop view of the structure of the $Na^+$/K19C6 complex with its side view,we can see that the mean plane is formed byfive out of six of its oxygen binding sites. This can also be seen from the distribution of the $Na^+$-O distances for the complex in Table 4-2, where only five out of six oxygens are coordinated to the $Na^+$.This makes up the five $Na^+$-O distances ranging from 2.367 Å to 2.507 Å, while a remaining $Na^+$-O distance of 3.568 Å. The crown ether of the $K^+$/G19C6 complex is also planar with the cation located in the middle of the plan. This time all six oxygen atoms are involved in forming the plane.

Table 4-3: Geometry parameters (GP)ofdifferentglycolipid crown ethers complexes with $Na^+$or $K^+$

| | GP | G15C5 | GP | G18C6 | GP | G21C7 | GP | G16C5 | GP | G19C6 |
|---|---|---|---|---|---|---|---|---|---|---|
| $Na^+$ | rNa-O3 | 2.371 | rNa-O3 | 3.487 | rNa-O3 | 4.502 | rNa-O4 | 2.365 | rNa-O4 | 3.568 |
| | rNa-O25 | 2.300 | rNa-O25 | 2.628 | rNa-O72 | 2.367 | rNa-O30 | 2.321 | rNa-O28 | 2.347 |
| | rNa-O28 | 2.388 | rNa-O28 | 2.451 | rNa-O69 | 2.423 | rNa-O27 | 2.409 | rNa-O25 | 2.409 |
| | rNa-O31 | 2.293 | rNa-O31 | 2.572 | rNa-O66 | 2.485 | rNa-O24 | 2.357 | rNa-O80 | 2.447 |
| | rNa-O2 | 2.351 | rNa-O34 | 2.471 | rNa-O63 | 2.448 | rNa-O6 | 2.341 | rNa-O24 | 2.399 |
| | | | rNa-O2 | 2.511 | rNa-O60 | 2.388 | | | rNa-O6 | 2.356 |
| | | | | | rNa-O2 | 3.162 | | | | |
| $K^+$ | rk-O3 | 2.732 | rk-O3 | 2.796 | rk-O3 | 3.852 | rk-O4 | 2.701 | rk-O4 | 2.802 |
| | rk-O25 | 2.705 | rk-O25 | 2.722 | rk-O72 | 2.826 | rk-O30 | 2.684 | rk-O28 | 2.794 |
| | rk-O28 | 2.756 | rk-O28 | 2.851 | rk-O69 | 2.811 | rk-O27 | 2.768 | rk-O25 | 2.854 |
| | rk-O31 | 2.739 | rk-O31 | 2.813 | rk-O66 | 2.867 | rk-O24 | 2.715 | rk-O80 | 2.864 |
| | rk-O2 | 2.938 | rk-O34 | 2.724 | rk-O63 | 2.887 | rk-O6 | 2.704 | rk-O24 | 2.755 |
| | | | rk-O2 | 2.972 | rk-O60 | 2.801 | | | rk-O346 | 2.908 |
| | | | | | rk-O2 | 2.874 | | | | |

From the geometrical parameters in Table 4-3, in general, within a complex, the cation $Na^+$ can bind with the donor oxygen more closely than the $K^+$. Moreover, the distribution of the cation-O distances within each complex in Table 4-3 implies that the majority of the complexes have all their oxygen atoms in the crown ethers coordinated to the cations. The complexes that do not have their oxygen atoms in crown ethers fully coordinated to the cations are $Na^+$/ G18C6, $Na^+$/G19C6, $Na^+$/G21C7 and $K^+$/G21C7. In these four complexes, the oxygen atoms in the crown ether rings that are not coordinated to the cation are those from the glucose ring, namely, O3 for $Na^+$/G18C6, O4 for $Na^+$/ G19C6, O2  and O3 for $Na^+$/G21C7,  and O3 for $K^+$/G21C7 (see Table 4-3). Furthermore, from Table 4-3, one can see that the pairs of oxygen atoms in the crown ether rings that belong to the sugar rings are most likely to be further away from the cation compared to other oxygen atoms in the crown ether. This indicates that some constraint is imposed by the glucose ring on the O2 and O3 or O4 and O6, resulting in the latter to be less involved in the coordination with the cation compared to the other oxygen atoms from the crown ether. This restriction from the sugar ring can be seen in all the complexes except $Na^+$/G15C5, $Na^+$/G16C5 and $K^+$/G16C5. The cavity size in G15C5 and G16C5 fit for $Na^+$ cation. Therefore, the O-$Na^+$ coordination distances do not vary much in the cases of $Na^+$/G15C5 and $Na^+$/G16C. On the other hand, $K^+$ is too big to be fully contained within the cavities of G15C5 and G16C5. For $K^+$/G15C5, the constrained sugar ring causes the O2 not to be as close to the cation as that of the O3, which has similar cation coordination distance as the other oxygen atoms. Meanwhile, both O4 and O6 in $K^+$/G16C5 have similar coordination distances to the cation. This is because, unlike the O2 in $K^+$/G15C5, the O6 has one C-C bond away from it sugar ring, therefore it has a greater flexibility. One way for the pairs of O2 and

O3 or O4 and O6 to minimize the coordination distances with the cation, is by reducing

their dihedral angles O2-C-C-O3 for G15C5, G18C6 and G21C7, and O4-C-C-C for the

G16C5 and G19C6, where the -C-C- belongs to the sugar rings (see Figure 4-1). This

can be verified by comparing the dihedral angles of the free crown ethers and those of

the complexes. The comparison is given in Table 4-4 and Table 4-5.

Table 4-4: Dihedral angle O2-C-C-O3 for optimized structures of moleculesG15C5, G18C6 and G21C7 and their complexes with cations Na$^+$ and K$^+$

| M(glycolipids crown ether) | Dihedral angles of O2-C-C-O3(°) | | |
|---|---|---|---|
| | M | Complex Na$^+$/M | Complex K$^+$/M |
| G15C5 | 71.047 | 61.831 | 61.855 |
| G18C6 | 74.375 | 61.141 | 64.613 |
| G21C7 | 69.845 | 68.067 | 67.362 |

Table 4-5: Dihedral angle O4-C-C-C for optimized structures of molecules G16C5 and G19C6 and their complexes with cations Na$^+$and K$^+$

| M(glycolipids crown ether) | Dihedral angles of O2-C-C-O3(°) | | |
|---|---|---|---|
| | M | Complex Na$^+$/M | Complex K$^+$/M |
| G16C5 | 65.158 | 59.809 | 63.114 |
| G19C6 | 68.018 | 62.116 | 58.571 |

From Table 4-4 andTable 4-5, we can see that these dihedral angles of the

glycolipid crown ethers generally become smaller when the complexes are formed due

to the interac- tion of the oxygen binding sites with the cation. As for the other dihedral

angles O-C-C-O, around each crown ethers beside the O2-C-C-O3, the optimized

structures in Figure 4-1 show that G18C6, G16C5 and G19C6 all have their dihedral

angles of O-C-C-O in their crown ethers, either in the state of gauche + (0°≤Φ<120°) or

gauche- (120° ≤Φ<0°). Besides the gauche+ and gauche- states, the G15C5 has one of

its O-C-C-O in the trans state (120°≤Φ and Φ<-120°), while G21C7 has two trans

states. However, all the trans states are transformed to the gauche states when the

optimum coordination of oxygen atoms to the cations was considered.

## 4.3 Binding and exchange enthalpies and Gibbs free energies

The thermodynamics properties of the five molecules calculated at the B3LYP levels of theory using 6-31 G* basis set are given in Table 4-6. All the results in Table 4-6 have been corrected for their BSSE using the counterpoise method. The table shows that the binding energies, $\Delta E^b$, of the molecules to smaller cation $Na^+$ are lower than the binding energies to the cation $K^+$ which are higher. This is consistent with previous experimental and theoretical studies of other crown ethers systems [172, 173] and crytand [174] systems in gas phase which have shown that the binding energies are lower for small size alkali cations. This is because smaller size cations can have higher charge density and are able to bond with the coordination oxygens in crown ethers. Hence, $Na^+$/glycolipid crown ethers complex are more stable than their counterpart complex of $K^+$/glycolipid crown ethers, as shown in their binding enthalpies (Table 4-6). Furthermore, the feasibility of the complex formation is given by the Gibbs free energy. The Gibbs free energies calculated are negative values, indicating that all the complexes formation in gas phase considered here are chemically feasible.

Comparing the $Na^+$ complexes, our results show that the trend of the binding energies, binding enthalpies and the Gibbs free energies is in the order of G21C7 < G19C6 < G18C6 < G16C5 < G15C5. For the $K^+$ complexes, the trend is slightly different and is given as G21C7 < G18C6 < G19C6 < G16C5 < G15C5. From this comparison, we may deduce that, in gas phase, the glycolipid crown ether G21C7 is the most reactive in forming the stable complex with both the cations $Na^+$ and $K^+$, while G15C5 is the least reactive. The sequence of the complex binding energies indicates that the higher the number of oxygen atoms in the crown ether ring, the more reactive is the formation of the complex with a cation. When comparing G16C5 and G15C5, both of which have the same number of oxygen atoms in their crown ether rings, suggests that

the additional flexibility in G16C5 makes it more reactive than G15C5 toward the formation of the complex. On the other hand, while Na$^+$ is small compared to the cavities of G18C6 and G19C6, the additional flexibility of the latter, enable it to encapsulate Na$^+$ better than the former. However, the formation of the K$^+$/G18C6 complex is more reactive than that of K$^+$/G19C6, which seems to suggest that the cavity of G18C6 fits better for K$^+$ compared to the cavity of G19C6.

Table 4-6:The binding energies $\Delta E^b$, binding enthalpies $\Delta H^b$, and Gibbs free energies $\Delta G^b$, in the gas phase for the complexes at 298K

| Molecule | Metal cation | $\Delta E^b$ (kcal/mol) | $\Delta H^b$ (kcal/mol) | $\Delta G^b$ (kcal/mol) |
|---|---|---|---|---|
| G15C5 | Na$^+$ | -79.4503 | -80.0433 | -69.2432 |
| | K$^+$ | -50.3658 | -50.9582 | -41.0366 |
| G18C6 | Na$^+$ | -83.6138 | -84.2074 | -74.8544 |
| | K$^+$ | -69.0568 | -69.6498 | -59.9580 |
| G21C7 | Na$^+$ | -90.3181 | -90.9118 | -80.0107 |
| | K$^+$ | -69.3405 | -69.9335 | -59.1654 |
| G16C5 | Na$^+$ | -81.7037 | -82.2967 | -73.0679 |
| | K$^+$ | -52.8257 | -53.4180 | -44.3599 |
| G19C6 | Na$^+$ | -84.0154 | -84.6084 | -75.9036 |
| | K$^+$ | -64.4974 | -65.0897 | -56.7369 |

To further understand the selectivity of these molecules toward Na$^+$ we calculated the exchange enthalpies and exchange free energy given by the chemical reaction of:

Na$^+$/glycolipid crown ether + K$^+$ $\longrightarrow$ K$^+$/glycolipid crown ether + Na

The results are tabulated in Table 4-7. The exchange enthalpies and Gibbs free energies for these molecules can be arranged in the following order G15C5 > G16C5 > G21C7 > G19C6 > G18C6. The exchange enthalpies for G15C5 and G16C5 are significantly higher than G21C6, G19C7 and G18C6, which implies two of the former show much higher selectivity toward Na$^+$against K$^+$. Although these results were obtained based on the gas phase condition, it is qualitatively similar to the experimental cation selectivity performed in an aqueous solution with an equimolar ratio of cations Na$^+$ and K$^+$[45],

where the measurements were done using electrospray ionization method. The significantly higher ion selectivity of the two compounds G16C5 and G15C5 to the $Na^+$ over $K^+$ than the others was also con- firmed by the experiment [45]. However, G21C7 was shown experimentally to have a slightly higher affinity toward $K^+$, in contradiction to the theoretical result obtained in the gas phase. Nevertheless, the selectivity patterns of the five molecules over $Na^+$ and $K^+$ were similar to those of crown ethers with a similar number of oxygen atoms in the crown in gas phase as measured in the experiment [175].

Table 4-7: Exchange enthalpies ΔH and Gibbs free energiesΔG for the cation exchange in the gas phase at 298 K

| Molecule | ΔH(kcal/mol) | ΔG(kcal/mol) |
|----------|--------------|--------------|
| G15C5 | 29.0851 | 28.2066 |
| G18C6 | 14.5576 | 14.8965 |
| G21C7 | 20.9783 | 20.8453 |
| G16C5 | 28.8786 | 28.7080 |
| G19C6 | 19.5187 | 19.1667 |

It is well known that the preference of the crown ether binding with a cation in the gas phase would shift toward a bigger cation in the aqueous solution [176, 177]. The crown ether G18 C6 is known to bond more strongly with $Na^+$ than $K^+$ in the gas phase, while in the aqueous solution it shifts toward a stronger bond with $K^+$ than $Na^+$. Two reasons have been suggested for this change of ion selectivity [92, 173, 178]. Firstly, the stronger solvation effect on the smaller cation $Na^+$ than $K^+$, to some extent, make the complexation of $K^+$/G18C6 preferable toward $Na^+$/G18C6. Secondly the stronger solvation of the complexes with a bigger cation $K^+$ adds to the extra stability of the solvated complexes of $K^+$/G18C6 compared to $Na^+$/G18C6. On the other hand, the glucose based crown ethers of G18C6 equivalents, studied by Bako *et al*. [179] in an experiment, shows that it prefers $Na^+$ over $K^+$ in an aqueous solution. The same effects on the glycolipid crown ethers can be expected, thus in aqueous condition these prefer

Na$^+$ over K$^+$, especially G18C6 and G19C6, which are the equivalent of G18C6. The solvation effect on the glycolipid crown ethers is undoubtedly interesting to the behavior of these molecules in aqueous solution as well as when they are dissolved in other solvents. This is currently under investigation and will be reported in the near future.

# CHAPTER 5

## RESULT AND DISCUSSION: ATOMISTICSIMULATION STUDIES OF THE α/β GLUCOSIDE AND GALACTOSIDE IN ANHYDROUS BILAYERS: EFFECT OF THE ANOMERIC AND EPIMERIC CONFIGURATIONS

In this chapter we shall report the result of the full atomistic molecular dynamics simulation studies of four different bilayer systems which performed using a set of glycosides namely n-octyl-$\beta$-D-glucopyranoside ($\beta$-C$_8$Glc), n-octyl-$\alpha$-D-glucopyranoside ($\alpha$-C$_8$Glc), n-octyl-$\beta$-D-galactopyranoside ($\beta$-C$_8$Gal) and n-octyl-$\alpha$-D-galactopyranoside ($\alpha$-C$_8$Gal).The present objective is to find molecular substantiation on the likely relationship between two pairs of liner glycolipids, namely, $\alpha/\beta$-octyl-galactosides ($\alpha/\beta$-C$_8$Gal) and $\alpha/\beta$ octyl-glucosides ($\alpha/\beta$-C$_8$Glc) using computer simulation method in the thermotropic liquid crystal phase.

## 5.1 Local density profiles (LDPs)

The 20ns block averages of the local density profiles for four systems ($\alpha/\beta$-C$_8$Gal and $\alpha/\beta$-C$_8$Glc) over the last 160 ns are given in Figure 5-1. The LDPs show the bilayers do not break or fluctuate far from the equilibrium values and there are only minor differences between different block averages during the simulations. The expected microphase separation of the hydrophilic and the hydrophobic regions is demonstrated by the maximum and minimum density values along the bilayer normal in this figure. This implies that throughout the simulation the structures are intact. The LDPs of the four systems ($\alpha/\beta$-C$_8$Gal and $\alpha/\beta$-C$_8$Glc) are qualitatively similar in general.However, the $d$-spacings (or precisely the Luzzati's thickness[180]) aredifferent, implying that these bilayers have slightly different packingarrangements whichaffecttheir melting points [181]. The experimental bilayer spacing at 25°C for $\beta$-C8Gal is 25.1 Å, while at 90°C this value is 25.8 Å(Table5-1), which is slightly less than the simulated value of 27.5Å at 90°C. Similarly, for $\beta$-C8Glc the simulated value of 27.5 Å is slightly more than the experimentally determined X-ray $d$-spacing of 25.6 Å and 25.3 Å at 70°C and 105°C respectively [182]. Generally the present data for $d$-spacings are accord with those from the X-ray measurements for these phases within

less than 10%. This percentage difference is not too dissimilar from those found in other simulation studies of disaccharides in thermotropic phase when compared with the experimental data[106, 108, 183]In addition, it seems for $\beta$-C8Glc/C8Gal increasing the temperature does not change the thickness very much. Table5-1also shows that the bilayer spacings for $\alpha$-anomers are smaller than those of the $\beta$-anomers, which imply the former pack more tightly compared to the latter. Comparing the $d$-spacing of the quartets ($\alpha$/$\beta$-C8Gal and $\alpha$/$\beta$-C8Glc) reveals that the anomeric effect is more dominant than the epimeric effect.

