Molecular modeling of some mono-and disaccharides

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ABSTRACT   The α- and β-forms of different saccharides are randomly selected to calculate their minimum energies using molecular mechanics (MM) methodology. The cff91-force field is used to optimize the sugars, employing the Newton-Raphson minimization method. In addition, the AMPAC/MOPAC program is used to calculate the electronic energies of the optimized sugars. The calculated results are discussed within the aspect of anomeric and solvation effects. In the cyclic versus open-chain glucose discussion, the theoretical results are compared with the spectral (NMR and IR) results of glucose. To conclude our study, a preliminary work on the united atom force field calculation is carried out by estimating the volume of the sugar heads represented as spherical and ellipsoidal models.

ABSTRAK   Bentuk α- dan β- bagi pelbagai gula sakarida dipilih secara rawak untuk mengira tenaga minimum menggunakan kaedah mekanik molekul MM).   Medan daya cff91 digunakan untuk mengoptimumkan struktur gula menggunakan cara Newton-Raphson. Program AMPAC/MOPAC juga digunakan untuk mengira tenaga minimum elektronik bagi gula tersebut. Keputusan yang dikira dibincang meliputi kesan anomerik dan pelarutan. Dalam perbincangan konfigurasi siklik melawan rantai terbuka, keputusan dari teori dibandingkan dengan spektra NMR dan IR. Sebagai kesimpulan, kerja permulaan pengiraan bagi medan daya atom bersekutu dicandangkan dengan menganggar isipadu gula yang diwakili oleh model sfera dan ellipsoid.

(molecular modeling, carbohydrate liquid crystals, anomeric effect, united atoms)

INTRODUCTION

Due to the fact that mesogenic compounds can be synthesized from the common, naturally occurring carbohydrates, particularly from glucose, and glucitol, research in carbohydrate chemistry, particularly in carbohydrate liquid crystals research, could not be more fascinating if not challenging.   Cyclic and acyclic carbohydrates with single *n*-alkyl or acyl chains of more than six carbon atoms are calamitic amphiphiles which form thermotropic smectic A_d (interdigitated bilayer) phases [1, 2]. In addition, most of the alkyl glycosides that display thermotropic behavior also possess lyotropic properties. The practical use of these compounds as non-ionic surfactants for extracting and crystallizing membrane proteins stimulated many of the earlier syntheses.   The first example, discovered in 1975, was the highly soluble octyl β-D-glucopyranoside, which displays lyotropic properties with water at room temperature, which are associated with ionic surfactants [3].

The synthesis of α- and β-glycosides with long chain aglycones, using a series of mono-, di-, and trisaccharides is not uncommon [4]. The fact that the synthesized glycosides resemble glycolipids, heighten the importance of this research. Glycolipids, as judged by the ubiquity of their occurrence in all cells, and their special physicochemical properties, as well as their strategic positioning (frequently outside the outer cell surface membranes), appear to be molecules particularly well-suited to serve as links at the lipid-water membrane interphase [5].   Their unique molecular combination of a hydrophilic carbohydrate and a lipophilic aliphatic hydrocarbon chain residue enable the glycolipids to mediate between the hydrophilic and the lipophilic environments.   In other words, glycolipids play salient roles in enabling the

membrane to perform its specialized functions such as cell communications and membrane rearrangements [6].

Research into the specific properties of the alkyl glycosides, for example, starts with knowledge of the three-dimensional structures of the saccharides. Indeed, our project involves the basic interdisciplinary effort to synthesize and characterize some of the sugar-based (carbohydrate) liquid crystals. However, prior to this work, some computational methodology is applied to assist in the design of these liquid crystalline compounds, among which is to study the relative stabilities of the sugars.

COMPUTATIONAL DETAILS

Figure 1 (i)-(ix) shows the cyclic conformations α- and β-anomers of different mono and disaccharides. Their corresponding minimized energy conformations using the molecular mechanics (MM) methodology are given.

Several modules of the MSI program including the graphical inteface INSIGHT, SKETCH for 2-D sketching tool and DISCOVER for energy minimization are exploited. The cff91-force field is used to optimize the sugars, employing the Newton-Raphson minimization method. The geometries of the sugars are optimized by the standard energy minimization routines, including all intramolecular degrees of freedom (bonds, angles, torsions, and etc.) [7]. Following this, the AMPAC/MOPAC program is used to calculate the electronic energies of the optimized sugars. AMPAC/MOPAC program is a general-purpose semi-empirical quantum mechanics package for the study of chemical structures and reactions. The semi-empirical AM1 parameterization is used in the electronic part of the calculation to obtain the electronic energies of the sugars with respect to their molecular geometries.

