Computational insights into octyl-\(D\)-xyloside isomers towards understanding the liquid crystalline structure: physico-chemical features

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**ABSTRACT**

We applied density functional theory to study octyl-\(D\)-xyloside isomers in order to explain the features responsible for the liquid crystal mesophases. Compared to a glucoside, the xylose headgroup has a proton instead of the hydroxymethyl group on C5. Thus, a xyloside has a reduced headgroup volume that renders it less hydrophilic. Our results have shown that the xylose headgroup may adopt stable pyranose and furanose conformations, which may lead to different effective headgroup hydrophilicities. These features are probably responsible for forming two non-equivalent inverse micelles, which are self-assembled into a cubic discontinuous phase with a space group of \(Fd3m\) commonly found for xylosides. While different factors are responsible for controlling the relative stability of each isomer, the role of intramolecular hydrogen bonding was highlighted for the investigated single molecule. The polarisable continuum model was used to take into account the solvent effect in order to understand the molecular behaviour in very polar systems. Results from calculations carried out in gas phase were used for comparative purposes. The molecular electrostatic potential calculations for these xylolipids demonstrate sugar amphoterism, which is implicated in the heterogeneity nature of lipid self-assembly.

**Abbreviations:** AIM: atoms in molecules; DFT: density functional theory; NBO: natural bond orbital

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Introduction

Nature is certainly the source of the most fascinating compounds, but scientists’ creative imagination with their design ability is another source that has proven equally successful to produce new challenging molecules for different purposes. This is accomplished by having a good understanding of the different molecular interactions, which thankfully now can be achieved to a relatively high accuracy by applying the density functional theory (DFT).[1–5] In the present work, we applied this tool to elucidate electro-molecular properties of octyl-D-xyloside (Figure 1) in order to contribute in establishing glycolipid liquid crystal property—structure correlations.

The alkyl xyloside structures, which consist of a sugar (as hydrophilic part) and a mono or branched alkyl chains (as hydrophobic part), allow an amphiphilic character. This property is responsible for their ability to self-assemble into different liquid crystal mesophases due to the minimisation of the Gibbs free energy.[6–9] The octyl xyloside comprises a sugar head of xylose connected via anomeric oxygen O₁ to an octyl chain group (Figure 1).

Xylose, which is a major constituent of the pentose fraction in hemicellulose, attracts the attention of many scientists since it is abundant in nature (up to 40% lignocellulosic biomass is hemicellulose) and convertible into various useful products and low-cost energy sources. For instance, this monosaccharide is a substrate for the production of xylitol, a low caloric sweetener and anti-cavity agent in dental products.[10] Additionally, alkyl xylosides have been researched for diverse applications. For example, they have been proved to possess a low toxicity towards human cells, which suggests their potential usefulness as cosmetic and detergent products. They are also used as wetting agents in the paper industry, and their liquid crystal properties have been studied quite extensively.[11–14] As sugar-based surfactants, xylosides belong to the larger chemical family of glycolipids, which can be found naturally or synthesised. Glycolipids constitute a particular class of liquid crystals with promising biological and pharmaceutical applications as they form the basis for the productions of many drugs and vitamins.[14–18] Additionally, they seem to be less damaging to the environment than many other synthetic surfactants as they are obtained from renewable resources.[19–23]

Since the structural features and liquid crystal behaviours are necessarily correlated, it is important to understand the molecular properties of glycolipids in order to rationalise the liquid crystalline phases and their locations in phase diagrams.[6,24,25] Thus, the present study aimed at investigating structural and electro-molecular properties of octyl-D-xyloside anomers and isomers using DFT calculations. Xylose itself (without the octyl chain unit) was also studied for comparison purpose.