Table5-1:$d$-spacing for $\beta$-C8Gal in L$_C$ phase, $\alpha$-C8Gal and $\alpha$/$\beta$-C8Glc in L$_\alpha$ phase and their average surface areas at the interface per lipid from160 ns simulations and the corresponding X-ray experimental data.

| Lipid | Simulation at 90°C | | Experimental data from X-ray | |
|---|---|---|---|---|
| | $d$-spacing/Å | Area/head group($Å^2$) | $d$-spacing/Å | Area/head group/$Å^2$ |
| $\beta$-C8Gal | 27.5 ± 0.4 (L$_c$) | 32.2 ± 0.4 | 25.1/25.8 (at 25/90°C)[182] | 34.49[a] |
| $\beta$-C8Glc | 27.6 ± 0.3 (L$_\alpha$) | 32.3 ± 0.3 | 25.6/25.3 (at 70/105°C)[182] | 36.1 [184, 185] |
| $\alpha$-C8Glc | 24.4 ± 0.2 (L$_\alpha$) | 36.0 ± 0.3 | 23.3 (at 75 °C)[186] | 39.1 [187]1 |
| $\alpha$-C8Gal | 25.4 ± 0.3 (L$_\alpha$) | 35.1 ± 0.4 | NA | - |

[a] calculated from the data of ref. [188]



Distane (A°)
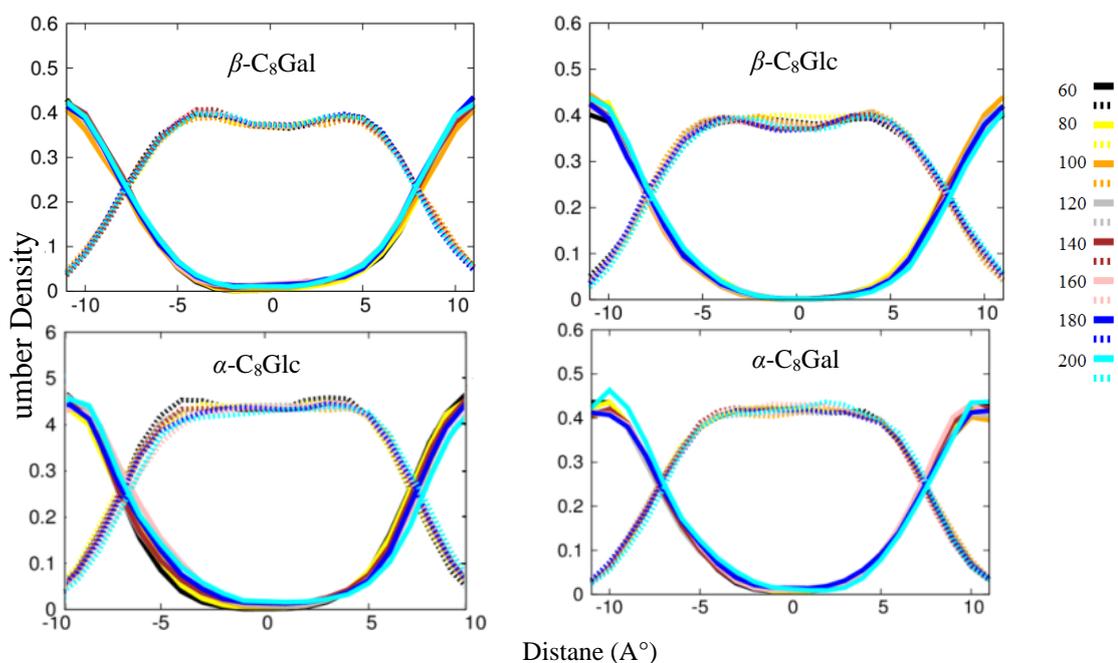
Figure 5-1:(A) Local density profiles: averages over block of 20 ns from 40 ns to 200 ns for (a) $\alpha$-C8Gal, (b) $\beta$-C8Glc, (c) $\alpha$-C8Glcand (d) $\beta$-C8Gal. The solid lines are for head group and the dotted lines are for alkyl chain. Each colored line in the legend shows the ldp of different 20 ns block averages spread over the 160 ns production stage.

## 5.2    Area at theinterface per sugar head

The average surface area at the interface per sugar head group over 160 ns dynamics runs for the four selected glycosides namely $\alpha/\beta$-C8Gal and $\alpha/\beta$-C8Glc, are given in Table5-1This data shows that the areas for $\alpha$-C8Glc and $\alpha$-C8Gal with the values of 36.0 and 35.1 $\mathring{A}^2$ respectively are greater than those of $\beta$-C8Glc and $\beta$-C8Gal by 10-12%. These results show the anomeric factor is important in controlling this property in the same manner as in the case of $d$-spacing. Thus, both thickness and interfacial area per head group are less sensitive to the C4 epimeric effect. According to the phase diagrams, both $\alpha/\beta$-C8Glc and $\alpha$-C8Gal are in the $L_\alpha$ phase. Therefore, chains within this phase are more fluid. In contrast, at this temperature $\beta$-C8Gal is in the $L_C$ phase but very close to the transition into the $L_\alpha$ phase. Hence, it was observed the $\beta$-C8Gal bilayer has the least area per head group $(32.2 \pm 0.4)$ $\mathring{A}^2$. Our results show that $\alpha$-anomers have higher surface area at the interface and lower densities than $\beta$-anomers.

## 5.3    Hydrogen bonds analysis

For a sugar-based surfactant system in a dry state, the sugar heads interact strongly with each other to stabilize the bilayer. This interaction originates mainly from the hydrogen bonds between sugar hydroxyl groups which makes sugar surfactants very fascinating in terms of their solid state behaviour[189] In addition, detailed sugar stereochemistry could generate hydrophobic or apolar surface on the sugar moiety giving its amphoteric character, which is important for molecular recognition[190]. Glycolipid system has the ability to participate in hydrogen bonding as both donor and acceptors, unlike phosphatidylcholines, which can act only as an acceptor[104, 191]. Each sugar head group in the bilayer system can be involved in two types of hydrogen bonds: inter- and intra-molecular hydrogen bonds. The results of hydrogen bonds for four sugar surfactants ($\alpha/\beta$-C8Glc and $\alpha/\beta$-C8Gal) are tabulated in Table 5-2,$\beta$-C8Gal has more affinity to be involved in both inter- (3.21) and intra-molecular (1.71)

hydrogen bonds compared to $\beta$-C8Glc whose values are 3.06 and 1.12 respectively. In the former the hydroxyl group at C4 is oriented axially[182]. On the other hand, the inter-molecular hydrogen bond for $\alpha$-C8Gal is 2.37 while that for $\alpha$-C8Glc is 3.10. But a reverse trend is observed for intra-molecular hydrogen bonds with the values of 1.31 and 1.71 for $\alpha$-C8Glc and $\alpha$-C8Gal respectively. Table 2 also shows that, the trend for the total hydrogen bonds of the four compounds is the same as that of the inter-molecular hydrogen bonds, i.e. $\beta$-C8Gal>$\alpha$-C8Glc>$\beta$-C8Glc>$\alpha$-C8Gal. This trend is also similar to the clearing temperatures of the four compounds, both from experimental and calculated based on the intermolecular hydrogen bond. In Table 5-3, the calculated clearing temperature assumes $\beta$-C8Glc is the reference compound. In the Supplementary, we have included all the calculated clearing temperatures, using different compounds as a reference. These predicted clearing temperatures are consistent with each other within less than 3%, except when using $\alpha$-C8Gal as a reference, where the difference is about 10%. Thus, it supports the previous proposal that inter-molecular hydrogen bonds contribute to the thermal stability of the bilayer assembly [192].

Moreover, the axially orientated hydroxyl group at C4 makes $\alpha/\beta$-C8Gal more capable of being involved in the intra-molecular hydrogen bonds than $\alpha/\beta$-C8Glc. Incidentally, these results agree with those reported by Mosapour*et al.*,[193]who had performed DFT calculations and analysed them using atoms in molecules approach (AIM) and natural bond orbital analysis (NBO).The AIM results proved that for $\beta$-C8Glc there is one intra-molecular hydrogen bond (HO6...O4), while for $\beta$-C8Gal, there are two extra bonds (HO6…O4 and HO6…O3) . In fact the inter- molecular hydrogen bond trend we observed here for the four glycosides agree with the same trend (intra-layer hydrogen bond) from the previous simulation[107].Of course quantitatively, the detailed numbers differ since their systems were simulated at 300 K, for 5ns simulation

run. The total lipid-lipid hydrogen bonds for these glycosides are about 40-50% higher than those of 1,2-di-*O*-palmitoyl-3-*O*-*β*-D-C8galactosyl-*sn*-glycerol (DP-C8GALA) and 1,2-di-*O*-palmitoyl-3-*O*-*β*-D-glucosyl-*sn*-glycerol (DP-GLUC) [104].Lower values of lipid-lipid inter-molecular hydrogen bonds for these glycoglycerol lipids are expected since the simulations were conducted in the lyotropic phase, where there was a variety of hydrogen bonds involving lipid-lipid, lipid-water, water-bridge and H-bonded water [104] However, the trend for hydrogen bonds (of DP-C8GALA versus DP-GLUC) agrees with the present results of galactosides versus glucosides. A similar pattern of dependency was also observed in the micellar ($L_1$) systems of for *β*-C8Gal and *β*-C8Glc, with the total number of inter head group hydrogen bonds at 2.14 and 1.8 respectively [106].

The role of polar interaction of the monosaccharide head group is important to stabilize the self-assembly. In theory, the maximum number of hydrogen bonds which a monosaccharide can make is 16, corresponding to 6 oxygen atoms able to accept 2 hydrogen bonds and 4 polar hydrogen atoms able to donate hydrogen bond. Simulation result of the bilayer system shows the values are less than 16 and these are 4.92, 4.41, 4.18 and 4.08 for *β*-C8Gal, *α*-C8Glc, *β*-C8Glc and *α*-C8Gal respectively. Orientation constraint of hydroxyl groups and the steric effect in the bulk environment are some of the reasons, which cause the decrease of hydrogen bonding ability of the sugar head group [108].It is interesting to calculate the distribution of these hydrogen bonds over the different OHs sites on the sugar moiety. Figure 5-2 shows the results of the individual donor and acceptor contributions to hydrogen bonding. A closer look into this in Figure 5-2 reveals that the interaction scheme of inter-lipid hydrogen bonding are dominated by oxygen O2 and O6 in all four compounds (α/*β*-C8Gal and α/*β*-C8Glc), which suggests greater availability of O2 and O6 to accept inter-head group hydrogen bonds.The low interaction for O1 and O5 is expected based on the missing hydrogen

donor ability due to the lack of a proton acceptor.In general O2 contributes almost 45% more in hydrogen bonding compared to O3 in all four compounds, but the order and trend of hydrogen bond of the quartet on both sites are almost the same (see Figure, 5-2).Specifically, the trend for the hydrogen bond distribution on O2 and O3 of the four compounds is $\alpha$-C8Gal> $\beta$-C8Gal> $\beta$-C8Glc>$\alpha$-C8Glc.But this trend is slightly differentfor the O6 site, which is $\alpha$-C8Glc> $\alpha$-C8Gal> $\beta$-C8Glc> $\beta$-C8Gal. Thus, on O2 and O3, the epimeric effect is more dominant,while on O6 the anomeric effect is more dominant. The hydrogen bonding trend on the O4 site is $\beta$-C8Gal> $\alpha$-C8Glc> $\beta$-C8Glc> $\alpha$-C8Gal, which is similar to the overall trend for hydrogen bonding. Even though $\beta$-C8Gal and $\alpha$-C8Glc are anomerically different, the hydrogen bonds on the O4 site of the former and the O6 site of the latter contribute nearly 80% of the total hydrogen bonds. The axial orientation of OH on the O4 epimer in $\beta$-C8Gal causes the increase in the capacity of donor and acceptor of this compound. On the other hand, for $\alpha$-C8Glc the exocyclic group at C6 position extends out to form a hydrogen bond with neighbouring lipids. These hydrogen bond interactions may be attributed to the high clearing temperatures of 127ºC and 116ºC for $\beta$-C8Gal and $\alpha$-C8Glc respectively.

Table 5-2: Total number of hydrogen bonds per sugar for $\alpha$-C8Glc, $\beta$-C8Glc, $\alpha$-C8Gal and $\beta$-C8Gal comprised of inter-molecular and intra-molecular hydrogen bonds.

| Mol/HB | $\beta$-C8Gal | $\alpha$-C8Glc | $\beta$-C8Glc | $\alpha$-C8Gal | Trend |
|---|---|---|---|---|---|
| Inter-mol | 3.21 | 3.10 | 3.06 | 2.37 | $\beta$-C8Gal> $\alpha$-C8Glc>$\beta$-C8Glc>$\alpha$-C8Gal |
| Intra-mol | 1.71 | 1.31 | 1.12 | 1.71 | $\alpha$-C8Gal> $\beta$-C8Gal> $\alpha$-C8Glc> $\beta$-C8Glc |
| Total | 4.92 | 4.41 | 4.18 | 4.08 | $\beta$-C8Gal> $\alpha$-C8Glc> $\beta$-C8Glc> $\alpha$-C8Gal |
| Exp. Clearing point °C | 127[182] | 116[182] | 107[182] | 98[10] | $\beta$-C8Gal> $\alpha$-C8Glc> $\beta$-C8Glc> $\alpha$-C8Gal |
| Calc. Clearing point °C | 132 | 115 | 107 | 72 | $\beta$-C8Gal> $\alpha$-C8Glc> $\beta$-C8Glc> $\alpha$-C8Gal |
| Exp. Melting point °C | 96[182] | 69[182] | 69[182] | 40[192] | |
| From other literatures | | | | | |
| Intra-layer [107]27(°C) | 2.9 | 2.77 | 2.70 | 2.43 | $\beta$-C8Gal> $\alpha$-C8Glc> $\beta$-C8Glc> $\alpha$-C8Gal |
| Inter-mol[104]70(°C) | 1.63[a] | - | 1.28[a] | - | DP-C8GALA >DP-GLUC |
| Inter-mol[106] | 2.14[b] | - | 1.8[b] | - | $\beta$-C8Gal> $\beta$-C8Glc |

[a] Calculation is in lyotropic phase, [b]Calculation is in micellar phase

Table 5-3: calculated clearing temperatures, using different compounds as a reference

| | Exp. T(°C) | Exp. T( K) | inter-mol-HB | Calc. T (K)[1] | % error | Calc. T(°C) | Calc. T (K)[2] | % error | Calc. T(°C) | Calc. T (K)[3] | % error | Calc. T(°C) | Calc. T (K)[4] | % error | Calc. T(°C) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| α-Gal | 98 | 371 | 2.74 | 344.77 | 7.07 | 71.77 | 340.37 | 8.26 | 67.37 | 346.06 | 6.72 | 73.06 | 371.00 | 0.00 | 98.00 |
| α-Glc | 116 | 389 | 3.08 | 387.55 | 0.37 | 114.55 | 382.61 | 1.64 | 109.61 | 389.00 | 0.00 | 116.00 | 417.04 | 7.21 | 144.04 |
| β-Gal | 127 | 400 | 3.22 | 405.17 | -1.29 | 132.17 | 400.00 | 0.00 | 127.00 | 406.68 | -1.67 | 133.68 | 435.99 | 9.00 | 162.99 |
| β-Glc | 107 | 380 | 3.02 | 380.00 | 0.00 | 107.00 | 375.16 | 1.27 | 102.16 | 381.42 | -0.37 | 108.42 | 408.91 | 7.61 | 135.91 |

1. β-Glc selected as reference.
2. β-Gal selected as reference.
3. α-Glc selected as reference.
4. α -Gal selected as reference.
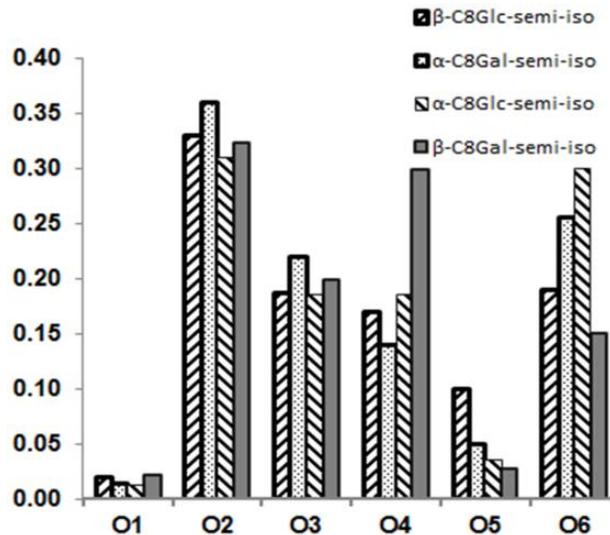
Figure 5-2:Inter-molecular hydrogen bond distribution over different oxygen locations (see Fig. 2) for $\beta$-C8Glc( ▣ ),$\alpha$-C8Gal ( ▱ ), $\alpha$-C8Glc ( ▱ ), and $\beta$-C8Gal ( ▣ )