All calculations are carried out on a Silicon Graphics Iris Indigo workstation running IRIX 5.3 operating system.

RESULTS AND DISCUSSION

i. Stability of Sugars and Anomeric Effect

Table 1. MM and QM calculation of the energies of saccharides

Sugars (Monosaccharides)	Molecular Mechanics Minimized Energy, E_{min} (kcal)	Semi-Empirical Electronic Energy, E_{elec} (eV)
Allose	α = -25.794 β = -27.324	α = -14501.906 β = -14349.600
Altrose	α = -26.152 β = -28.013	α = -14532.645 β = -14407.654
Galactose	α = -26.413 β = -28.256	α = -14459.626 β = -14372.622
Glucose	α = -25.596 β = -27.356	α = -14350.803 β = -14210.219
Gulose	α = -27.193 β = -28.761	α = -14512.693 β = -14360.094
Idose	α = -27.267 β = -29.114	α = -14609.591 β = -14489.515

Mannose	$\alpha = -25.576$ $\beta = -27.361$	$\alpha = -14408.905$ $\beta = -14347.794$
Talose	$\alpha = -26.369$ $\beta = -28.135$	$\alpha = -14611.802$ $\beta = -14457.692$

Note: The given values are accurate to three decimal places to display the numerical differences.

Table 1. (continued)

Sugars (Disaccharides)	Molecular Mechanics Minimized Energy, E_{min} (kcal)	Semi-Empirical Electronic Energy, E_{elec} (eV)
Isomaltose	$\alpha = -49.460$ $\beta = -51.199$	$\alpha = -37419.766$ $\beta = -37242.091$
Lactose	$\alpha = -52.298$ $\beta = -53.968$	$\alpha = -38092.730$ $\beta = -37833.378$
Maltose	$\alpha = -49.401$ $\beta = -52.210$	$\alpha = -38397.104$ $\beta = -38168.497$
Maltotriose (trisaccharide)	$\alpha = -73.982$ $\beta = -76.982$	$\alpha = -68795.352$ $\beta = -68314.954$
Sucrose	- 44.350	-39071.951

Note: The given values are accurate to three decimal places to display the numerical differences.

The results from the molecular mechanics calculations imply that the β- anomer of each sugar is the more stable conformation as compared to its α-anomer. In the case of glucose, X-Ray analysis has confirmed that ordinary D-(+)-glucose has the α-configuration at the anomeric carbon atom but the one with the higher melting temperature (hence more stable) has the β configuration [8]. By use of the specific rotation values, the percentages of the α- and β-anomers at equilibrium can be calculated. These percentages, 36% for the α-anomer and 64% β-anomer, are in accord with a greater stability for the β-D-glucopyranose (E_{min} = -27.356 kcal). This preference is what we might expect on the basis of its having only equatorial groups.

On the other hand, our semi-empirical calculations show that the α-anomer of each sugar displays a lower electronic energy compared to its β-anomer, hence suggesting that the α-anomer is more stable than the β-anomer. The stability of the α-anomer can be explained in terms of the *anomeric effect*. Chemists, have determined experimentally that many reactions which introduce oxygen or halogen atoms at the anomeric carbon atom of a pyranose ring give a stereoisomer with the new group at the axial position, as a major product [9]. This preference of electronegative substituents for the axial position, at the anomeric carbon atom, is called the *anomeric effect*.

The operation of the anomeric effect is of the greatest significance in carbohydrate chemistry since it not only controls the composition of anomer equilibria, but also the conformational preference of individual molecules. For compound (A) in Figure 2, the preferred

conformation is that with the substituents in the axial orientation, and that the extent of this preference decreases in solvents of increasing polarity and increases with increase in electronegativity of X. This effect is mainly due to polar interaction, which results from repulsions between unshared electrons (B) or from unfavorable dipolar repulsions (C)

operating in the equatorial forms [10]. In addition, however, the axial forms may be stabilized to some degree by overlap of the antibonding lobe of the C-X bond with the unshared electrons of the ring oxygen atom.
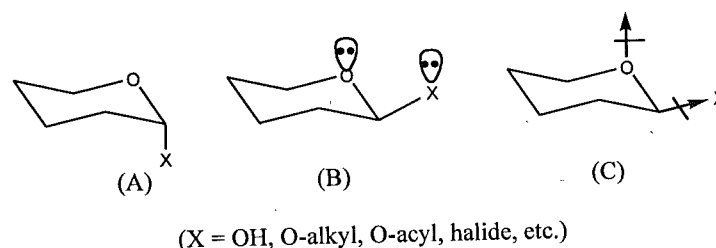

(A)   (B)   (C)

(X = OH, O-alkyl, O-acyl, halide, etc.)