Methods of calculations

Conformational analysis and interaction energies were carried out using DFT under the B3LYP functional and the 6–31 + G(d,p) basis set. The frequency analysis was performed at the same level of calculation at 298 K and 1 atm. All calculations were performed using either Gaussian 09 or ORCA.[26,27] Atoms in molecules (AIM) theory[28] and natural bond orbital (NBO) analysis[29] were used to analyse hydrogen bonds. The molecular orbital (MO) analysis was investigated using the time-dependent density functional theory (TD-DFT) formalism[30] at the same B3LYP/6–31 + G(d,p) level of theory. Molecular electrostatic potentials (MEPs) have been applied to elucidate electronic properties of the investigated molecules. The solvent effect was taken into account implicitly, using the polarisable continuum model (PCM). This model considers the studied structures as confined in a shape-adapted cavity surrounded by a dielectric continuum characterised by its macroscopic dielectric constant ε.[31] Water was selected as being the solvent used to measure the physico-chemical properties of molecules (εwater = 78.36). The refined dispersive DFT-D2 method as developed by Grimme to accurately describe intermolecular non-covalent interactions[32] was used to analyse the pentahydrated xyloside complex. The def2-SVP/QZVP basis set was chosen as it provides a good compromise between accuracy and computational time; in this case, the basis set superposition error (BSSE) can be neglected.[33] Both GaussView[34] and visual molecular dynamics (VMD)[35] pieces of software were used for visualisation of molecules.
**Results and discussion**

**Thermodynamic properties**

In the present work, all octyl-D-xyloside isomers including cyclic and acyclic forms were investigated. The cyclic isomers comprise octyl-D-xylopyranosides (1 and 2), featuring a six-membered C5O ring, and octyl-D-xylofuranosides (3 and 4) that include a five-membered C4O rings (Figure 1). The conformational analysis for the octyl-D-xylopyranoside anomers in solvent phase showed that two conformations are stable for each anomer according to their low energy difference (Table 1). However, in gas phase, only one conformation is stable for each anomer (Table S1). Calculations at the same level for octyl-D-xylofuranosides showed one stable conformation for each anomer in both phases. All

![Chemical Structures](image)

### Table 1. Calculated properties of xyloside isomers in solvent phase, including dipole moment \( \mu \) (Debye), Gibbs and relative free energy (kcal.mol\(^{-1}\)), H bonds (HB) and O–H bonds lengths as well as dihedral angles between OH groups involved in HB (all at B3LYP/6–31 + G(d,p) level).

| Molecule                      | \( \mu \) (D) | Calculated G | Relative G | HB \((O_xH_x\cdots O_y)\) | Ox–Hx (Å) | H\(_x\)–O\(_y\) (Å) | Dihedral angle \(O_x–C_x–C_y–O_y\) (°) |
|------------------------------|---------------|--------------|------------|--------------------------|-----------|-----------------------|----------------------------------|
| α-C8-xylopyranoside (1a)     | 3.32          | −556,536.80  | 0.00       | O\(_4\)H\(_4\)\cdots O\(_3\) | 2.47      | 0.968                 | −64.62                           |
| α-C8-xylopyranoside (1b)     | 3.55          | −556,535.36  | 1.44       | O\(_3\)H\(_3\)\cdots O\(_4\) | 2.56      | 0.968                 | −67.26                           |
| β-C8-xylopyranoside (2a)     | 3.20          | −556,536.54  | 0.26       | O\(_4\)H\(_4\)\cdots O\(_3\) | 2.48      | 0.969                 | −65.85                           |
| β-C8-xylopyranoside (2b)     | 3.13          | −556,535.44  | 1.36       | O\(_4\)H\(_4\)\cdots O\(_3\) | 2.38      | 0.969                 | −63.39                           |
| α-C8-xylofuranoside (3)      | 4.27          | −556,534.05  | 2.75       | O\(_5\)H\(_5\)\cdots O\(_2\) | 2.04      | 0.972                 | −44.78                           |
| β-C8-xylofuranoside (4)      | 4.91          | −556,533.91  | 2.89       | O\(_5\)H\(_5\)\cdots O\(_1\) | 1.87      | 0.975                 | 45.12                            |

Acyclic-xyloside (5)
optimised geometries and corresponding thermodynamic results are shown in Table 1 and Table S1.