## 5.4     Head group orientation

Figure 5.3 shows the distribution of the angle between the C9-O4 vector and the bilayer normal[104].  From the non-Gaussian plots, we observe the population maxima occur at 28° and 36°for $\beta$-anomeric pairs, $\beta$-C8Gal and $\beta$-C8Glc respectively; whereas, for the $\alpha$-anomeric pairs, $\alpha$-C8Glc and $\alpha$-C8Gal, these occur at 42° and 40°respectively.We notice that $\beta$-C8Gal, which is in the $L_C$ phase, is tilting significantly less compare to the other isomers, which are in the fluid $L_\alpha$.As expected, $\beta$-anomers are tilting less than $\alpha$-anomers for the equatorially linked anomeric carbon to the glycosidic oxygen. The angle distribution profiles for $\beta$-C8Glc and $\beta$-C8Gal from the current study are similar to those from the published work by Rog*et al*. [104], for $\beta$-anomers of DP-C8GALAand DP-GLUC with di-palmitic chains in $L_\alpha$lyotropic phase. This similarity indicates that the orientation of sugar head group is not much affected by the branching and chain length. Moreover, in these cases the maxima occured at about 38°,which is

not too different from our measurement for the $\beta$-C8Glc (36°), in the anhydrous $L_\alpha$, but is strikingly different from the dry $L_C$ phaseof $\beta$-C8Gal (28°).
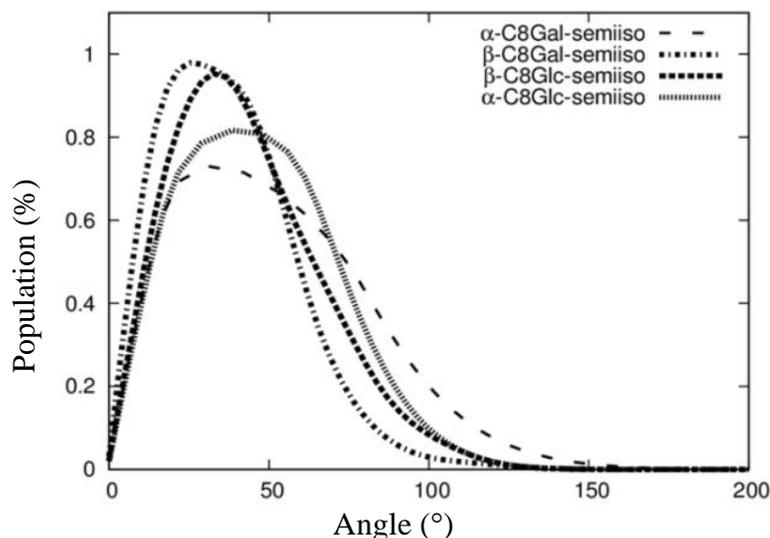


Figure 5-3:Distribution of angles between C9-O4 vector and bilayer normal in$\alpha$-C8Gal (- -),$\beta$-C8Gal (5----), $\beta$-C8Glc(---) and $\alpha$-C8Glc (॥॥॥) bilayers

## 5.5 Order parameter

Chain ordering in the bilayer is an interesting property used to determine the type of phase of the lipid assemblies [194]. Experimentally, $^2$H-NMR (deuterium Nuclear Magnetic Resonance) measurement is used to determine the C-D bond order of the deuterated chain[195]. But, in a simulation, the order parameter is calculated using C-H bond and the Saupe ordering tensor, and this is correlated with, the $-\langle S_{CD}\rangle$ [104] Figure 5.4 shows the $-\langle S_{CD}\rangle$ as a function of the methylene carbon position [196, 197] for the four compounds. In general, the plot shows the bond (C-H) order parameter decreasing from C9 to C14 for the quartet $\alpha/\beta$-C8Gal and $\alpha/\beta$-C8Glc. The farther the position of the carbon from glycosidic bond, the less the order becomes; hence the increase in the flexibility of the chain. Van Buuren*et al*. also found the same diminishing chain ordering behaviour for $\alpha/\beta$-C10Glc in lyotropic systems [198]. It is interesting to note that the chain order parameters profiles (which are in the hydrophilic

region) can be differentiated for the four compounds despite a diminutive difference in the head group stereochemistry. The two $\beta$ compounds ($\beta$-C8Gal and $\beta$-C8Glc) have higher chain order parameter profiles compared to $\alpha$ compound ($\alpha$-C8Gal and $\alpha$-C8Glc). Except for $\beta$-C8Gal which is in the $L_c$ phase, all other lipids are in the liquid crystalline, $L\alpha$ phase. This leads to the expectation that the bond order parameter of $\beta$-C8Gal will be higher compared to that of the other three lipids. This is because in the $L\alpha$ the chains are expected to be more disordered compared to those in the $L_c$ phase. However, we observed a contradicting behaviour, where $\beta$-C8Gal which is in the $L_C$ phase, has a lower $-\langle S_{CD} \rangle$ profile than does $\beta$-C8Glc. This could be related to the higher hydrogen bonding interaction at C4 (see Figure 5-2, O4) compare to those for the other lipids. The melting temperature of $\beta$-C8Gal is $96 \pm (5\text{-}8)°C$[182] which is very close to the simulated temperature 90°C. This observation may be justified from the thermal fluctuation viewpoint according to Sakya *et al.,*[182] the high hydrogen bonding at the O4 position constrain the head group, but allows the chain to fluctuate more, thus lowering the order parameter in the $L_C$ phase of $\beta$-C8Gal. Meanwhile, from Figure 5-4 a higher degree of chain ordering is also related to a lower tilt angle of the chains. When the tilt angle is high, less chain packing is expected. Therefore, $\beta$-C8Glc and $\beta$-C8Gal with the smaller tilt angles have higher chain ordering.

Comparing the $\alpha/\beta$ anomers, $\alpha$-anomers have lower order parameter compared to $\beta$-anomers. $\alpha$-anomers give a bent molecular shape especially at the sugar head group to carbon chain and the arrangement in bilayer ordering of these molecules causes the akyl chains to pack less densely. Similar results were observed for the n-decyl-$\alpha$-D-glucopyranoside and n-decyl-$\beta$-D-glucopyranoside monolayers at the water-decane inter-face [198] which suggests that increased tilt of the $\alpha$-glucose head groups leads to poorer packing of the decyl chains.
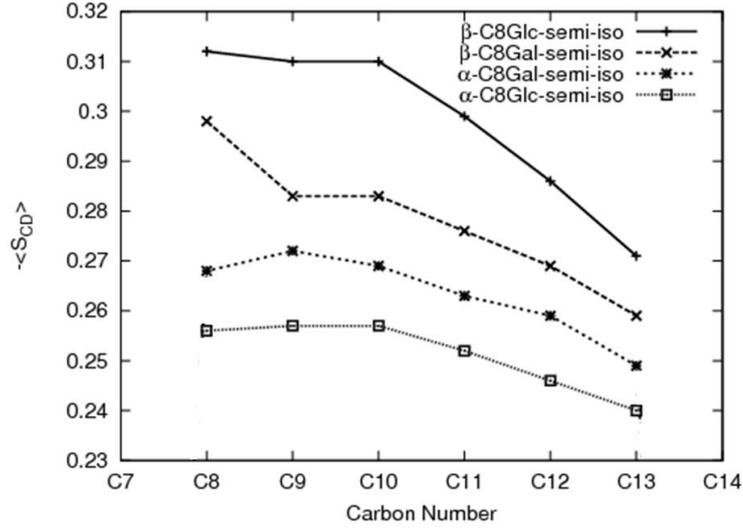
Figure (5.4) The average bond order parameters of C-H along the chain, $-\langle S_{CD} \rangle$, for $\beta$-C8Gal ($*$), $\beta$-C8Glc ($\square$), $\alpha$-C8Gal (+), and $\alpha$-C8Glc ($\times$), Connecting lines drawn only as a guide. The error in these values is less than 4%.

## 5.6    Lipid Dynamics in Anhydrous Bilayer

The Einstein relation (also known as Einstein–Smoluchowski relation) of diffusion coefficient and mobility, for a typical system, where the particles motion is Brownian, should be linear[199]. For this diffusion process, the mean square displacement (MSD) is linear in time with a constant slope representing the diffusion coefficient $D$. Deviation from this linearity indicates anomalous behaviour, which can be categorized sub- or super-diffusion, and the MSD can be more generally defined as:

$$g\left\langle \Delta r^2(t) \right\rangle = Dt^{\alpha} \text{ with } 0 < \alpha < 1 \qquad (5.1)$$

$$lg\left\langle \Delta r^2(t) \right\rangle = lg\,D + \alpha\,lg\,t \qquad (5.2)$$

where $t$ denotes the time axis, and $D$ is the diffusion coefficient which has the dimensionality of cm$^2$/sec$^{\alpha}$[200].The double logarithmic regression enables the determination of the power $\alpha$ of the diffusion law. When Einstein relation is satisfied $\alpha$

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equals to one. On the other hand, when α is not equal to 1, the system experiences either a sub- (α <1) or super-diffusion (α >1). In *Nature*, sub-diffusion is necessary for local interactions in cells,[201]even though it slows down long-distance diffusional surface-bulk exchange[202]. For instance, the localization of objects such as chromosomes or membrane channels and the formation and dynamics of membrane domains, all depend on the magnitude of the exponent α.

Table 5-4:The anomalous diffusion exponent, α and diffusion coefficient, $D$ [$\times 10^{-8}$ m$^2$/s] for α/β-C8Gal and α/β-C8Glc (40-200 ns) in dry state.

| Lipid | Exponent α | Calc. $D$ [$\times 10^{-9}$ cm$^2$/s$^\alpha$] | Cis/Trans-epimer/anomer |
|---|---|---|---|
| β-C8Gal | 0. 7 ± (0.3%) | 9.0 ± 0.3 | Cis |
| β-C8Glc | 0.6 ± (0.2%) | 6.4 ± 0.4 | Trans |
| α-C8Gal | 0.5 ± (0.3%) | 6.2 ± 0.3 | Trans |
| α-C8Glc | 0.5 ± (0.4%) | 2.0 ± 0.8 | Cis |
| | Exp. $D$ [$\times 10^{-8}$ cm$^2$/s] | Calc. $D$ [$\times 10^{-8}$ cm$^2$/s] | |
| DPhPC | 18.1 ± 5.6 [70,71] | 13.7±0.5 [70] | In water |
| DPPD | 20.7 ± 2.8[70,71] | 35.3±0.6 [70] | In water |

In order to evaluate the lateral diffusion process in our bilayer systems, the double log MSD was calculated as a function of time (see Figure 5-5), which displays the anomalous diffusion characteristics of the four lipid systems. This is based on equation(5.2), which describes the diffusion for both normal and anomalous systems [72]. This linear graph gives the exponent α and the diffusion coefficient, $D$are given in Table (5-4).The observed sub-diffusive behavior of these lipids is reasonable and is attributed to the unique structural complexity of the sugar head group, consistent with those observed for phospholipids in the liquid disordered, liquid ordered and gel phases [200]. From Table (5-4)we note also that the trans-epimer/anomer pair (β-C8Glc and α-C8Gal) in the L$_\alpha$ phase, have similar values of diffusion coefficients 6.4 and 6.2 ($\times 10^{-9}$ cm$^2$/s$^\alpha$) respectively. The diffusion of the trans-epimer/anomer pair is similar to the gel phase of phospholipids bilayer membrane[200]. In contrast the cis-epimer/anomer pair has strikingly different values of diffusion coefficient, i.e. 9.0 $\times 10^{-9}$ cm$^2$/s$^\alpha$ for β-C8Gal

(L$_C$ phase), and 2.0 ×10$^{-9}$ cm$^2$/s$^\alpha$ for α-C8Glc (L$_\alpha$ phase). These results may be understood from considering the thermal stability of these glycosides assembly with respect to their molecular structures. The thermal stability of amphiphilic liquid crystal is due to the hydrogen bond networks and the ability to store energy without disrupting the assembly. In the chain region, most of the energy will be stored in the vibrations of the alkyl chains [182]. Figure 5-6 shows the packing density and hydrogen bonding for α/β-anomeric pairs. The more linear shape of β-glycosides leads to a significantly more dense packing of the alkyl tails compared to the bent shaped of the α-anomers. The former has less hydrophobic area for the chains to vibrate, and so they eventually push each other apart, hence greater diffusion is expected. On the other hand, the chain groups of the α-anomers vibrate more due to the extra area in the chain region, and so the L$_\alpha$ phase is stable to higher temperatures [182].

In Table (5-4) we have included some experimental and simulation results of DPhPC and DPPC in the lyotropic phase for comparison. As expected, these lyotropic systems has larger diffusion coefficient compare to our dry systems.We have included some experimental and simulation results of DPhPC and DPPC in the lyotropic phase for comparison. As expected, these lyotropic systems has larger diffusion coefficient compare to our dry systems.
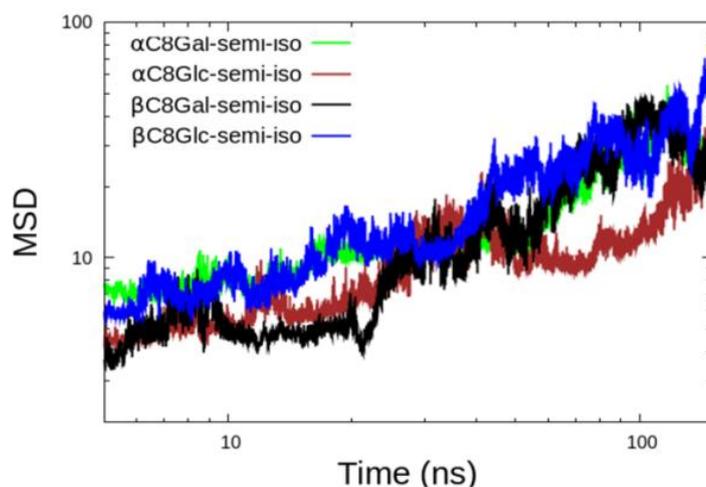


Figure 5- 5:Logarithmic scale of diffusion in $xy$ direction for
160 ns for α/β-C8Gal and α/β-C8Glc.
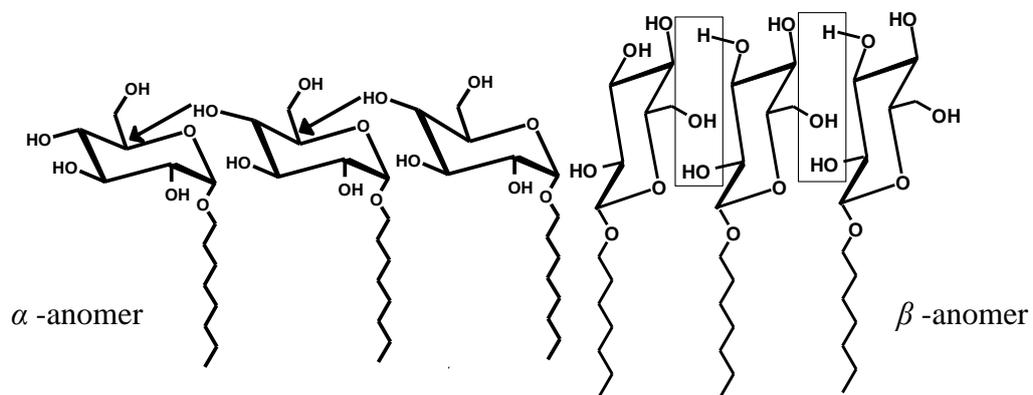
Figur (5-6)Packingdensity and hydrogen bonding for $\alpha/\beta$-anomeric pairs

# CHAPTER 6

## RESULT AND DISCUSSION: MOLECULAR DYNAMICS SIMULATION OF LYOTROPIC REVERSE HEXAGONAL (H$_{II}$) OF GUERBET BRANCHED CHAIN *B*-D-GLUCOSIDE

## 6.1    Structure of the reverse hexagonal H$_{II}$

The final configurations from the simulations of the two systems with different concentrations are given inFigure 6-1, which showthe stable hexagonal arrangements, with box dimensions of 11.8nm×6.9nm×4.8nm and 11.8nm×6.9nm×4.8nm, respectively. The stability of the simulation systems over the course of the simulation time was checked by monitoring the profile of the lattice parameter (i.e. average distance between two cylinders) and the radial density over time Here, the distance between two cylinders is defined as a two dimensional (i.e. X and Y axes) distance between the centres of mass of the two water columns (the lattice parameter). For each time frame, the lattice parameter between two neighboring cylinders is evaluated from all thepossible pairs of neighbors from the six cylinders. The time averaged lattice parameters are tabulated in Table 6-1, which is in relatively good agreement with the experimental measurements.



|  (a) | (b) |
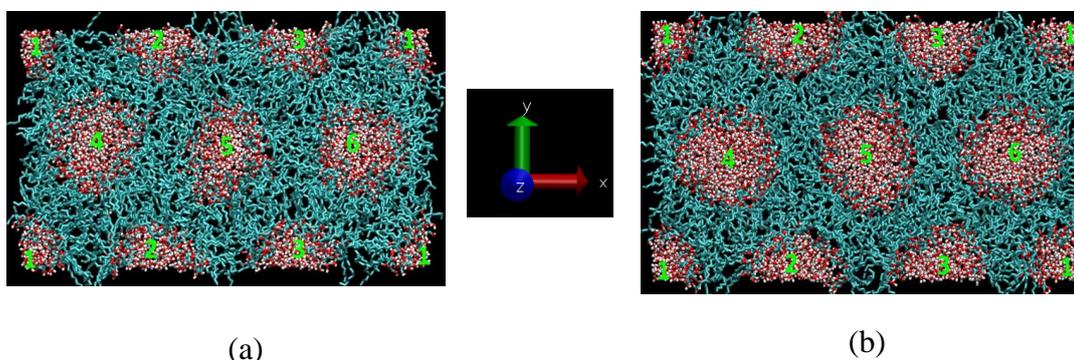
Figure 6-1: The Configurations of the H$_{II}$ phase after 50 ns for C$_8$C$_{12}\beta$-D-Glc system with (a) 14% water and (b) 22% water.