Figure 2. The anomeric effect phenomenon.

**Table 2.** QM calculations for peracetylated saccharides

Sugars	Semi-Empirical Electronic Energy, E_{elec} (eV) α-anomer (peracetylated)	Semi-Empirical Electronic Energy, E_{elec} (eV) β-anomer (peracetylated)
Glucose	-44465.190	-44104.887
Galactose	-44438.071	-44333.901
Mannose	-44382.793	-44285.884
Maltose	-107134.653	-106218.450
Lactose	-106615.684	-104390.886
Isomaltose	-104441.456	-103163.248
Maltotriose	-184939.892	-183509.969
Sucrose	-108565.448	

Note: The given values are accurate to three decimal places to display numerical differences.

In a separate calculation using the same computational methodology, we calculate the percetylated form of some selected sugars. Our calculations also show that the peracetylated sugars are more stable in the axial forms than in the equatorial forms. In chemical experiments, complete acetylation of unsubstituted sugars produces mixtures of isomeric products, whereby the proportions depend upon the conditions used and upon the sugar, and to some degree, the esterifying conditions can be selected to favor a required isomer. Acetate is a common protecting group, and is used in our synthetic work, though the list of potential protecting groups is extensive. In addition, the catalysts most frequently employed are $ZnCl_2$ (or other similar Lewis acids; in our case, we use $SnCl_4$), sodium acetate, or pyridine [10, 11]. Acid catalysts also causes anomerization of the glycosyl acetates, and since the anomeric effect is of preeminent importance under these conditions, the pyranose peracetates having the axial anomeric ester groups are generally formed in the largest proportion [1].

The best known of all the carbohydrates is probably sucrose – common table sugar. Sucrose is a disaccharide in which D-glucose and D-fructose are joined at their anomeric carbons by a glycosidic bond. Since sucrose does not have a free anomeric hydroxyl group, it does not undergo mutarotation. Our semi-empiral calculations show that the electronic energies of sucrose in the normal form (E_{elec} = -39071.951 eV) and the perecetylated form (E_{elec} = -108565.448 eV) give lower value than that of the other disaccharides.

Sucrose

ii. Solvation Effect

peracetylated α-D-glucopyranoside
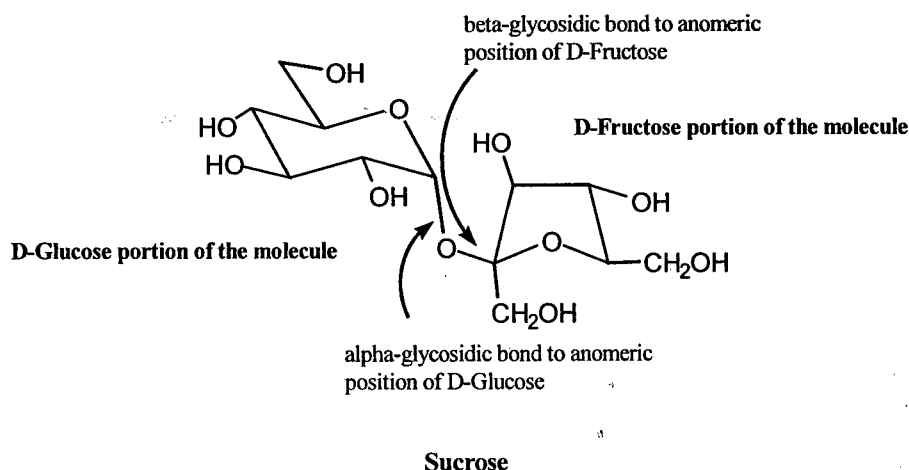
peracetylated β-D-glucopyranoside
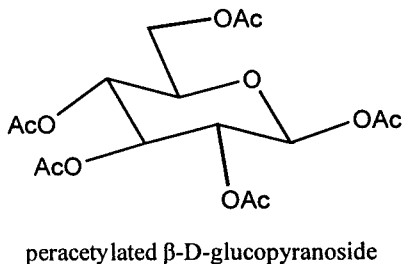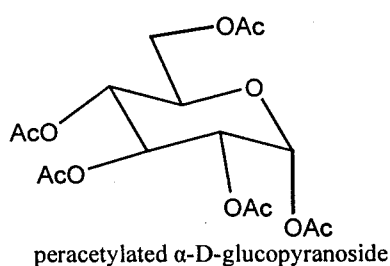
OAc = OCOCH$_3$

In our synthetic work, the alkylation of the peracetylated β-D-glucopyranoside requires the use of tin tetrachloride, $SnCl_4$, as our acid catalyst. According to the general procedure proposed by Vill et al., the preparation of the β-glycoside requires a reaction time of 2-4 hours, and that of the α-glycoside takes approximately 48 hours [4]. The stability of the α-glycoside in an acidic condition is in accord with the experimental results when glucose is peracetylated in the presence of $ZnCl_2$ as the acid catalyst, producing peracetylated α-D-glucopyranoside in 63-72% yield [12]. The work is extended by running separate molecular mechanic calculations to confirm the stability of the glucose in an acidic condition. Calculation is performed in a dielectric media to simulate the acidic environment. For the purpose of comparison, we also carry out the calculation in vacuum and water. Results are tabulated in Table 3.