The thermodynamics details showed that the stability of the octyl-α-D-xylopyranoside (1a) is similar to that of octyl-β-D-xylopyranoside (2a) in both gas and solvent phases (Table 1 and S1). This is in agreement with the number of hydrogen bonds, which are three in both anomers. Other factors contribute to the stability of each anomer, such as the coplanarity of all three hydroxyl oxygen atoms as well as the ether oxygen atom with the anomeric oxygen atom (O₁) for the beta derivatives (unlike the alpha anomer), and the lengths of hydrogen bonds that are shorter in alpha than in beta conformer. Regarding the furanose isomers, the octyl-α-D-xylofuranoside (3) is energetically more stable than the octyl-β-D-xylofuranoside (4) by 2.30 and 1.16 kcal.mol⁻¹ in gas and solvent phase, respectively, due to the extra hydrogen bond (O₂H⋯O₁) in the alpha anomer. Furthermore, the inclusion of solvent to the system increases considerably the stability of geometries for all derivatives according to their respective difference of energies (Table 1 and Table S1).

Dipole moments indicate the charge separation in molecules and measure the net molecular polarity.[36] The larger the difference in electronegativities of bonded atoms (i.e. highest charge separation), the larger the dipole moment (μ). As expected,[37,38] the polarity of solvent (water, ε = 78.36) increases the dipole moment in all isomers (Table 1 and Table S1). Interestingly, in both phases, the acyclic form (5) has the highest dipole moment and furanose isomers have systematically higher μ than pyranosides (Table 1). This difference in dipole moment between isomers induces a difference of electronegativity, which could explain the formation of Fd3m self-assembly structure often found in glycolipid/water with xylose head group,[11,39–42] although in these reported cases, the xylosides have different chain designs. Fd3m is a cubic space group consisting of a three-dimensional periodically ordered complex packing of two non-equivalent (in size) inverse micellar aggregates.[40,43–45] Thus, we expected that the more electronegative (more polar) isomers (i.e. furanosides) form the bigger aggregates and vice-versa. From the literature reports, [11,25,41,46–48] the formation of inverse structures such as Fd3m requires a longer hydrocarbon chain length possibly with branching that gives a tendency for splay to these molecules and obviously will not be observed in the octyl xylosides studied here. In summary, the present thermodynamics results in solvent phase showed that the octyl-α-D-xylopyranoside (1a) and the octyl-β-D-xylopyranoside (2a) are the most stable followed by octyl-α-D-xylopyranoside (1b) and octyl-β-D-xylopyranoside (2b), octyl-α-D-xylofuranoside (3), acyclic xyloside (5) and octyl-β-D-xylofuranoside (4): 1a ≈ 2a > 2b ≈ 1b > 3 > 5 > 4, with an energy difference that does not exceed 4 kcal.mol⁻¹, indicating that all isomers may occur in solution. On the other hand, the acyclic form has an intermediate stability, which explains that the interconversion between pyranosides and furanosides is possible through the acyclic form. Consequently, we suspect that the acyclic isomer is a reactive form corresponding to a transition state between the cyclic isomers, and probably cannot be observed using the commonly applied experimental spectroscopy like infrared (IR). Nevertheless, if in controlled conditions, this acyclic form can be isolated, the calculated IR spectra showed the two specific peaks at 1785 and 3810 cm⁻¹ corresponding to the carbonyl (C = O) and hydroxyl (O-H) groups, respectively, differentiating it from other isomers as predicted in the present computational study as shown in Figure 2. It must be reminded that parameters, such as temperature,