Table 6-1: The average lattice parameters and surface area per molecule obtained from the MD simulations and compared with thoseof experimental measurements and estimations.

| Water concentration % | Lattice parameter (Å) | | Surface area per molecule estimated (Å2) | |
|---|---|---|---|---|
| | SAXS Exp. [203] | MD simulation | Estimation from Exp.[14] | MD simulation |
| 14 | 39 | 40 ± 1 | 33 | 39 ± 4 |
| 22 | 42 | 41± 1 | 43 | 44± 4 |

The lyotropic H$_{II}$ self-assembly of C$_8$C$_{12}\beta$-D-Glc has threeregions, namely water, sugar head region and hydrocarbon chain. Slightoverlapping between regions is

expected at the interface. Takingadvantage of the hexagonal symmetry, we calculatedthe radialdistribution of the mass density with a center located in thewater region of cylinder number 5 (see Figure 6-1) as a referencepoint. The radial density distributionsare as displayed in Figure 6-2. Extensiveoverlapping exists in the $H_{II}$ of $C_8C_{12}\beta$-D-Glc with 14% waterconcentration Figure 6-2 (a), implying the sugar head group penetrates into the water channel. In contrast, the overlapping ofsugar and water density profiles is less in the system with 22% water. This suggests at low water concentration, the sugar head isless able to separate from the water region, compare to the case of a higher water concentration where water column free of sugar head group is found. Based on these results, we estimated the area per head group, A, using the equation,

$$A = \frac{2\pi rL}{N}.$$
(6.1)
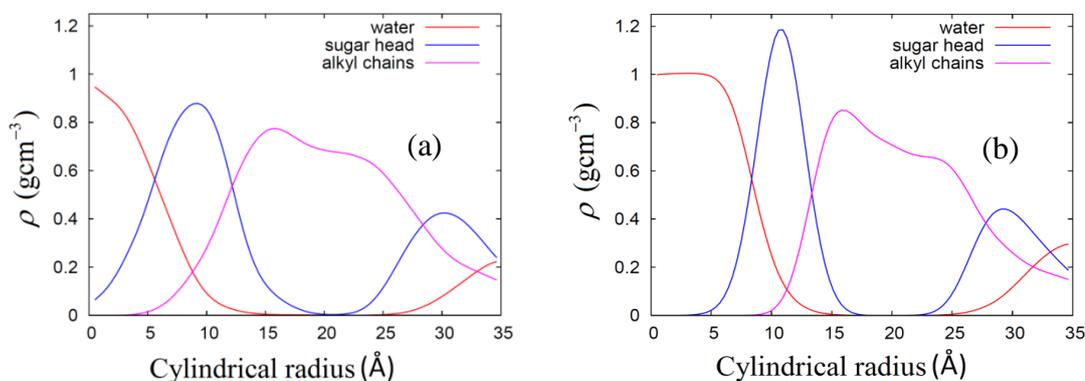


Figure 6-2: The radial density profiles of water, sugar head group and alkyl chains for $C_8C_{12}\beta$-D-Glc system of $H_{II}$ with (a) 14% water and (b) 22% water.

where, $r$ denotes the average radial distance of the sugar head group from the centre of the cylinder, estimated based on the position of the first peak of the sugar head density inFigure 6-2, which is 9.5 Å and 11.5 Å for systems of 14% and 22% water, respectively. $L$ denotes the length of the cylinder and $N$ denotes the number of molecule $C_8C_{12}\beta$-D-Glc forming the cylinder. For bothsystems, $N$ is 70, while $L$ is about 46 Å and

47 Å for the 14% and 22% water systems, respectively. In the SAXS experiment, the area per head group can be estimated based on the lattice parameter[17, 183, 204]. The simulated area per head group and its estimation based on the SAXS experiment are given in Table 6-1. For the 22% system, our simulation shows the area per head group being remarkably close to that estimated by the SAXS data. But for the system at lower water concentration (14%), the results from the two techniques differ by about 15%, which is still acceptable to within the error of the measurements for area per lipid, commonly observed for many lipidic systems[180]. Thus, the simple united atom model applied here is effective to represent the hexagonal phase formed by the chosen Guerbet glycoside [205]. These two concentrations, (14%) and (22%), were chosen based on the small angle X-ray measurements which have been reported corresponding to the reverse hexagonal phase. The later concentration, in excess water, is more relevant in biological environment.

## 6.2 Diffusion of water molecules in the water channel of H$_{II}$

It is well known that the dynamics of water confined in the nanoscale space is different from that of bulk water [206, 207], since the interactions between the water molecules to its wall is significant in an overall system. These interactions depend on the type of functional groups on the wall [208, 209], which could be stronger in the confined environment than in the bulk[210, 211]. The famous examples of such a condition are water inside the carbon nanotube [212, 213] and the aquaporin [214-216]. One of the direct consequences of the water wall interaction is the flow properties of the confined water. Recent experiment has found heterogeneity in the diffusion of the water regions within the H$_{II}$ system formed by the hexaethylene glycol, a non-ionic surfactant [217]. Since C$_8$C$_{12}\beta$-D-Glc is also a non-ionic surfactant, we believe the behavior of waters in its H$_{II}$ phase resembles that of a hydrophilic nano-channel, similar to the case

of hexaethylene glycol referred to previously[217].The experimental results showed that in the reverse hexagonal phase, H$_{II}$, there are two types of diffusions, namely ordinary Einstein's diffusion (due to the thermal effect) and an anomalous diffusion, which may be due to the restricted motion. The Einstein diffusion phenomena can be described by the Einstein relation, $\langle \Delta r^2 \rangle \sim t$, where $\langle \Delta r^2 \rangle$ is the mean square displacement of particles and $t$ is the time. This relationship can be written into Einstein's diffusion equation,

$$\langle \Delta r^2 \rangle = 2dDt, \tag{6.2}$$

where $d$ is the dimension of the displacement and, $D$ is the diffusion coefficient. Meanwhile in the anomalous diffusion phenomena, the relationship between $\langle \Delta r^2 \rangle$ and $t$ is accordingly to the power law as:

$$\langle \Delta r^2 \rangle \sim t^\alpha \text{where } \alpha \neq 1. \tag{6.3}$$

We investigated the diffusion behavior of two simulated systems by calculating the mean square displacement of the water molecules. The mean square displacement along the columnar axis, i.e. the $z$-axis, was calculated separately from the mean square displacement in the plane perpendicular to the columnar axis, i.e. the $xy$-plane. These calculations were performed using the utility program $g\_msd$in the GROMACS software package. The log-log plots of the mean square displacement as a function of time are given Figure 6-3.
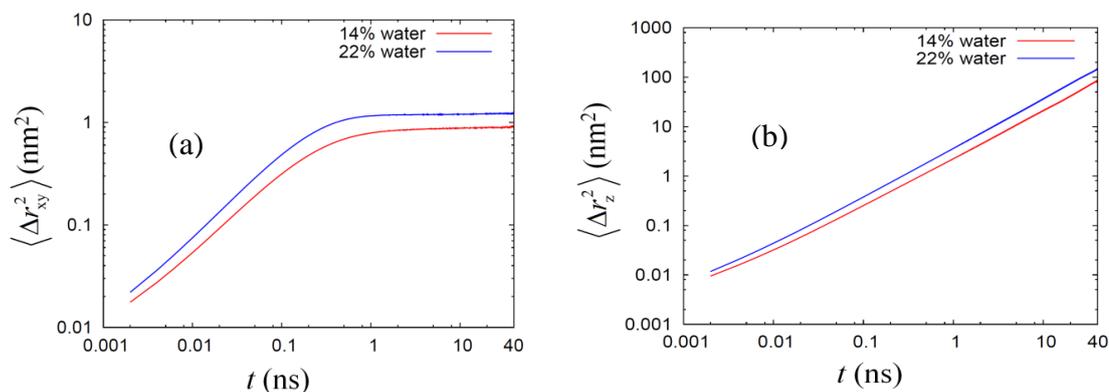
Figure 6-3: The mean square displacements of water versus time (a) in the xy plane and (b) in the z direction

Figure 6-3 shows the mobilities of confined water in the *z* direction and the *xy* plane are higher for the system of higher water concentration. Figure 6-3 (a), shows the diffusion of water in the *xy* direction is anomalous, with the exponents α equal to 0.76 and 0.81 for system of 14% water and 22% water, respectively (see Table 6-2) for the region less than 100ps. These results were obtained by a linear regression analysis, where values ofα were calculated from the slope of the linear fitting lines. We observed that the time scale for the anomalousdiffusion is independent of the water concentration. Beyond 100ps, the mean square displacement of water levels off at different limiting values for differentconcentrations. Moreover, the limiting mean square displacement for the 22% system is larger compared to that for the lower concentration system. In the former, the motion of water is less confined since it has a biggerwater channel. In addition, upon close inspection of these long time-scale diffusions, we found that these are not completely flat. Instead, both have significantly measurable gradients (see Table 6-2). In contrast, the diffusion along the *z*-direction in Figure 6-3 (b), for the 22% system conforms to the Einstein's relation, while for the less concentrated system 14% water, this deviates slightly from the Einstein's relation (see Table 6-2). Ignoring the slight deviation, and assuming a normal behavior for both, the values of the diffusion coefficients for the 14% and 22% systems are $(1.0 \pm 0.1) \times 10^{-5} cm^2 s^{-1}$ and $(1.8 \pm 0.1) \times 10^{-5} cm^2 s^{-1}$, respectively. Compared to the diffusion of SPC water measured

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in a bulk system, which is $(4.20 \pm 0.01) \times 10^{-5} cm^2 s^{-1}$ [218], these simulated values are 4–2 times slower.

Table 6-2: The exponents α for the diffusion of water in the *xy* plane and the *z* direction and the diffusion coefficient D in the *z* direction for the C₈C₁₂β-D-Glc system at 14% and 22% water.

| System | Diffusion in the xy plane | | Diffusion in the z axis | |
|---|---|---|---|---|
| | α when t ≤100 ps | α when t ≥ 5 ns | α over the production | D (10-5 cm2/s) |
| 14% water | 0.76 | 0.02 | 0.98 | 1.1 ± 0.1 |
| 22% water | 0.81 | 0.01 | 1.00 | 1.8 ± 0.1 |

Since C₈C₁₂β-D-Glc is a non-ionic surfactant and the sugar head group is not too different from the glycol moiety of a similar common surfactant hexaethylene glycol (C₁₂E₆) the water diffusion phenomena for both should be relatively similar. Therefore our simulation results could offer an alternative detailed explanation for the particles tracking experiment in the H$_{II}$phase formed by hexaethylene glycol.They measured the diffusion of polystyrene (PS) probes using optical tweezers techniquein isotropic, reverse hexagonal and lamellar phases at threeconcentrations, 20%, 50% and 80% of C₁₂E₆respectively. They found that the diffusions of PS in both lamellar and isotropic phases conform to a normal diffusion pattern, but in the reverse hexagonal phase, both normal diffusion and sub-diffusion behavior was observed. They explained that the presence of two diffusions phenomena is due to the heterogeneous local environment within the reverse hexagonal structure, i.e. the presence of an isotropic local domain where PS diffusion is normal, and a hexagonal local domain where the PS diffusion is restricted giving the sub-diffusion phenomenon. However, basedon our simple simulation model of the reverse hexagonal phase, the diffusion of water in the *z* axis along the column is normal but in the *xy* plane is sub-diffusion. Since the particle tracking experiment only captured two-dimensional displacements of the PS, the diffusion pattern of the probe in 2D is necessarily subdiffusion depending on the orientation of the water column with respect to the laboratory Z axis. Therefore, we

believe that the origin of heterogeneity in the local environment is due rather to the existence of the local domains of $H_{II}$ in the measured sample with different columnar orientations. The probe particles inserted during the experiment could have been distributed among these local domains, therefore various diffusion behaviours were observed. To show how is the orientation of columnar axis affects the two-dimensional diffusion pattern, we begin with a three dimensional mean square displacement of a probe particle in a certain columnar phase, denoted by $\langle r_{XYZ}^2 \rangle$, where the labels X, Y and Z represent the laboratory axes. $\langle r_{XYZ}^2 \rangle$ can be defined as:

$$\langle r_{XYZ}^2 \rangle = \langle \Delta X^2 \rangle + \langle \Delta Y^2 \rangle + \langle \Delta Z^2 \rangle, \tag{6.4}$$

where $\Delta X$, $\Delta Y$ and $\Delta Z$ are the components of the displacements in the laboratory axis. Next, we define a columnar axis system denoted as $x$, $y$ and $z$ for a column in the $H_{II}$ phase, where $z$ is theprincipal axis of a particular column, while $x$ and $y$ axes form the plane perpendicular to the principal axis. The mean square displacement based on this reference axes is written as $\langle r_{xyz}^2 \rangle$ such that,

$$\langle r_{xyz}^2 \rangle = \langle \Delta x^2 \rangle + \langle \Delta y^2 \rangle + \langle \Delta z^2 \rangle. \tag{6.5}$$

Here, $\Delta X$, $\Delta Y$ and $\Delta Z$ are the displacements according to the columnar axis system. In principle,

$$\langle r_{XYZ}^2 \rangle = \langle r_{xyz}^2 \rangle. \tag{6.6}$$

If the $z$axis of this column deviates from the Zaxis by an angle $\theta$,

$$\Delta Z = \Delta z \, cos \, \theta. \tag{6.7}$$

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In the particles-tracking experiment, the two-dimensional displacement measured is $\left\langle r_{XY}^2 \right\rangle$. Consequently,

$$\left\langle r_{XY}^2 \right\rangle = \left\langle r_{XYZ}^2 \right\rangle - \left\langle \Delta Z^2 \right\rangle = \left\langle r_{xyz}^2 \right\rangle - \left\langle \Delta z^2 \right\rangle cos^2 \theta. \tag{6.8}$$

As shown in our simulation, the diffusion of water molecules in the confined *xy* plane behaves anomalously, hence the probe particles' diffusion should behave likewise. This implies that:

$$\left\langle r_{xy}^2 \right\rangle = 4D_{xy}t^\beta, \tag{6.9}$$

and

$$\left\langle \Delta z^2 \right\rangle = 2D_z t, \tag{6.10}$$

where $0 < \beta < 1$, $D_{xy}$ and $D_z$ represent the diffusion coefficients in the *xy* plane and in the *z*-axis, respectively.Substituting, equation (6.9) and equation (6.10) into equation (6.8) we obtain,

$$\left\langle r_{XY}^2 \right\rangle = \left[ 4D_{xy}t^\beta + 2D_z t \right] - \left( 2D_z t \right) cos^2 \theta = 4D_{xy}t^\beta + 2D_z t \left( 1 - cos^2 \theta \right) =$$
$$\left( 1 + \frac{2D_{xy}}{D_z \left( 1 - cos^2 \theta \right)} t^{\beta-1} \right) 2D_z t \left( 1 - cos^2 \theta \right). \tag{6.11}$$

Equation (6.11) shows that the particle displacement measurement in two dimensions can deviate from the normal diffusion phenomenadepending on the orientation of the columnar axis. One can be seethat as long as $\theta \neq 0$, the time-dependent term,

$\frac{2D_{xy}}{D_z (1 - cos^2 \theta)} t^{\beta-1}$ will decrease as time increases. Eventually, $\frac{2D_{xy}}{D_z (1 - cos^2 \theta)} t^{\beta-1}$

becomes insignificant, then equation (6.11) effectivelyconform to Einstein's diffusion relation. Therefore, for a longenough time, the two-dimensional diffusion in the H$_{II}$ is normal, except when the direction of the $z$axis of the column coincideswith the laboratory Zaxis, i.e. when $\theta=0$, where the anomalousdiffusion will be observed. Moreover, when these two axes do notcoincide but the time of measurement is long enough, onlynormal diffusion is observed, such that,

$$\left\langle r_{XY}^{2}\right\rangle \approx 2D_{z}t\left(1-cos^{2}\theta\right). \tag{6.12}$$

This means the diffusion coefficient measured in the laboratory reference axes, $D_{lab}$, is effectively related as,

$$D_{lab}=D_{z}\left(1-cos^{2}\theta\right)/2. \tag{6.13}$$

which is different according to the deviation angle between theprincipal $z$ axis of the column and the Zaxis in the laboratoryframe.