Table 3. Solvation effect on glucose (MM energies)

Selected Peracetylated Sugar	Minimized Energy, E_{min} (kcal) Vacuum ($\varepsilon = 1$)	Minimized Energy, E_{min} (kcal) Water ($\varepsilon = 78.54$ at 25°C)	Minimized Energy, E_{min} (kcal) $SnCl_4$ ($\varepsilon = 2.90$ at 20°C)
Glucose	α-anomer = 41.666 β-anomer = 51.339	α-anomer = 41.666 β-anomer = 51.339	α-anomer = 41.666 β-anomer = 51.339

Note: The given values are accurate to three decimal places to display numerical differences.

iii. Cyclic versus Open-Chain Glucose

Even before spectroscopic data were obtained for glucose, chemists had evidence that an open-chain aldehyde was not the best way to represent glucose. Early chemists got their information from polarimetry, the determination of the optical rotation of glucose. When a freshly prepared solution of glucose that has been recrystallized from methanol and has a melting point of 147°C is put into the tube of a polarimeter, an initial specific rotation of +112.2° is observed. When the solution is left to stand in the polarimeter, the rotation falls until it reaches a value of +52.7° [9]. If glucose is recrystallized from water at high temperatures, another crystalline form with a melting point of 150°C is obtained. A freshly prepared solution of these crystals placed in the tube of polarimeter has an initial specific rotation of +18.7°. On standing, the optical rotation of this solution rises to +52.7°. Either solution can be evaporated and recrystallized under the conditions described above to give back the original form of glucose. Thus, the change in rotation is not a result of the decomposition of glucose in solution. This change of optical rotation for a compound on standing in solution is called *mutarotation*. The phenomenon observed for the two forms of glucose, with both solutions arriving at the same final rotation, suggests an equilibrium between stereochemically different forms of the compound [9]. These are the α- and the β-anomers of the glucose. Table 4 tabulates the MM energy of the open-chain form of glucose versus that of the cyclic form, whereby both anomers of the cyclic forms of glucose give lower energy values than that of the open-chain forms.

Table 4. Cyclic versus open-chain glucose

Glucose	Minimized Energy, E_{min} (kcal) Vacuum ($\varepsilon = 1$)	Minimized Energy, E_{min} (kcal) Water ($\varepsilon = 78.54$ at 25°C)	Minimized Energy, E_{min} (kcal) Acid ($\varepsilon = 2.90$ at 20°C)
Open-chain form	27.966	- 15.046	3.922
Cyclic form (α-anomer)	- 25.596	- 25.596	- 25.596
Cyclic form (β-anomer)	-27.357	-27.357	- 25.357

Note: The given values are accurate to three decimal places to display numerical differences.

These calculations are supported by the following spectral results of glucose in Figures 3 to 6. These spectra are interesting for a reason. The infrared spectra do not show absorption in the region we would expect for the carbonyl group of an aldehyde (~ 1740-1720 cm^{-1}). Similarly, the band typical of the hydrogen atom of an aldehyde ($\sim \delta 9.7$) does not show up in both of the proton magnetic resonance spectra glucose. Hence, the depiction of glucose as pentahydroxyaldehyde does not fit the spectroscopic evidence.
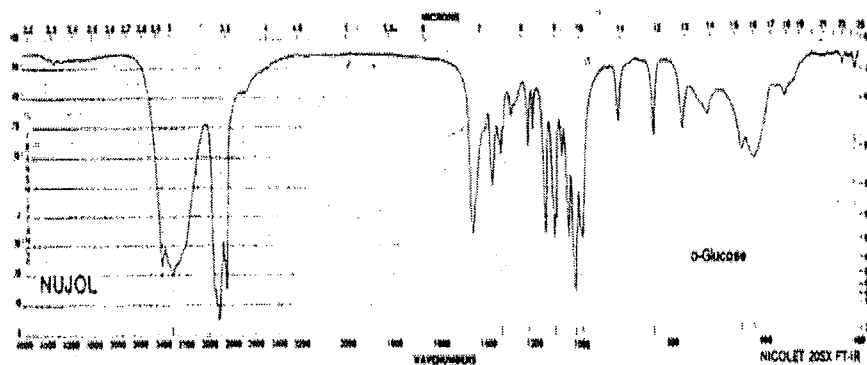

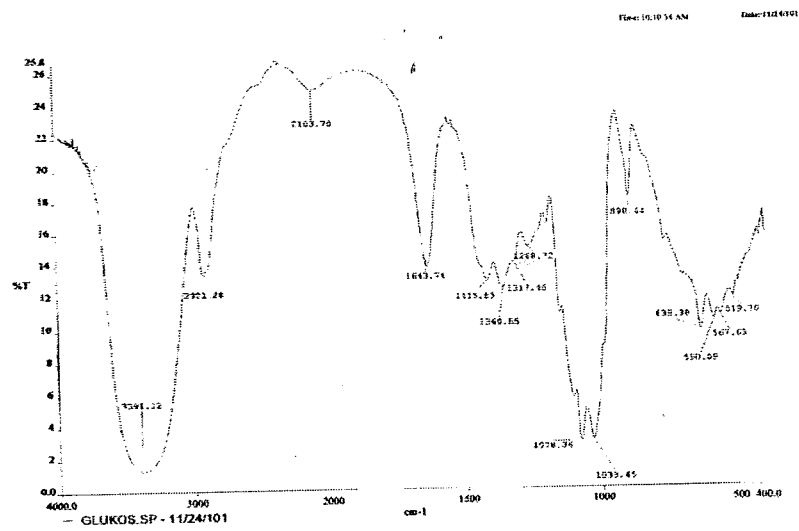**Figure 3**   Infrared spectrum of α-D-glucose [9]

Figure 4 Infrared spectrum of β-D-(+)-glucose standard, min 97% (remainder primarily α-anomer, Sigma G5250)
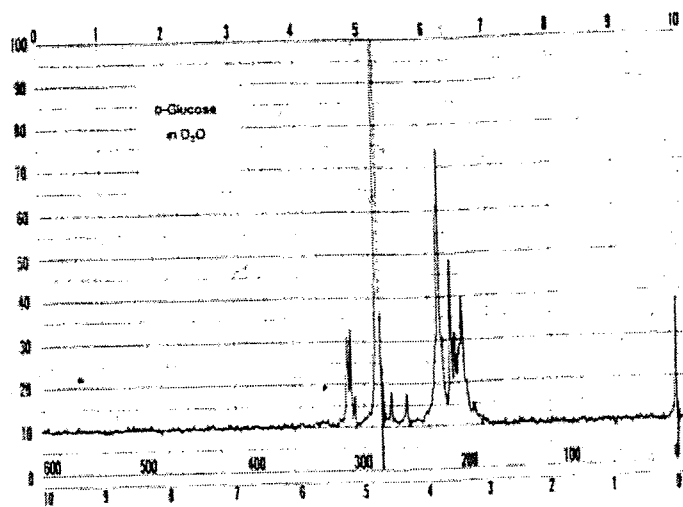

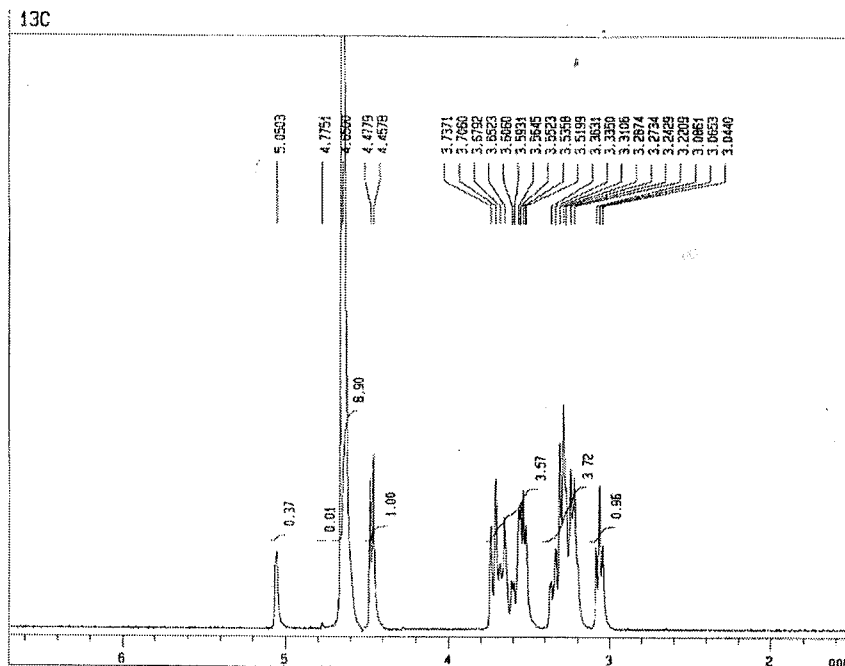**Figure 5** Proton magnetic resonance spectrum of D-glucose [9].