From this analysis, we show that the 2D diffusion patternobserved depends on the columnar orientation with respect to thelaboratory axis. In reality, the columns' orientations in the H$_{II}$ atthermal equilibrium are not perfectly uniform due to the existenceof local domains, which leads to deformations and defects in thesystem that can be observed under the polarizing microscope[219]. Inthe experiment, different probe particles inserted might fall intosome parts of the columnar phase with different orientations,leading to different diffusion patterns observed. This seems to explainthe diffusion phenomena H$_{II}$ of C$_{12}$E$_{6}$given by theexperiment[217].

## 6.3 Interaction between water and sugar head group at different water concentrations

Within the reverse hexagonal phase, $H_{II}$, the water moleculesinteract extensively with the sugar head group at the interface between the water region and the sugar head region. One of the important interactions is the hydrogen bond,which involves the water molecules and the oxygen atoms from the sugar head group. Thesehydrogen bonding interactions can be extracted from thesimulations. A hydrogen bond is characterized according to thegeometric criteria such that the oxygen to oxygen atom distancemust be less than 3.5 Å and the O-H…O angle less than 30º[220, 221]. Based on these criteria and using the *g_hbond* utilities software inGROMACS, we calculated the time-averaged number of hydrogen bond per sugar head for each hydroxyl group (donor)and the oxygen atoms (acceptor) on the sugar head itself (see Figure 6-4). The results of the calculations for the two waterconcentrations system are given in Table 6-3. It shows that for bothwater concentrations, among the six oxygen atoms acting as hydrogen bonding acceptors on the sugar head, O6 gives the highest number of hydrogen bond with water molecules, followed by O3, O2, O4, O5 and finally O1. Meanwhile, among the four hydroxyl groups on the sugar head, the highest hydrogen bond is the donor O4-H, followed by O3-H, O6-H and O2-H (Table 6-3).

Table 6-3also shows that for each site, (both for donor and acceptor) the number of hydrogen bonds is higher for a high water system due to the higher availability of water molecules to participate in the hydrogen bond formation and a larger interface in the system of high water content.
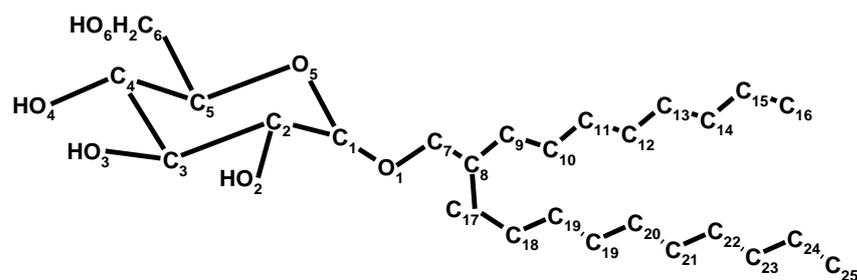
Figure 6-4: Designation of oxygen atoms on the sugar head for $C_8C_{12}\beta$-D-Glc.

Table 6-3: Average number of hydrogen bonds on different oxygen sites of the sugar head and their respective lifetime

| Water-sugar hydrogen bond | | Average no. of hydrogen bond per sugar head | | Hydrogen bond lifetime (ps) | |
|---|---|---|---|---|---|
| | | 14%water | 22%water | 14%water | 22%water |
| Acceptor | O1…H-O$_{water}$ | 0.02 | 0.03 | 1.5 | 1.5 |
| Acceptor | O2…H-O$_{water}$ | 0.30 | 0.36 | 30.8 | 18.0 |
| Acceptor | O3…H-O$_{water}$ | 0.44 | 0.50 | 13.1 | 9.4 |
| Acceptor | O4…H-O$_{water}$ | 0.27 | 0.29 | 15.6 | 13.6 |
| Acceptor | O5…H-O$_{water}$ | 0.08 | 0.12 | 8.3 | 5.2 |
| Acceptor | O6…H-O$_{water}$ | 0.57 | 0.69 | 16.7 | 11.9 |
| Donor | O2-H…O$_{water}$ | 0.26 | 0.36 | 53.0 | 38.3 |
| Donor | O3-H…O$_{water}$ | 0.34 | 0.40 | 32.5 | 25.1 |
| Donor | O4-H…O$_{water}$ | 0.46 | 0.50 | 25.9 | 20.5 |
| Donor | O6-H…O$_{water}$ | 0.34 | 0.43 | 39.0 | 31.8 |

The dynamics of the hydrogen bonding interactions between water and sugar head were also investigated. The lifetime of the hydrogen bond was analysed by calculating the autocorrelation function of the hydrogen bond existence, C(τ), defined as,

$$C(\tau)=\langle s_i(t)\rangle s_i\langle(t+\tau)\rangle, \tag{6.14}$$

Where $s_i(t)=\{0,1\}$ [217, 222]. The lifetime of the hydrogen bond is,
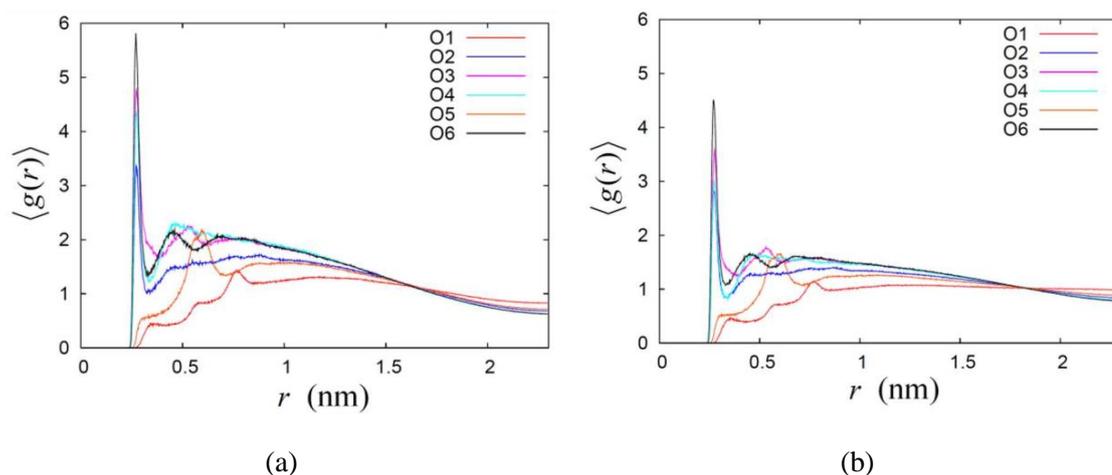
Figure 6-5: The radial distribution function (RDF) of water-oxygen around the six oxygen atoms for two systems (a) 14% and (b) 22% water concentrations

$$\tau_{life} = \int_0^\infty C(\tau)d\tau. \tag{6.15}$$

Table 6-3 gives the results of this analysis and shows that in bothsystems, the donor hydrogen bond at O2-H$\ldots$ O$_{water}$ has thelongest lifetime compared to other sites. In addition, the hydrogen bond O2$\ldots$H-O$_{water}$has the longest lifetime among acceptoroxygen. This indicates that the water molecules are more confined, whenbonded to the hydroxyl O2-H site compared to when bonded withthe other hydroxyl groups. Consequently, water molecules closeto the O2 site penetrate deeper into the sugar region and are somewhat trapped. On the other hand, even though the glycosidicoxygen O1 and O5 are located deeper within the sugar structure,their partial charges are less negative than those of O2. Therefore,the hydrogen bonds on O1 and O5 are less stable than that of O2.Table 3 also shows that the lifetime of each particular hydrogen bond considered for the system of 14% water, is longer than thatof the 22% water system. This is expected since the diffusion of water molecules in smaller size water channels of 14% water is lower than in the 22% water system, which has a larger water channels.

Both systems also show differences in the number of hydrogenbonds with water at different hydroxyl group sites or oxygen atoms on the sugar head. This feature indicates different degreesof exposure of different parts of the sugar head group to the watermolecules at the interface. This can be further illustrate by theradial distribution function (RDF) of the water oxygen atoms with respect to the six oxygen sites on the sugar head denoted as RDF_O$x$, where $x$ = 1,2...6 denoting the particular site (see Figure 6-4). The RDF_O$x$of the two systems were calculatedusing the *g_rdf* utilities software in GROMACS, whose resultsare given inFigure 6-5. Qualitatively, the results of RDF_O$x$ for both systems arerather similar regardless of the water concentration. For the twosystems, RDF_O2, RDF_O3, RDF_O4 and RDF_O6 show theformation of hydration shells around the oxygen atoms O2, O3,O4 and O6. The RDF_O2 of both systems show only onedefinite water structure such that it peaks at the radial distance of2.7 Å (seeFigure 6-5), which corresponds to the first hydration shellaround O1. Two water structures can be seen in the RDF_O3 andRDF_O4 of the two systems indicating twolayers of hydration formed around their O3 and O4, while the RDF_O6 shows the existence of three hydration layers around the O6 site. The positions of the peaks inthese four RDF_O$x$, for both systems, are similar and given inTable 6-4. Our simulation results were found to be comparable tothose measurements for the peak positions of  the water RDF withrespect to another water molecule, namely RDF_OW, obtainedfrom experimental measurement[223] except the positions of secondpeak for RDF_O3. Based on the number of hydration layers aswell as the height of the RDF_O first peak, we can conclude thathydroxyl group O6-H is most exposed to water, and this isfollowed by O3-H, O4-H and O2-H. This also means that the oxygenO6penetrates deepest into the water region, and belongs to the outermost region of the water-sugar interface.

Table 6-4: The peak positions in the oxygen to oxygen RDF of water for the four oxygen atoms from the hydroxyl groups, namely O2, O3, O4 and O6. These are compared with those from the experimental measurements for RDF of oxygen to oxygen in the bulk water.

| RDF | Peak positions (Å) | | |
| --- | --- | --- | --- |
| | 1st | 2nd | 3rd |
| RDF_O2 | 2.72 | Nil | Nil |
| RDF_O3 | 2.74 | 5.31 | Nil |
| RDF_O4 | 2.74 | 4.60 | Nil |
| RDF_O6 | 2.70 | 4.50 | 6.82 |
| RDF_OW[223] | 2.88 | 4.50 | 6.73 |

On the other hand, RDF_O1 and RDF_O5 show the highest peak at the radial distance of 7.6 Å and 6.0 Å, respectively. The radialdistances of these two peaks can be explained approximately asthe distance of O1 and O5, to the water structure right outside the outermost region of water–sugar interface formed by O6-H, as explained previously.The estimated distances are obtained by approximating the distances of O1and O5 to O6, i.e. 6.0 Å and 3.7 Å, plus the radial distance of firstwater structure for O6, which is 2.7 Å. This gives approximately8.7 Å and 6.4 Å for O1 and O5, respectively, which are close totheir respective peaks positions in the RDF_O.

## 6.4 The packing of the alkyl chains

It is known that the cross-section of a column in the $H_{II}$ is not asmooth circular shape, but instead this is a hexagon with smooth corners[17, 224-226]. This hexagonal shaped column is necessary for the columnar structure to fill the space while maintaining thehexagonal lattice arrangement. This would mean the alkyl chains have tostretch out to the corner and be compressed on the face of thehexagon. The energy of compression and the extension of thealkyl chains is called the frustration energy[19]. To see this effect in our simulation systems, we calculated the distribution of the radialdistance from the methyl group, $CH_3$, from the centre of its cylinder with respect

to the angle around the column axis. We focusedour analysis on the middle cylinder number 5 for the two systems from 10ns to 50ns, i.e. during the production stage.

Figure 6-6 gives the time averaged radial distances of CH3 from the centre of the cylinder as a function of the angle around the column for the two simulation systems. The averaged radial distances of CH3 for the two systems peaked roughly at the six hexagonal corners, indicated by the vertical straight lines in

Figure 6-6. On the other hand, the radial distances of CH3 are lowest in between the two peaks, implying the compression of alkyl chain at the faces of the hexagon. In

Figure 6-6, the non-uniform heights among the peaks and the dips indicate imperfection in the cylindrical symmetry of the columnar phase.
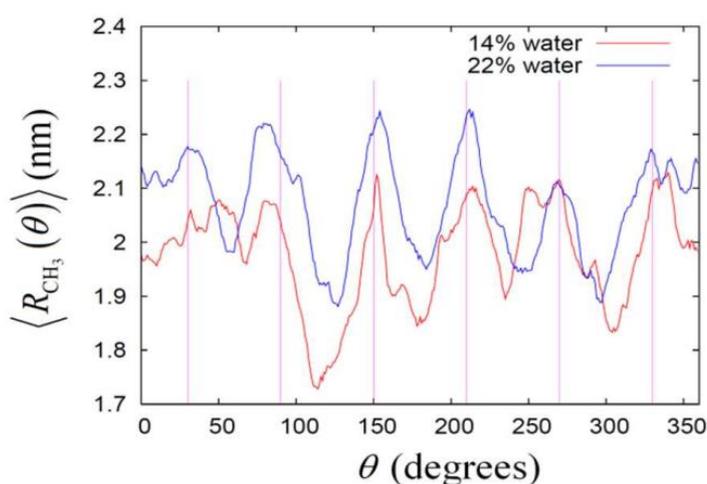


Figure 6-6: The distribution of the average radial distance of the $CH_3$ over angles around the cylinder, where the straight vertical lines are at the angles 30º, 90º, 120º, 180º, 240º and 270º

# CHAPTER 7

## CONCLUSION

In this chapter we shall bring the conclusion of each investigation separately and followed by the future research in this area.

## 7.1    Conclusion

In the first part of this thesis the geometrical and electronic structures of a series of five glycolipid crown ethers and their complexes with $Na^+$ and $K^+$ cations were studied using the B3LYP with the 6-31 G* basis set. The condensed Fukui functions were evaluated to give the local reactivity of the oxygen atoms on the crown ethers of each molecule to the nucleophilic attacks. It was found that these oxygen atoms were partially reactive, while the most reactive sites of each molecule tend to be located a distance away from the sugar ring. The calculated global nucleophilicity index revealed that upon optimization, smaller crown ethers size generally gave higher nucleophilicity. The five molecules give the energy gaps, which are close to one another. Among them, G16C5 has the highest energy gap, which means it has the highest chemical hard-ness. These molecules also have rather similar ionization potential but their electron affinities are sensitive to the difference in the geometrical size of their crown ethers. The lowest electron affinity is given by G16C5.

From the optimized structures of the glycolipid crown ethers, it was found that the cavity size of G15C5 is the best match with the $Na^+$ cation. The cavity size of G18C6 and G19C6 fits with $K^+$ better than other glycolipid crown ethers, where the cation is located at the mean plane of the crown ethers with all the oxygen coordinated to the encapsulated cation. On the other hands, there are a few cases, where the cavity sizes of the crown ether rings are too big such that some oxygen atoms are not coordinated to the cation. Furthermore, we observed that the sugar oxygen atoms O2, O3, O4 and O6 in their respective glycolipid crown ethers are in most cases further

away from the cation compare to other oxygen atoms in their respective crown ether rings. Constrained by the sugar ring, these sugars' oxygen atoms are hindered from getting nearer to the cation. These oxygen atoms move toward the cation by lowering their dihedral angles of O2-C-C-O3 or O4-C-C-C from their initial optimized structures.

The calculated binding energies, enthalpies and Gibbs energies in the gas phase at temperature 298 K showed that all five molecules bound more strongly with cation $Na^+$ than $K^+$. Based on this, the molecular binding stability with $Na^+$ could be arranged in the order of G21C7 > G19C6 > G18C6 > G16C5 G15C5, while that with $K^+$ was in the order of G21C7 > G18C6 > G19C6 > G16C5 > G15C5. The exchange enthalpies and Gibbs energies for the exchange reaction calculated showed that the ion selective capability toward $Na^+$ over $K^+$ of these molecules was in the order of G15C5 > G16C5 > G21C7 > G19C6 > G18C6. Among them, the exchange enthalpy of G16C5 was close to G15C5 and both were significantly higher than the others. This was similar to the selectivity pattern found in the experiment in aqueous solution of equimolar cation $Na^+$ and $K^+$, [16] except for the G21C7, which might be due to the effect of the solvation of the water.

The second part of this thesis includes the fully atomistic MD simulations of the epimeric/anomeric quartet liner glycolipids with the same octylchain group, namely, $\alpha/\beta$ octyl-galactosides and $\alpha/\beta$octyl-glucosidesto investigate the stereo-chemical relationship. Local density profile, inter- and intra-molecular hydrogen bonds, average area at the interface per sugar, head group tilt angle and chain order parameter are some of the properties which have been used to scrutinisethe effect of subtle stereochemical changes of these systems.

The results show that, the anomeric stereochemistry or the axial/equatorial orientation of C1-O1 ($\alpha/\beta$) is an important factor controlling the area and *d*-spacing of glycolipid bilayer systems in thermotropic phase, while the epimeric sterochemistry is secondary. Thus, thickness for $\beta$-C8Glc/C8Gal is larger than that for $\alpha$-C8Glc/C8Gal. Meanwhile the area per lipid head group is higher for the $\alpha$-compound than for the $\beta$-compound. In addition, the head group tilt angles are similar for those in the fluid L$\alpha$ of about 36–42, which is significantly larger than that for $\beta$-C8Gal in the L$_C$ phase. Similarly, for the chain ordering property of the bilayer, the $\alpha$-anomer was found to be less ordered compared to the $\beta$-anomer. Additionally, the assembly of sugar surfactant with $\alpha$-anomer, in which the sugar head group bent to the hydrocarbon chain gave a slightly bent shape molecular structure, while in bilayer arrangement the alkyl chains of these surfactants packed less densely.

The C4-epimeric (axial/equatorial) stereochemistry becomes dominant together with the anomeric one for the inter-molecular hydrogen bond. Thus, the trend in hydrogen bonding goes as $\beta$-C8Gal>$\alpha$-C8Glc>$\beta$-C8Glc>$\alpha$-C8Gal, which is in agreement with the previous studies of Hashim *et al*.[10] and Rog *et.al*., _ENREF_28[47] implying the axial orientation of the hydroxyl group on the C4 position in $\beta$-C8Gal increases the capacity of donor and acceptor of this compound. Likewise, the $\alpha$-glucoside has a similar behaviour. Therefore, these results support the proposal that when the hydroxyl group at the C4 carbon is cis with respect to the C1-O1 (i.e. $\beta$-C8Gal and $\alpha$-C8Glc), greater bilayer stability is achieved compared to the case when these links are in a trans-configuration (i.e. $\beta$-C8Glc and $\alpha$-C8Gal). The thermotropic bilayer of the four lipids studied here exhibited anomalous diffusion behaviours, where the observed trend for the diffusion coefficient for these compounds is ($\beta$-C8Gal >$\beta$-C8Glc >$\alpha$-C8Gal >$\alpha$-C8Glc). This trend shows that for a given epimer

(gluco- orgalacto-), $\beta$-anomer is more diffusive than the$\alpha$-anomer. The latter has more space in the hydrophobic region, causing both chain vibration and chain disorganization to increase, but reducing the overall molecular diffusion, since thermal energy is dispensed more entropically for the chain region.

In the third part of this desertation, we have modelled and simulated the system of lyotropic $H_{II}$formed by $C_8C_{12}\beta$-D-Glc at two different water concentrations, 14% and 22%, for 50 ns simulation. The average lattice parameters and area per head group obtained from the simulations for these systems agree quantitatively to within the error with those estimated from the SAXS measurements. At 14% water concentration the radial distribution of density profile shows the sugar head group region and the water region overlap each other, such that the water column is not completely free of the sugar head group. Meanwhile, at the higher concentration of 22% water, the water region in the column does not overlap extensively with the sugar head group and in fact, we also observed a sugar free water region. Two water diffusion processes are detected. While in the $xy$plane, the water mobility is anomalous for both systems. However, in the $z$ direction the diffusion of 22% water system obeys Einstein's relationship, but for the less water system (14%), the diffusion is slightly anomalous. The anomalous diffusion in $xy$ plane is caused by the confined space in the plane. Thus, our findings provide alternative explanation to the recent experimental results by Penaloza *et al.*, who found the space heterogeneity of diffusion in the water region of a lyotropic $H_{II}$.

The interactions between the sugar head and water molecules were investigated by the hydrogen bond analysis and the calculations of RDF of water oxygen atom around the six sugar oxygen atoms. In a system of 14% water, the number of hydrogen bonding between water and sugar is lower, but a longer lifetime was observed compared to that of the 22% water system. This is attributed to the smaller surface area of water-

sugar interface and lower mobility of water in the 14% water compared to that of the 22% water system. The RDF of water oxygen atom around the six sugar oxygen atoms relates the level of contact or exposure of individual oxygen on sugar to the water molecules, which follows the ordering of O6 > O3 > O4 > O2 > O5 > O1 regardless of the water concentrations. Finally, we examined the extension and compression of the alkyl chain by calculating the distribution of average radial distance of $CH_3$ group over angle around a cylinder. The profile of the distribution conforms to the description in the frustration theory.

To summarise, we have used extensively the computer modelling and simulation techniques to understand and explore the self-assembly behaviour of bulky systems (micellar, bilayers and hexagonal phases). In future, we can use quantum mechanical calculation to obtain the electronic properties of branched synthetic glycolipid systems. This will give an improved force-field for these materials to study their self-assembly in both polar and nonpolar solvents. In addition, the hybrid QM/MM approach is another molecular simulation method which uses both QM (for improved accuracy) and MM (for higher speed) calculations, thus allowing for the study of chemical processes in solution and in proteins. The development of the hybrid QM/MM approaches is guided by the general idea that large chemical systems may be partitioned into an electronically important region which requires a quantum chemical treatment and a remainder which only acts in a perturbation fashion and thus admits a classical description. Therefore, in future we plan to usethis method to study the complex self-assembly behaviour.

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## Appendix A.1

### Prepin file for n-octyl-*α*-D-galactoside

```
This is a remark line
molecule.res
Gal    INT  0
CORRECT      OMIT DU   BEG
  0.0000
   1  DUMM  DU   M    0  -1  -2   0.000    .0         .0       .00000
   2  DUMM  DU   M    1   0  -1   1.449    .0         .0       .00000
   3  DUMM  DU   M    2   1   0   1.522  111.1        .0       .00000
   4  C31   CG   M    3   2   1   1.540  111.208   180.000   0.00000
   5  H46   HC   E    4   3   2   1.089   35.485     1.903   0.00000
   6  H47   HC   E    4   3   2   1.090  145.001     1.650   0.00000
   7  H48   HC   E    4   3   2   1.090   89.947   127.059   0.00000
   8  C30   CG   M    4   3   2   1.559   89.816  -123.486   0.00000
   9  H44   HC   E    8   4   3   1.090  102.499  -157.743   0.00000
  10  H45   HC   E    8   4   3   1.091  109.493   -36.865   0.00000
  11  C29   CG   M    8   4   3   1.458  119.158    90.103   0.00000
  12  H42   HC   E   11   8   4   1.090  105.354   -64.264   0.00000
  13  H43   HC   E   11   8   4   1.090  109.432    56.092   0.00000
  14  C28   CG   M   11   8   4   1.258  115.364  -179.958   0.00000
  15  H40   HC   E   14  11   8   1.090  111.112   -58.572   0.00000
  16  H41   HC   E   14  11   8   1.090  109.474    61.468   0.00000
  17  C27   CG   M   14  11   8   1.431  106.963  -179.997   0.00000
  18  H38   HC   E   17  14  11   1.090  112.882   -57.154   0.00000
  19  H39   HC   E   17  14  11   1.090  109.462    63.012   0.00000
  20  C26   CG   M   17  14  11   1.439  104.147   179.965   0.00000
  21  H36   HC   E   20  17  14   1.090  115.521   -55.421   0.00000
  22  H37   HC   E   20  17  14   1.090  109.421    65.199   0.00000
  23  C25   CG   M   20  17  14   1.559   99.872  -179.982   0.00000
  24  H34   HC   E   23  20  17   1.090  112.890   -57.144   0.00000
  25  H35   HC   E   23  20  17   1.089  109.454    63.081   0.00000
  26  C24   CG   M   23  20  17   1.524  104.046  -179.964   0.00000
  27  H32   H1   E   26  23  20   1.090  112.808   -59.437   0.00000
  28  H33   H1   E   26  23  20   1.090  109.474    60.747   0.00000
  29  O7    OS   M   26  23  20   1.213  104.229   177.781  -0.19400
  30  C2    CG   M   29  26  23   1.398  115.772  -168.336   0.46500
  31  H10   H2   E   30  29  26   1.117  115.448    44.992   0.00000
  32  O1    OS   M   30  29  26   1.392  105.704   158.586  -0.52700
  33  C3    CG   M   32  30  29   1.404  116.165    62.187   0.21600
  34  C14   CG   3   33  32  30   1.535  104.188   178.248   0.30800
  35  H20   H1   E   34  33  32   1.108  111.719   -50.234   0.00000
  36  O21   OH   S   34  33  32   1.387  110.896    75.550  -0.68400
  37  H23   HO   E   36  34  33   0.966  108.280   -62.744   0.41800
  38  H22   H1   E   34  33  32   1.104  110.764  -168.835   0.00000
  39  H19   H1   E   33  32  30   1.117  111.107   -64.033   0.00000
  40  C4    CG   M   33  32  30   1.531  111.355    57.467   0.20400
  41  O13   OH   S   40  33  32   1.393  112.027    60.573  -0.67300
  42  H15   HO   E   41  40  33   0.963  108.032    76.051   0.43600
  43  H16   H1   E   40  33  32   1.118  109.393  -175.335   0.00000
  44  C6    CG   M   40  33  32   1.536  108.901   -55.752   0.25300
  45  O12   OH   S   44  40  33   1.386  112.075   179.767  -0.70100
  46  H17   HO   E   45  44  40   0.967  109.623   -57.996   0.43300
  47  H18   H1   E   44  40  33   1.117  110.115   -65.845   0.00000
  48  C5    CG   M   44  40  33   1.533  109.147    56.037   0.33900
  49  H8    H1   E   48  44  40   1.117  110.597    65.122   0.00000
  50  O9    OH   M   48  44  40   1.390  112.228  -171.196  -0.72400
  51  H11   HO   E   50  48  44   0.966  108.230   -48.504   0.43100
```

# Appendix A.2

## Prepin file for n-octyl-$\alpha$-D-glycoside

```
This is a remark line
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Glc    INT  0
CORRECT      OMIT DU   BEG
  0.0000
   1  DUMM DU   M    0  -1  -2   0.000      .0        .0      .00000
   2  DUMM DU   M    1   0  -1   1.449      .0        .0      .00000
   3  DUMM DU   M    2   1   0   1.522   111.1        .0      .00000
   4  C30  CG   M    3   2   1   1.540   111.208  180.000   0.00000
   5  H46  HC   E    4   3   2   1.090    39.755   -3.207   0.00000
   6  H47  HC   E    4   3   2   1.089   126.912   69.213   0.00000
   7  H48  HC   E    4   3   2   1.081    69.867  168.690   0.00000
   8  C29  CG   M    4   3   2   1.536   120.094  -88.232   0.00000
   9  H44  HC   E    8   4   3   1.086   110.300 -137.143   0.00000
  10  H45  HC   E    8   4   3   1.087   110.385  -19.092   0.00000
  11  C28  CG   M    8   4   3   1.528   110.956  101.911   0.00000
  12  H42  HC   E   11   8   4   1.088   110.472  -59.056   0.00000
  13  H43  HC   E   11   8   4   1.087   110.356   58.908   0.00000
  14  C27  CG   M   11   8   4   1.525   110.723  179.879   0.00000
  15  H40  HC   E   14  11   8   1.088   110.193  -57.562   0.00000
  16  H41  HC   E   14  11   8   1.089   110.217   60.091   0.00000
  17  C26  CG   M   14  11   8   1.524   110.919 -178.697   0.00000
  18  H38  HC   E   17  14  11   1.088   110.263  -58.587   0.00000
  19  H39  HC   E   17  14  11   1.090   109.955   59.036   0.00000
  20  C25  CG   M   17  14  11   1.522   110.358 -179.914   0.00000
  21  H36  HC   E   20  17  14   1.088   109.917  -56.094   0.00000
  22  H37  HC   E   20  17  14   1.088   109.923   61.546   0.00000
  23  C24  CG   M   20  17  14   1.522   110.814 -177.054   0.00000
  24  H34  HC   E   23  20  17   1.087   110.528  -58.365   0.00000
  25  H35  HC   E   23  20  17   1.087   110.238   59.758   0.00000
  26  C23  CG   M   23  20  17   1.533   110.164 -179.663   0.00000
  27  H32  H1   E   26  23  20   1.099   110.180  -52.977   0.00000
  28  H33  H1   E   26  23  20   1.098   109.572   64.547   0.00000
  29  O7   OS   M   26  23  20   1.421   104.698 -173.819  -0.19400
  30  C2   CG   M   29  26  23   1.420   113.999 -154.614   0.50900
  31  H22  H2   E   30  29  26   1.098   113.486   30.342   0.00000
  32  O1   OS   M   30  29  26   1.427   106.730  146.462  -0.57400
  33  C3   CG   M   32  30  29   1.438   111.887   59.124   0.28300
  34  H8   H1   E   33  32  30   1.098   113.184  -62.358   0.00000
  35  C9   CG   3   33  32  30   1.557   102.500  178.694   0.27600
  36  O16  OH   S   35  33  32   1.427   112.332  -53.737  -0.68200
  37  H19  HO   E   36  35  33   0.991   105.270  -42.870   0.41800
  38  H20  H1   E   35  33  32   1.095   108.640 -179.565   0.00000
  39  H21  H1   E   35  33  32   1.092   107.435   63.386   0.00000
  40  C4   CG   M   33  32  30   1.567   111.527   58.385   0.25400
  41  O10  OH   S   40  33  32   1.437   112.505 -174.104  -0.71000
  42  H18  HO   E   41  40  33   0.985   105.281  -70.031   0.43600
  43  H11  H1   E   40  33  32   1.089   108.450   62.603   0.00000
  44  C6   CG   M   40  33  32   1.548   110.958  -55.037   0.28600
  45  O14  OH   S   44  40  33   1.430   111.833  171.095  -0.69900
  46  H17  HO   E   45  44  40   0.985   104.006   64.969   0.42700
  47  H15  H1   E   44  40  33   1.089   107.081  -65.731   0.00000
  48  C5   CG   M   44  40  33   1.545   109.173   52.842   0.24600
  49  H12  H1   E   48  44  40   1.094   107.492   64.574   0.00000
  50  O13  OH   M   48  44  40   1.435   111.904 -172.249  -0.71300
  51  H31  HO   E   50  48  44   0.988   103.430  -58.120   0.43700
     0    0    2
```

# Appendix A.3

## Prepin file for n-octyl-*β*-D-glycoside

```
This is a remark line
molecule.res
Gal     INT  0
CORRECT      OMIT DU   BEG
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   1  DUMM  DU   M    0  -1  -2    0.000       .0        .0     .00000
   2  DUMM  DU   M    1   0  -1    1.449       .0        .0     .00000
   3  DUMM  DU   M    2   1   0    1.522    111.1        .0     .00000
   4  O13   OH   M    3   2   1    1.540    111.208   180.000  -0.72600
   5  H23   HO   E    4   3   2    0.943    128.989    93.757   0.43200
   6  C5    CG   M    4   3   2    1.404     58.575  -179.570   0.35700
   7  H14   H1   E    6   4   3    1.115    107.200  -178.640   0.00000
   8  C4    CG   M    6   4   3    1.530    109.138    60.547   0.25900
   9  H11   H1   E    8   6   4    1.117    110.901   -52.091   0.00000
  10  O12   OH   S    8   6   4    1.405    110.054    65.739  -0.69400
  11  H19   HO   E   10   8   6    0.942    106.371   -63.428   0.43300
  12  C3    CG   M    8   6   4    1.533    109.401  -173.799   0.20300
  13  H9    H1   E   12   8   6    1.116    111.148   176.351   0.00000
  14  O10   OH   S   12   8   6    1.404    108.589   -66.690  -0.66400
  15  H18   HO   E   14  12   8    0.943    106.951   -59.849   0.43700
  16  C2    CG   M   12   8   6    1.537    110.159    53.127   0.14000
  17  H7    H1   E   16  12   8    1.117    109.449    62.622   0.00000
  18  C8    CG   3   16  12   8    1.534    114.052  -177.643   0.31900
  19  H16   H1   E   18  16  12    1.114    111.575  -179.125   0.00000
  20  H17   H1   E   18  16  12    1.114    111.266   -56.604   0.00000
  21  O20   OH   S   18  16  12    1.402    110.446    62.372  -0.69300
  22  H21   HO   E   21  18  16    0.942    107.634  -172.573   0.41900
  23  O1    OS   M   16  12   8    1.414    110.178   -55.189  -0.40200
  24  C6    CG   M   23  16  12    1.409    112.541    61.602   0.37400
  25  H15   H2   E   24  23  16    1.117    111.020    60.502   0.00000
  26  O22   OS   M   24  23  16    1.410    103.034   178.304  -0.19400
  27  C24   CG   M   26  24  23    1.413    113.044   -67.771   0.00000
  28  H32   H1   E   27  26  24    1.115    109.397   -53.419   0.00000
  29  H33   H1   E   27  26  24    1.115    108.405    66.952   0.00000
  30  C25   CG   M   27  26  24    1.534    109.146  -173.373   0.00000
  31  H34   HC   E   30  27  26    1.116    109.868   -55.326   0.00000
  32  H35   HC   E   30  27  26    1.116    109.653    62.725   0.00000
  33  C26   CG   M   30  27  26    1.538    110.020  -176.257   0.00000
  34  H36   HC   E   33  30  27    1.117    109.275   -58.299   0.00000
  35  H37   HC   E   33  30  27    1.116    109.166    58.812   0.00000
  36  C27   CG   M   33  30  27    1.535    112.601  -179.831   0.00000
  37  H38   HC   E   36  33  30    1.116    109.387   -58.186   0.00000
  38  H39   HC   E   36  33  30    1.116    109.468    59.412   0.00000
  39  C28   CG   M   36  33  30    1.537    111.239  -179.275   0.00000
  40  H40   HC   E   39  36  33    1.116    109.414   -58.793   0.00000
  41  H41   HC   E   39  36  33    1.116    109.479    58.508   0.00000
  42  C29   CG   M   39  36  33    1.536    111.752   179.816   0.00000
  43  H42   HC   E   42  39  36    1.115    109.327   -58.656   0.00000
  44  H43   HC   E   42  39  36    1.116    109.301    58.726   0.00000
  45  C30   CG   M   42  39  36    1.537    111.917  -179.995   0.00000
  46  H44   HC   E   45  42  39    1.116    109.640   -58.743   0.00000
  47  H45   HC   E   45  42  39    1.116    109.649    58.833   0.00000
  48  C31   CG   M   45  42  39    1.534    111.470  -179.974   0.00000
  49  H46   HC   E   48  45  42    1.115    111.068   179.968   0.00000
  50  H47   HC   E   48  45  42    1.114    111.066   -60.052   0.00000
  51  H48   HC   E   48  45  42    1.114    111.066    60.110   0.00000
```