84

Figure 6   Proton magnetic resonance spectrum of β-D-(+)-glucose standard, min 97% (remainder primarily α-anomer, Sigma G5250)

iv.   United Atom Models

In the previous calculations, it is assumed that all of the atoms in the system are explicitly represented in the model. However, as the number of non-bonded interactions scales with the square of the number of interaction sites present, there are advantages if the number of interaction sites can be reduced. The simplest way to achieve this is to subsume some or all of the atoms (usually the hydrogen atoms) into the atoms to which they are bonded [7]. Such representation of a molecule is known as a single *pseudo-atom* or *united atom*.
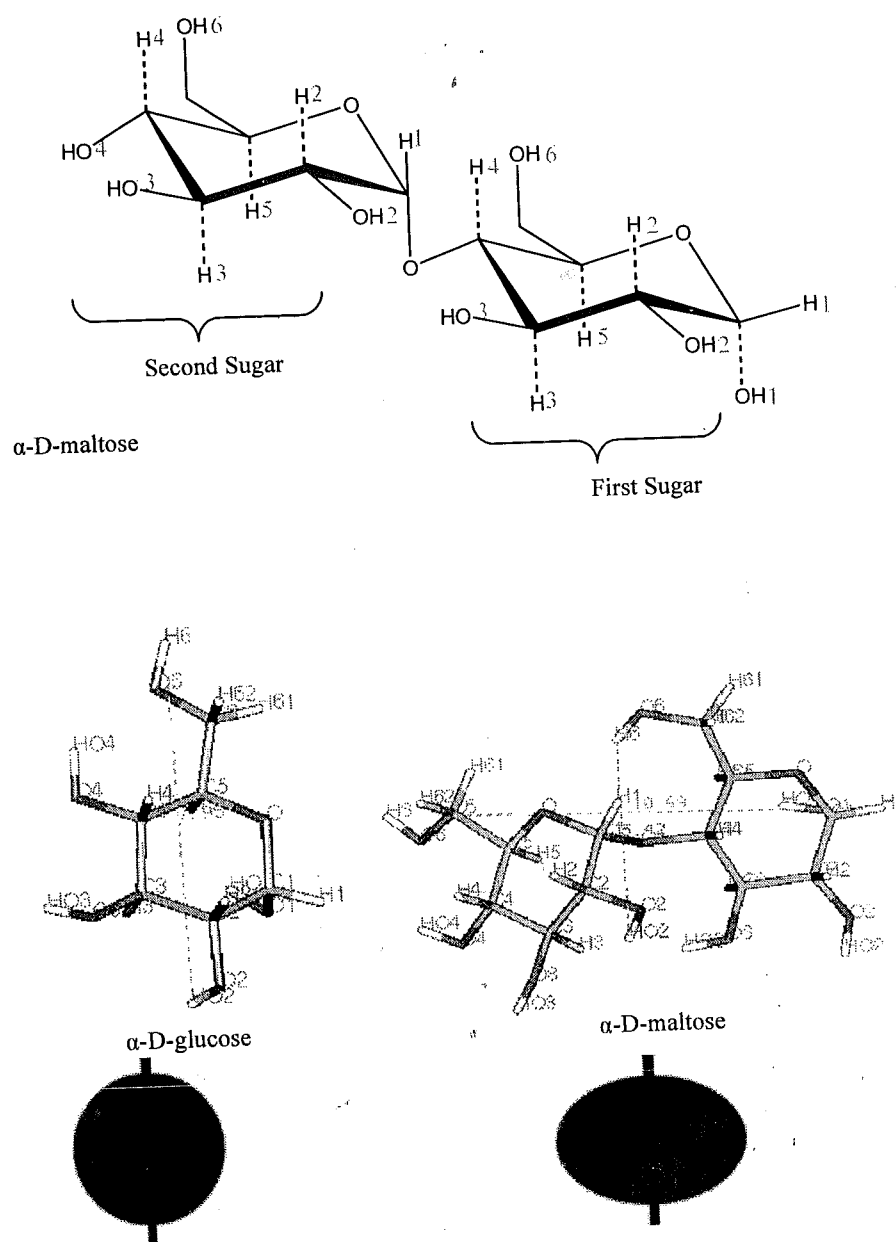
Figure 7 showing α-D-maltose structure with Second Sugar and First Sugar labels, α-D-glucose and α-D-maltose molecular models with sphere and ellipsoid representations.