Prepin file for n-octyl-*β*-D-galactoside

```
     0    0    2

This is a remark line
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    2  DUMM  DU   M    1   0  -1   1.449      .0       .0     .00000
    3  DUMM  DU   M    2   1   0   1.522   111.1       .0     .00000
    4  O6    OH   M    3   2   1   1.540   111.208  180.000  -0.68800
    5  H16   HO   E    4   3   2   0.980    70.570  155.654   0.42400
    6  C6    CG   M    4   3   2   1.432    81.728  -95.670   0.28200
    7  H6    H1   E    6   4   3   1.090   109.287 -126.380   0.00000
    8  H7    H1   E    6   4   3   1.091   108.904   -7.665   0.00000
    9  C5    CG   M    6   4   3   1.535   111.055  112.409   0.22500
   10  H5    H1   E    9   6   4   1.092   107.901  179.790   0.00000
   11  O5    OS   E    9   6   4   1.442   108.280  -61.942  -0.47100
   12  C4    CG   M    9   6   4   1.541   111.780   59.774   0.27600
   13  H4    H1   E   12   9   6   1.091   109.398  -58.297   0.00000
   14  O4    OH   S   12   9   6   1.434   109.378   61.214  -0.71400
   15  H14   HO   E   14  12   9   0.980   105.444 -174.215   0.44000
   16  C3    CG   M   12   9   6   1.538   109.640 -177.826   0.28400
   17  H3    H1   E   16  12   9   1.091   108.932  -67.420   0.00000
   18  O3    OH   S   16  12   9   1.435   109.427  173.654  -0.70900
   19  H13   HO   E   18  16  12   0.981   105.371  172.804   0.43200
   20  C2    CG   M   16  12   9   1.539   110.503   52.429   0.31000
   21  H2    H1   E   20  16  12   1.091   109.219   66.605   0.00000
   22  O2    OH   S   20  16  12   1.435   109.451 -173.904  -0.71800
   23  H12   HO   E   22  20  16   0.980   105.480 -172.964   0.43700
   24  C1    CG   M   20  16  12   1.538   109.510  -52.985   0.38400
   25  H1    H2   E   24  20  16   1.092   108.787  -62.371   0.00000
   26  O1    OS   M   24  20  16   1.439   109.544  177.925  -0.19400
   27  C21   CG   M   26  24  20   1.437   108.871  167.268   0.00000
   28  H29   H1   E   27  26  24   1.091   110.393   61.516   0.00000
   29  H30   H1   E   27  26  24   1.090   109.780  -59.213   0.00000
   30  C22   CG   M   27  26  24   1.542   109.326 -178.702   0.00000
   31  H31   HC   E   30  27  26   1.091   109.411   57.296   0.00000
   32  H32   HC   E   30  27  26   1.091   109.399  -62.542   0.00000
   33  C23   CG   M   30  27  26   1.543   109.595  177.259   0.00000
   34  H33   HC   E   33  30  27   1.090   109.291   58.827   0.00000
   35  H34   HC   E   33  30  27   1.090   109.320  -60.724   0.00000
   36  C24   CG   M   33  30  27   1.542   110.344  179.001   0.00000
   37  H35   HC   E   36  33  30   1.090   109.589   59.840   0.00000
   38  H36   HC   E   36  33  30   1.091   109.308  -60.046   0.00000
   39  C25   CG   M   36  33  30   1.544   109.719  179.977   0.00000
   40  H37   HC   E   39  36  33   1.090   109.296   57.559   0.00000
   41  H38   HC   E   39  36  33   1.090   109.282  -61.986   0.00000
   42  C26   CG   M   39  36  33   1.543   110.234  177.684   0.00000
   43  H39   HC   E   42  39  36   1.091   109.413   61.049   0.00000
   44  H40   HC   E   42  39  36   1.090   109.389  -58.783   0.00000
   45  C27   CG   M   42  39  36   1.543   109.746 -178.803   0.00000
   46  H41   HC   E   45  42  39   1.090   109.486   60.056   0.00000
   47  H42   HC   E   45  42  39   1.090   109.497  -59.720   0.00000
   48  C28   CG   M   45  42  39   1.542   110.216 -179.881   0.00000
   49  H43   HC   E   48  45  42   1.090   109.712   60.711   0.00000
   50  H44   HC   E   48  45  42   1.090   109.631  -59.489   0.00000
   51  H45   HC   E   48  45  42   1.091   109.361 -179.317   0.00000
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# Appendix B

Sample coordinate file for Prepin file for n-octyl-*β*-D-galactoside

```
REMARK
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ATOM     2   C2  Gal    1        43.267  30.868 -21.183
ATOM     3   C3  Gal    1        43.550  32.900 -22.324
ATOM     4   C4  Gal    1        44.921  32.455 -22.898
ATOM     5   C5  Gal    1        44.572  30.282 -21.769
ATOM     6   C6  Gal    1        45.510  31.429 -21.946
ATOM     7   O7  Gal    1        43.419  31.568 -19.929
ATOM     8   H8  Gal    1        44.366  29.834 -22.746
ATOM     9   O9  Gal    1        45.147  29.323 -20.869
ATOM    10   H10 Gal    1        42.562  30.026 -21.076
ATOM    11   H11 Gal    1        45.817  28.770 -21.334
ATOM    12   O12 Gal    1        46.732  30.940 -22.397
ATOM    13   O13 Gal    1        44.814  31.908 -24.248
ATOM    14   C14 Gal    1        42.860  33.812 -23.355
ATOM    15   H15 Gal    1        44.304  32.484 -24.764
ATOM    16   H16 Gal    1        45.595  33.307 -22.932
ATOM    17   H17 Gal    1        46.612  30.689 -23.288
ATOM    18   H18 Gal    1        45.729  31.914 -21.014
ATOM    19   H19 Gal    1        43.732  33.482 -21.402
ATOM    20   H20 Gal    1        42.531  33.179 -24.167
ATOM    21   O21 Gal    1        41.736  34.490 -22.786
ATOM    22   H22 Gal    1        43.569  34.501 -23.812
ATOM    23   H23 Gal    1        41.029  33.903 -22.792
ATOM    24   C24 Gal    1        43.277  30.704 -18.853
ATOM    25   C25 Gal    1        43.526  31.540 -17.587
ATOM    26   C26 Gal    1        43.449  30.583 -16.324
ATOM    27   C27 Gal    1        43.675  31.415 -15.037
ATOM    28   C28 Gal    1        43.383  30.519 -13.773
ATOM    29   C29 Gal    1        43.518  31.377 -12.441
ATOM    30   C30 Gal    1        43.013  30.557 -11.241
ATOM    31   C31 Gal    1        43.017  31.417  -9.967
ATOM    32   H32 Gal    1        44.083  29.984 -18.995
ATOM    33   H33 Gal    1        42.334  30.224 -18.936
ATOM    34   H34 Gal    1        42.843  32.380 -17.516
ATOM    35   H35 Gal    1        44.555  31.923 -17.674
ATOM    36   H36 Gal    1        44.247  29.842 -16.340
ATOM    37   H37 Gal    1        42.462  30.101 -16.266
ATOM    38   H38 Gal    1        43.014  32.280 -15.125
ATOM    39   H39 Gal    1        44.685  31.829 -15.007
ATOM    40   H40 Gal    1        44.005  29.626 -13.785
ATOM    41   H41 Gal    1        42.336  30.150 -13.817
ATOM    42   H42 Gal    1        42.915  32.274 -12.505
ATOM    43   H43 Gal    1        44.564  31.664 -12.258
ATOM    44   H44 Gal    1        43.611  29.679 -11.129
ATOM    45   H45 Gal    1        41.965  30.292 -11.513
ATOM    46   H46 Gal    1        42.287  32.148  -9.982
ATOM    47   H47 Gal    1        43.940  31.961  -9.863
ATOM    48   H48 Gal    1        42.771  30.806  -9.169
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Sample topology file for Prepin file for n-octyl-$\beta$-D-galactoside