Figure 7 Two examples of saccharides representing united atom models. The monosaccharides are viewed as spheres, while the di- and trisaccharides are viewed as oblate ellipsoids whereby the axis of revolution revolves along the semi-minor axis of the ellipse.

This is a preliminary work of the united atom force fields calculation. With the optimized sugars configurations, each monosaccharide is estimated to revolve around the volume of a sphere, while for the di- and trisaccharide, it is assumed that each molecule is taking up the volume of an ellipsoid (Figure 7). For the spherical model, the estimated volume is

calculated by first measuring the longest bond distance from one atom to the other. In the case of the monosaccharides, both the α- and β-anomer gives the longest bond distance between the hydrogen atoms of the hydroxyl group on C2 and C6. The radius (bond distance/2) is estimated to sweep the volume of a sphere (V = $\frac{4}{3}\pi r^3$). On the other hand, the disaccharides and trisaccharide are modeled as oblate ellipsoids ($V_x = \frac{4}{3}\pi ab^2$). The term *a* is the semi-major axis while *b* is the semi-minor axis. The atom-to-atom estimation of *a* and *b* varies for each molecule in order to provide the best approximation of the volume of the ellipsoid. In the case of α-D-maltoside, *a* is measured from OH6 of the first sugar molecule to OH2 of the second. The semi-minor axis, *b*, is measured from HO2 of the first sugar component to OH6 of the second. The volumes of the spherical and ellipsoidal united atoms are tabulated in Table 5 and 6.

Table 5 Volumes of monosaccharides modeled as spherical united atoms

Monosaccharides	α-anomer (*d* is between HO2 → H6)	β-anomer (*d* is between HO2 → H6)
Allose	$d^\ddagger = 7.93$ $V^* = 261.11$	$d = 7.94$ $V = 262.10$
Altrose	$d = 7.23$ $V = 197.89$	$d = 7.21$ $V = 196.25$
Galactose	$d = 7.91$ $V = 259.14$	$d = 7.90$ $V = 258.15$
Glucose	$d = 7.95$ $V = 263.09$	$d = 7.95$ $V = 263.09$
Gulose	$d = 7.89$ $V = 257.18$	$d = 7.90$ $V = 258.15$
Idose	$d = 7.26$ $V = 200.36$	$d = 7.24$ $V = 198.71$
Mannose	$d = 7.16$ $V = 192.19$	$d = 7.17$ $V = 193.00$
Talose	$d = 7.25$ $V = 199.53$	$d = 7.24$ $V = 198.71$

‡ *d* is bond distance in Å
* *V* is volume of sphere

Table 6 Volumes of di- and trisaccharide modeled as ellipsoidal united atoms

Disaccharides	α-anomer	β-anomer
Isomaltose	$a^‡ = 11.74$ (H6 → HO2) $b^{‡‡} = 4.95$ (HO2 → H61) $V^* = 150.61$	$a = 11.56$ (H6 → HO2) $b = 4.94$ (HO2 → H61) $V = 147.71$
Lactose	$a = 11.04$ (H6 → H1) $b = 4.86$ (HO2 → HO3) $V = 136.53$	$a = 11.66$ (H6 → HO1) $b = 4.85$ (HO2 → HO3) $V = 143.61$
Maltose	$a = 10.69$ (H6 → H1) $b = 5.42$ (HO2 → H6) $V = 164.43$	$a = 11.30$ (H6 → HO1) $b = 5.46$ (HO2 → H6) $V = 176.38$
Maltotriose (trisaccharide)	$a = 13.59$ (HO3 → H1) $b = 6.71$ (HO2 → H61) $V = 320.38$	$a = 14.03$ (HO3 → HO1) $b = 6.73$ (HO2 → H61) $V = 332.73$
Sucrose	$a = 10.49$ (HO3 → HO121) $b = 5.61$ (H61 → H51) $V = 172.86$	

‡ *a* is semi-major axis in Å
‡‡ *b* is semi-minor axis in Å
* *V* is volume of oblate ellipsoid
Each arrow indicates that the axis is measured from an atom from the first sugar molecule to that of the second. For maltotriose, *a* is measured from the first sugar to the third, while *b* is measured between two atoms in the second sugar.

The calculated volumes will be useful in understanding the role of the inter-relationship between the sugar head group with the lipophilic chain of an alkyl glycoside towards the value of the clearing point. Studies by Vill et al. show that the clearing points of alkyl glycosides increase with a large number of hydrogen bonds between the carbohydrate moieties, a rope-like structure, which contributes to a reduced volume required by the rotating molecule, and a delicately balanced ratio between the number of polar hydroxy groups and the length of the alkyl chain [4].

The general chain length dependency of homologous series of alkyl glycosides is shown in Figure 8. The mesophase behavior begins with a minimal chain length of 6, 7, or 8. An elongation of the alkyl chain contributes to a big increase of the clearing temperature. The higher number of hydroxyl groups requires higher numbers of alkyl groups.
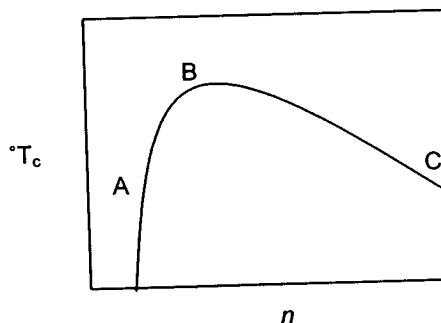

Figure 8 The general chain length dependency of homologous series

With this background, the calculated volumes of the united atoms can be utilized to estimate the length of the paraffin chain that will give the optimum configuration, and make comparison with the experimental data.

There were many reported works on united atom model, among which was a study by Schuler et al. The aggregates of *n*-dodecyl phosphate was studied to present a model system of simple phospholipid amphiphile supramolecular structures, employing the united atom model of GROMOS96 [13]. Utilizing the molecular dynamics (MD) simulation, the properties of planar bilayer membranes and spherical micelles under various simulated conditions were presented. Among the studies that was carried out using the MD calculation is to study the diffusion of the amphiphiles within aggregates,

and to determine the lifetime of hydrogen bonds between amphiphiles and to water.

Another approach in studying the united atoms is to create a CPK-ball-covered ellipsoid. Balls of a certain radius will represent the sugar head groups, and the paraffin chain attached will be extended down towards the center of the ellipsoid. [14]. The side-chains can be drawn using the CPK_STICK mode. Such a model represents spherical micelles, and like the Schuler group, similar MD calculations are possible to investigate on the aggregate structures.

Mesogenic molecules can also be represented using the Gay-Berne model. The anisotropic interaction between two particles is based on the Gay-Berne intermolecular potentials:

$$v(r_{ij}) = 4\varepsilon(\hat{u}_i, \hat{u}_j, \hat{r}) \left\{ \left[\frac{\sigma_0}{r_{ij} - \sigma(\hat{u}_i, \hat{u}_j, \hat{r}) + \sigma_0} \right]^{12} - \left[\frac{\sigma_s}{r_{ij} - \sigma(\hat{u}_i, \hat{u}_j, \hat{r}) + \sigma_s} \right]^{6} \right\} \quad \text{(Eq. 1)}$$

$\hat{u}_i$ and $\hat{u}_j$ are unit vectors that describe the orientations of the two molecules i and j, and $\hat{r}$ is a unit vector along the line connecting the centers [7]. The molecules can be considered as ellipsoids which have a shape that is reflected in two size parameters, σ_s, and σ_e. σ_s, and σ_e are the separations at which the attractive and repulsive terms in the potential cancel for the end-to-end and side-by-side arrangements respectively

(Figure 9). Depending upon the parameters chosen, simulations performed using the Gay-Berne potential show behavior typical of liquid crystalline materials [7, 15]. Hence, it will be interesting to use the pseudo-atoms of alkyl glycosides to predict the behavior of the compounds. By modifying the potential, one can resolve what contributions will affect the liquid crystalline properties of these compounds.
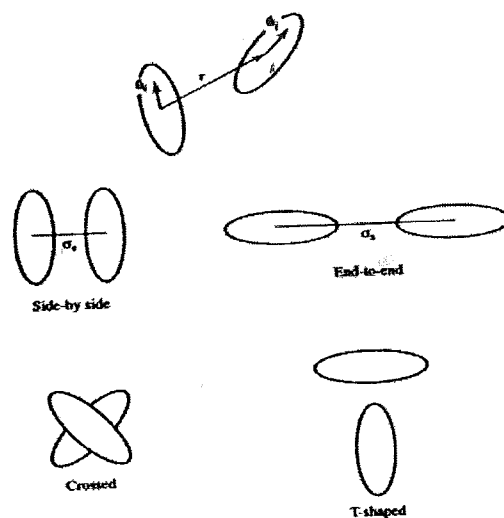
Figure 9 The Gay-Berne model for liquid crystal systems and some typical arrangement [7].

CONCLUSIONS

The purpose of these calculations is not merely to quantify the energies of the saccharides, but also to discern from the calculations what are the factors responsible for their stability and instability, which include the anomeric and the solvation effect. This molecular modeling study is extremely helpful because it gives an insight of what will be expected in the reactions of the sugars during the synthesis work.

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