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C6  O12 H17 H18 C5  H8  O9  H11 C31 H46 H47 H48 C30 H44 H45 C29 H42 H43 C28 H40
H41 C27 H38 H39 C26 H36 H37 C25 H34 H35 C24 H32 H33 O7  C2  H10 O1  C3  C14 H20
O21 H23 H22 H19 C4  O13 H15 H16 C6  O12 H17 H18 C5  H8  O9  H11 C31 H46 H47 H48
C30 H44 H45 C29 H42 H43 C28 H40 H41 C27 H38 H39 C26 H36 H37 C25 H34 H35 C24 H32
H33 O7  C2  H10 O1  C3  C14 H20 O21 H23 H22 H19 C4  O13 H15 H16 C6  O12 H17 H18
C5  H8  O9  H11 C31 H46 H47 H48 C30 H44 H45 C29 H42 H43 C28 H40 H41 C27 H38 H39
C26 H36 H37 C25 H34 H35 C24 H32 H33 O7  C2  H10 O1  C3  C14 H20 O21 H23 H22 H19
C4  O13 H15 H16 C6  O12 H17 H18 C5  H8  O9  H11 C31 H46 H47 H48 C30 H44 H45 C29
H42 H43 C28 H40 H41 C27 H38 H39 C26 H36 H37 C25 H34 H35 C24 H32 H33 O7  C2  H10
O1  C3  C14 H20 O21 H23 H22 H19 C4  O13 H15 H16 C6  O12 H17 H18 C5  H8  O9  H11
C31 H46 H47 H48 C30 H44 H45 C29 H42 H43 C28 H40 H41 C27 H38 H39 C26 H36 H37 C25
H34 H35 C24 H32 H33 O7  C2  H10 O1  C3  C14 H20 O21 H23 H22 H19 C4  O13 H15 H16
C6  O12 H17 H18 C5  H8  O9  H11 C31 H46 H47 H48 C30 H44 H45 C29 H42 H43 C28 H40
H41 C27 H38 H39 C26 H36 H37 C25 H34 H35 C24 H32 H33 O7  C2  H10 O1  C3  C14 H20
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%FLAG NONBONDED_PARM_INDEX
%FORMAT(10I8)
       1       2       4       7      11      16      22       2       3       5
       8      12      17      23       4       5       6       9      13      18
      24       7       8       9      10      14      19      25      11      12
      13      14      15      20      26      16      17      18      19      20
      21      27      22      23      24      25      26      27      28
%FLAG RESIDUE_LABEL
%FORMAT(20a4)
Gal Gal Gal Gal Gal Gal Gal Gal Gal Gal Gal Gal Gal Gal Gal Gal Gal Gal Gal Gal
Gal Gal Gal Gal Gal Gal Gal Gal Gal Gal Gal Gal Gal Gal Gal Gal Gal Gal Gal Gal
Gal Gal Gal Gal Gal Gal Gal Gal Gal Gal Gal Gal Gal Gal Gal Gal Gal Gal Gal Gal
Gal Gal Gal Gal Gal Gal Gal Gal Gal Gal Gal Gal Gal Gal Gal Gal Gal Gal Gal Gal
Gal Gal Gal Gal Gal Gal Gal Gal Gal Gal Gal Gal Gal Gal Gal Gal Gal Gal Gal Gal
Gal Gal Gal Gal Gal Gal Gal Gal Gal Gal Gal Gal Gal Gal Gal Gal Gal Gal Gal Gal
Gal Gal Gal Gal Gal Gal Gal Gal Gal Gal Gal Gal Gal Gal Gal Gal Gal Gal Gal Gal
Gal Gal Gal Gal Gal Gal Gal Gal Gal Gal Gal Gal Gal Gal Gal Gal Gal Gal Gal Gal
Gal Gal Gal Gal Gal Gal Gal Gal Gal Gal Gal Gal Gal Gal Gal Gal Gal Gal Gal Gal
Gal Gal Gal Gal Gal Gal Gal Gal Gal Gal Gal Gal Gal Gal Gal Gal Gal Gal Gal Gal
%FLAG RESIDUE_POINTER
%FORMAT(10I8)
       1      49      97     145     193     241     289     337     385     433
     481     529     577     625     673     721     769     817     865     913
     961    1009    1057    1105    1153    1201    1249    1297    1345    1393
    1441    1489    1537    1585    1633    1681    1729    1777    1825    1873
    1921    1969    2017    2065    2113    2161    2209    2257    2305    2353
    2401    2449    2497    2545    2593    2641    2689    2737    2785    2833
    2881    2929    2977    3025    3073    3121    3169    3217    3265    3313
    3361    3409    3457    3505    3553    3601    3649    3697    3745    3793
    3841    3889    3937    3985    4033    4081    4129    4177    4225    4273
    4321    4369    4417    4465    4513    4561    4609    4657    4705    4753
    4801    4849    4897    4945    4993    5041    5089    5137    5185    5233
    8161    8209    8257    8305    8353    8401    8449    8497    8545    8593
    8641    8689    8737    8785    8833    8881    8929    8977    9025    9073
    9121    9169    9217    9265    9313    9361    9409    9457    9505    9553
%FLAG BOND_FORCE_CONSTANT
%FORMAT(5E16.8)
  5.53000000E+02  3.40000000E+02  3.20000000E+02  3.10000000E+02  2.85000000E+02
  3.40000000E+02  3.40000000E+02
%FLAG BOND_EQUIL_VALUE
%FORMAT(5E16.8)
  9.60000000E-01  1.09000000E+00  1.43000000E+00  1.52000000E+00  1.46000000E+00
  1.09000000E+00  1.09000000E+00
%FLAG ANGLE_FORCE_CONSTANT
%FORMAT(5E16.8)
  6.00000000E+01  5.50000000E+01  4.50000000E+01  7.00000000E+01  4.50000000E+01
  4.50000000E+01  7.00000000E+01  6.00000000E+01  6.00000000E+01  4.50000000E+01
  5.00000000E+01  1.00000000E+02  4.50000000E+01  4.00000000E+01
%FLAG ANGLE_EQUIL_VALUE
%FORMAT(5E16.8)
  1.91986300E+00  1.91113635E+00  1.93731630E+00  1.87622975E+00  1.98094955E+00
  1.91113635E+00  1.89368305E+00  1.91986300E+00  1.91986300E+00  1.93731630E+00
  1.94778828E+00  1.95476960E+00  1.96524158E+00  1.91113635E+00
%FLAG DIHEDRAL_FORCE_CONSTANT

```
%FORMAT(5E16.8)
  1.80000000E-01  1.70000000E-01  5.00000000E-02 -1.00000000E-01  9.50000000E-01
  5.50000000E-01  1.50000000E-01  1.00000000E-01  4.50000000E-01  1.60000000E-01
 -2.70000000E-01 -1.10000000E+00  2.50000000E-01  6.00000000E-01  2.70000000E-01
  1.08000000E+00  1.38000000E+00  9.60000000E-01  1.30000000E-01
%FLAG DIHEDRAL_PERIODICITY
%FORMAT(5E16.8)
  3.00000000E+00  3.00000000E+00  3.00000000E+00  1.00000000E+00  2.00000000E+00
  3.00000000E+00  3.00000000E+00  3.00000000E+00  1.00000000E+00  3.00000000E+00
  1.00000000E+00  1.00000000E+00  2.00000000E+00  2.00000000E+00  3.00000000E+00
  1.00000000E+00  2.00000000E+00  3.00000000E+00  3.00000000E+00
%FLAG DIHEDRAL_PHASE
%FORMAT(5E16.8)
  0.00000000E+00  0.00000000E+00  0.00000000E+00  0.00000000E+00  0.00000000E+00
  0.00000000E+00  0.00000000E+00  0.00000000E+00  0.00000000E+00  0.00000000E+00
  0.00000000E+00  0.00000000E+00  0.00000000E+00  0.00000000E+00  0.00000000E+00
  0.00000000E+00  0.00000000E+00  0.00000000E+00  0.00000000E+00
%FLAG SOLTY
%FORMAT(5E16.8)
  0.00000000E+00  0.00000000E+00  0.00000000E+00  0.00000000E+00  0.00000000E+00
  0.00000000E+00  0.00000000E+00
%FLAG LENNARD_JONES_ACOEF
%FORMAT(5E16.8)
  1.04308023E+06  9.71708117E+04  7.51607703E+03  6.78771368E+04  4.98586848E+03
  3.25969625E+03  6.28541240E+05  5.33379252E+04  3.63097246E+04  3.61397723E+05
  4.68930885E+04  3.25969625E+03  2.09814978E+03  2.44050579E+04  1.32801250E+03
  7.91544157E+05  6.82786631E+04  4.66922514E+04  4.58874091E+05  3.15360051E+04
  5.81803229E+05  0.00000000E+00  0.00000000E+00  0.00000000E+00  0.00000000E+00
  0.00000000E+00  0.00000000E+00  0.00000000E+00
%FLAG LENNARD_JONES_BCOEF
%FORMAT(5E16.8)
  6.75612247E+02  1.26919150E+02  2.17257828E+01  1.06076943E+02  1.76949863E+01
  1.43076527E+01  5.85549272E+02  1.04986921E+02  8.66220817E+01  4.95732238E+02
  8.81685417E+01  1.43076527E+01  1.14788417E+01  7.10161395E+01  9.13231543E+00
  6.93079947E+02  1.25287818E+02  1.03606917E+02  5.89183300E+02  8.51470647E+01
  6.99746810E+02  0.00000000E+00  0.00000000E+00  0.00000000E+00  0.00000000E+00
  0.00000000E+00  0.00000000E+00  0.00000000E+00
%FLAG BONDS_INC_HYDROGEN
%FORMAT(10I8)
     138     141       1     132     135       2     123     126       1     120
     129       2     111     114       1     108     117       2      96      99
       1      90      93       2      90     102       2      87     105       2
      78      81       6      66      69       2      66      72       2      57
      60       7      57      63       7      48      51       7      48      54
       7      39      42       7      39      45       7      30      33       7
      30      36       7      21      24       7      21      27       7      12
      15       7      12      18       7       0       3       7       0       6
       7       0       9       7     282     285       1     276     279       2
     267     270       1     264     273       2     255     258       1     252
     261       2     240     243       1     234     237       2     234     246
       2     231     249       2     222     225       6     210     213       2
     210     216       2     201     204       7     201     207       7     192
     195       7     192     198       7     183     186       7     183     189
    2055    2061       7    2046    2049       7    2046    2052       7    2037
    2040       7    2037    2043       7    2028    2031       7    2028    2034
       7    2016    2019       7    2016    2022       7    2016    2025       7
    2298    2301       1    2292    2295       2    2283    2286       1    2280
    2289       2    2271    2274       1    2268    2277       2    2256    2259
       1    2250    2253       2    2250    2262       2    2247    2265       2
    2238    2241       6    2226    2229       2    2226    2232       2    2217
    2220       7    2217    2223       7    2208    2211       7    2208    2214
.
.
.
%FLAG DIHEDRAL_FORCE_CONSTANT
%FORMAT(5E16.8)
  1.80000000E-01  1.70000000E-01  5.00000000E-02 -1.00000000E-01  9.50000000E-01
  5.50000000E-01  1.50000000E-01  1.00000000E-01  4.50000000E-01  1.60000000E-01
 -2.70000000E-01 -1.10000000E+00  2.50000000E-01  6.00000000E-01  2.70000000E-01
  1.08000000E+00  1.38000000E+00  9.60000000E-01  1.30000000E-01
%FLAG DIHEDRAL_PERIODICITY
%FORMAT(5E16.8)
  3.00000000E+00  3.00000000E+00  3.00000000E+00  1.00000000E+00  2.00000000E+00
  3.00000000E+00  3.00000000E+00  3.00000000E+00  1.00000000E+00  3.00000000E+00
  1.00000000E+00  1.00000000E+00  2.00000000E+00  2.00000000E+00  3.00000000E+00
  1.00000000E+00  2.00000000E+00  3.00000000E+00  3.00000000E+00
%FLAG DIHEDRAL_PHASE
%FORMAT(5E16.8)
  0.00000000E+00  0.00000000E+00  0.00000000E+00  0.00000000E+00  0.00000000E+00
```

```
   0.00000000E+00   0.00000000E+00   0.00000000E+00   0.00000000E+00   0.00000000E+00
   0.00000000E+00   0.00000000E+00   0.00000000E+00   0.00000000E+00   0.00000000E+00
   0.00000000E+00   0.00000000E+00   0.00000000E+00   0.00000000E+00
%FLAG SOLTY
%FORMAT(5E16.8)
   0.00000000E+00   0.00000000E+00   0.00000000E+00   0.00000000E+00   0.00000000E+00
   0.00000000E+00   0.00000000E+00
%FLAG LENNARD_JONES_ACOEF
%FORMAT(5E16.8)
   1.04308023E+06   9.71708117E+04   7.51607703E+03   6.78771368E+04   4.98586848E+03
   3.25969625E+03   6.28541240E+05   5.33379252E+04   3.63097246E+04   3.61397723E+05
   4.68930885E+04   3.25969625E+03   2.09814978E+03   2.44050579E+04   1.32801250E+03
   7.91544157E+05   6.82786631E+04   4.66922514E+04   4.58874091E+05   3.15360051E+04
   5.81803229E+05   0.00000000E+00   0.00000000E+00   0.00000000E+00   0.00000000E+00
   0.00000000E+00   0.00000000E+00   0.00000000E+00
%FLAG LENNARD_JONES_BCOEF
%FORMAT(5E16.8)
   6.75612247E+02   1.26919150E+02   2.17257828E+01   1.06076943E+02   1.76949863E+01
   1.43076527E+01   5.85549272E+02   1.04986921E+02   8.66220817E+01   4.95732238E+02
   8.81685417E+01   1.43076527E+01   1.14788417E+01   7.10161395E+01   9.13231543E+00
   6.93079947E+02   1.25287818E+02   1.03606917E+02   5.89183300E+02   8.51470647E+01
   6.99746810E+02   0.00000000E+00   0.00000000E+00   0.00000000E+00   0.00000000E+00
   0.00000000E+00   0.00000000E+00   0.00000000E+00
%FLAG BONDS_INC_HYDROGEN
%FORMAT(10I8)
      138     141       1     132     135       2     123     126       1     120
      129       2     111     114       1     108     117       2      96      99
        1      90      93       2      90     102       2      87     105       2
       78      81       6      66      69       2      66      72       2      57
       60       7      57      63       7      48      51       7      48      54
        7      39      42       7      39      45       7      30      33       7
       30      36       7      21      24       7      21      27       7      12
       15       7      12      18       7       0       3       7       0       6
        7       0       9       7     282     285       1     276     279       2
      267     270       1     264     273       2     255     258       1     252
      261       2     240     243       1     234     237       2     234     246
        2     231     249       2     222     225       6     210     213       2
      210     216       2     201     204       7     201     207       7     192
      195       7     192     198       7     183     186       7     183     189
        7     174     177       7     174     180       7     165     168       7
      165     171       7     156     159       7     156     162       7     144
.
.
.
%FLAG HBOND_ACOEF
%FORMAT(5E16.8)

%FLAG HBOND_BCOEF
%FORMAT(5E16.8)

%FLAG HBCUT
%FORMAT(5E16.8)

%FLAG AMBER_ATOM_TYPE
%FORMAT(20a4)
CG  HC  HC  CG  HC  HC  CG  HC  HC  CG  HC  HC  CG  HC  HC  CG  HC  HC  CG
HC  HC  CG  H1  H1  OS  CG  H2  OS  CG  CG  H1  OH  HO  H1  H1  CG  OH  HO  H1
CG  OH  HO  H1  CG  H1  OH  HO  CG  HC  HC  HC  CG  HC  HC  CG  HC  HC  CG  HC
HC  CG  HC  HC  CG  HC  HC  CG  HC  HC  CG  H1  H1  OS  CG  H2  OS  CG  CG  H1
OH  HO  H1  H1  CG  OH  HO  H1  CG  OH  HO  H1  CG  H1  OH  HO  CG  HC  HC  HC
CG  HC  HC  CG  HC  HC  CG  HC  HC  CG  HC  HC  CG  HC  HC  CG  HC  HC  CG  H1
H1  OS  CG  H2  OS  CG  CG  H1  OH  HO  H1  H1  CG  OH  HO  H1  CG  OH  HO  H1
CG  HC  HC  HC  CG  HC  HC  CG  HC  HC  CG  HC  HC  CG  HC  HC  CG  HC  HC  CG
CG  OH  HO  H1  CG  H1  OH  HO  CG  HC  HC  HC  CG  HC  HC  CG  HC  HC  CG  HC
HC  CG  HC  HC  CG  HC  HC  CG  HC  HC  CG  H1  H1  OS  CG  H2  OS  CG  CG  H1
OH  HO  H1  H1  CG  OH  HO  H1  CG  OH  HO  H1  CG  H1  OH  HO  CG  HC  HC  HC
CG  HC  HC  CG  HC  HC  CG  HC  HC  CG  HC  HC  CG  HC  HC  CG  HC  HC  CG  H1
H1  OS  CG  H2  OS  CG  CG  H1  OH  HO  H1  H1  CG  OH  HO  H1  CG  OH  HO  H1
CG  HC  HC  CG  HC  HC  CG  H1  H1  OS  CG  H2  OS  CG  CG  H1  OH  HO  H1  H1
.
.
.
%FLAG TREE_CHAIN_CLASSIFICATION
%FORMAT(20a4)
M   E   E   M   E   E   M   E   E   M   E   E   M   E   E   M   E   E   M
E   E   M   E   E   M   M   E   S   3   3   E   S   E   E   E   3   S   E   E
B   S   E   E   M   E   M   E   M   E   E   E   M   E   E   M   E   E   M   E
E   M   E   E   M   E   E   M   E   E   M   E   E   M   M   E   S   3   3   E
S   E   E   E   3   S   E   E   B   S   E   E   M   E   M   E   M   E   E   E
```

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```
E   M   M   E   S   3   3   E   S   E   E   E   3   S   E   E   B   S   E   E
M   E   M   E   M   E   E   E   M   E   E   M   E   E   M   E   E   M   E   E
M   E   E   M   E   E   M   E   E   M   M   E   S   3   3   E   S   E   E   E
3   S   E   E   B   S   E   E   M   E   M   E   M   E   E   E   M   E   E   M
E   E   M   E   E   M   E   E   E   M   E   E   M   E   E   E   M   E   M   M
S   3   3   E   S   E   E   E   3   S   E   E   B   S   E   E   M   E   M   E
M   E   E   E   M   E   E   M   E   E   M   E   E   M   E   E   M   E   E   M
E   E   M   E   E   M   M   E   S   3   3   E   S   E   E   E   3   S   E   E
B   S   E   E   M   E   M   E   M   E   E   E   M   E   E   M   E   E   M   E
E   M   E   E   M   E   E   M   E   E   M   E   E   M   M   E   S   3   3   E
.
.
.
%FLAG JOIN_ARRAY
%FORMAT(10I8)
       0       0       0       0       0       0       0       0       0       0
       0       0       0       0       0       0       0       0       0       0
       0       0       0       0       0       0       0       0       0       0
       0       0       0       0       0       0       0       0       0       0
       0       0       0       0       0       0       0       0       0       0
       0       0       0       0       0       0       0       0       0       0
       0       0       0       0       0       0       0       0       0       0
       0       0       0       0       0       0       0       0       0       0
       0       0       0       0       0       0       0       0
.
.
.
%FLAG SOLVENT_POINTERS
%FORMAT(3I8)
     200     200     201
%FLAG ATOMS_PER_MOLECULE
%FORMAT(10I8)
      48      48      48      48      48      48      48      48      48      48
      48      48      48      48      48      48      48      48      48      48
      48      48      48      48      48      48      48      48      48      48
      48      48      48      48      48      48      48      48      48      48
      48      48      48      48      48      48      48      48      48      48
      48      48      48      48      48      48      48      48      48      48
      48      48      48      48      48      48      48      48      48      48
      48      48      48      48      48      48      48      48      48      48
      48      48      48      48      48      48      48      48      48      48
      48      48      48      48      48      48      48      48      48      48
      48      48      48      48      48      48      48      48      48      48
      48      48      48      48      48      48      48      48      48      48
      48      48      48      48      48      48      48      48      48      48
      48      48      48      48      48      48      48      48      48      48
      48      48      48      48      48      48      48      48      48      48
.
.
.
%FLAG BOX_DIMENSIONS
%FORMAT(5E16.8)
  9.00000000E+01  8.09690000E+01  8.21070000E+01  3.57570000E+01
%FLAG RADIUS_SET
%FORMAT(1a80)
modified Bondi radii (mbondi)
%FLAG RADII
%FORMAT(5E16.8)
  1.70000000E+00  1.30000000E+00  1.30000000E+00  1.30000000E+00  1.70000000E+00
  1.30000000E+00  1.30000000E+00  1.70000000E+00  1.30000000E+00  1.30000000E+00
  1.70000000E+00  1.30000000E+00  1.30000000E+00  1.70000000E+00  1.30000000E+00
  1.30000000E+00  1.70000000E+00  1.30000000E+00  1.30000000E+00  1.70000000E+00
  1.30000000E+00  1.30000000E+00  1.70000000E+00  1.30000000E+00  1.30000000E+00
  1.50000000E+00  1.70000000E+00  1.30000000E+00  1.50000000E+00  1.70000000E+00
  1.70000000E+00  1.30000000E+00  1.50000000E+00  8.00000000E-01  1.30000000E+00
  1.30000000E+00  1.70000000E+00  1.50000000E+00  8.00000000E-01  1.30000000E+00
  1.70000000E+00  1.50000000E+00  8.00000000E-01  1.30000000E+00  1.70000000E+00
  1.30000000E+00  1.50000000E+00  8.00000000E-01  1.70000000E+00  1.30000000E+00
  1.30000000E+00  1.30000000E+00  1.70000000E+00  1.30000000E+00  1.30000000E+00
  1.70000000E+00  1.30000000E+00  1.30000000E+00  1.70000000E+00  1.30000000E+00
  1.30000000E+00  1.70000000E+00  1.30000000E+00  1.30000000E+00  1.70000000E+00
  1.30000000E+00  1.30000000E+00  1.70000000E+00  1.30000000E+00  1.30000000E+00
  1.70000000E+00  1.30000000E+00  1.30000000E+00  1.50000000E+00  1.70000000E+00
  1.30000000E+00  1.50000000E+00  1.70000000E+00  1.70000000E+00  1.30000000E+00
  1.50000000E+00  8.00000000E-01  1.30000000E+00  1.30000000E+00  1.70000000E+00
  1.50000000E+00  8.00000000E-01  1.30000000E+00  1.70000000E+00  1.50000000E+00
  1.70000000E+00  1.30000000E+00  1.50000000E+00  8.00000000E-01  1.70000000E+00
  1.30000000E+00  1.30000000E+00  1.30000000E+00  1.70000000E+00  1.30000000E+00
  1.30000000E+00  1.70000000E+00  1.30000000E+00  1.30000000E+00  1.70000000E+00
```

# LIST OF SCIENTIFIC CONTRIBUTIONS

## Piblications

**Academic Journal**

1. Sara Ahmadi, Vijayan Manickam Achari, Hock Seng Nguan and Rauzah Hashim, Atomistic Simulation Studies of the $\alpha/\beta$-Glucoside and Galactoside in Anhydrous Bilayers: Effect of the Anomeric and Epimeric Configurations, Journal of molecular modeling, 2014 (in press.).

2. Nguan, H., S. Ahmadi, and Hashim DFT study of glucose based glycolipid crown ethers and their complexes with alkali metal cations $Na^+$ and $K^+$. Journal of molecular modeling, 2012. 18(12): p. 5041-5050.

3. Nguan, H., S. Ahmadi, and HashimMolecular Dynamics Simulation of the Lyotropic Reverse Hexagonal ($H_{II}$) of Guerbet Branched-Chain $\beta$-D-Glucoside, Journal of Physical Chemistry Chemical Physics, Phys. Chem. Chem. Phys., 2014, 16, 324-.334

**Extended Abstract**

1. Sara Ahmadi, Nguan Hock Seng, Thorsten Heidelberg and Rauzah Hashim. Modelling and Molecular Dynamics on a Hexagonal Glycolipid Assembly. 6thMathematics and Physical Sciences Graduate Congress 2010, 13th- 15th December 2010, Faculty of science, University of Malaya, Malaysia.

## Presentations

**Oral**

1. Sara Ahmadi, Hock Seng Nguan and Rauzah Hashim, Computer Simulation of Glycolipids in Hexagonal Phase. Fundamental Science Congress (FSC2012), 17th-18th July 2012, University Putra Malaya, Kuala Lumpur, Malaysia.