![Figure 2](image-url). Calculated IR spectra for β-octyl-D-xylopyranoside (2a), β-octyl-D-xylofuranoside (4) and acyclic octyl-D-xyloside (5).
concentration and type of solvent, influence the rate of formation of the different forms as well as the subsequent self-assembly structures as observed on the phase diagram of the glycolipid system. We also noticed that the environment affects the physico-chemical properties of the octyl-D-xylosides. Indeed, in all cases, we observed that the solvent stabilises the molecules. Nevertheless, the solvent was accounted implicitly in order to reduce the computational cost, and this is not without effect in both molecular and electronic point of view. The inclusion of explicit solvent remains essential to define strict property/structure correlations. Obviously, the inclusion of explicit solvent will induce a competition between intra- and intermolecular hydrogen bonding that influence their behaviours and liquid crystal structures. We evaluated, as an example, the stability of the pentahydrated complex consisting of the octyl-β-D-xylopyranoside (2) and five explicit water molecules, which seems to be thermodynamically highly stable according to its association energy of −74.12 kcal mol⁻¹ (Figure 3).

**Hydrogen bonding**

Both inter- and intramolecular hydrogen bonding do exist within glycolipid assemblies.[14,49–51] In general, with each xylose unit possessing three polar hydroxyl groups able to donate a hydrogen bond and five oxygen atoms each able to accept up to two hydrogen bonds, the maximum possible number of hydrogen bonds a xylose headgroup can be involved in reaches 13. Unsurprisingly, simulations on liposaccharides (e.g. octyl-β-D-glucopyranosides) in aqueous solution have observed far fewer than this idealised theoretical number (four out of eight theoretical H bonds for the above example).[49] Hydrogen bonding (OₓHₓ⋯Oᵧ) is associated with the Oₓ−Hₓ bond length in the hydroxyl group whose hydrogen is being shared and with the dihedral angle Oₓ − Cₓ − Cᵧ − Oᵧ. As previously demonstrated, hydrogen bonding plays an important role in stabilising glycolipids and inducing their different liquid crystal phases.[50,51] In fact, similarly to xylose, the hydroxyl groups located around the xylose head group of the octyl xylosides can form a chain of rather weak intramolecular hydrogen bonds. The lipid chain in C1 position does not significantly affect the hydrogen bond lengths, as seen by comparing the xylopyranosides with and without octyl side chain (Table 2). The hydrogen bonds for pyranosides, furanosides and acyclic forms were visualised and their lengths were measured (Table 1 and Table S1 in solvent and gas phase, respectively).

For the furanose forms, intramolecular hydrogen bond OₓHₓ⋯Oᵧ is observed for both anomers (molecules 3 and 4), with one more extra intramolecular hydrogen bond OₓHₓ⋯O₁ in the case of the octyl-α-D-xylofuranoside (3). In the acyclic form (5), two intramolecular hydrogen bonds (OₓHₓ⋯O₂ and O₂Hₓ⋯O₁) were observed. The calculated intramolecular hydrogen bond lengths range from 1.87 to 2.55 Å. In both gas and solvent phases, hydrogen bond lengths are slightly shorter and thus stronger in furanosides compared with those in pyranosides (Table 1 and S1). This is correlated to the presence of the hydroxymethyl (−CH₂OH) unit on C4 carbon atom in the furanosides (Figure 1). Indeed, the H atom of the O₅H₅ establishes an H bond with the O atom of the O₃H₃, thus forming a six-membered pseudo-ring. In contrast, all other intramolecular H bonds would form five-membered pseudo-rings, which, by definition, are more strained and do not allow short and strong H bonds. There is one additional hydrogen bond (O₂Hₓ⋯O₁) in compound 3 compared to 4. This is simply due to the specific conformation of this alpha furanoside that brings both oxygen atoms at close range (2.69 Å in 3, as opposed to 3.24 Å in 4).

Further, AIM analysis was used to investigate hydrogen bonds through topological parameters. In the case of pyranose forms, the intramolecular hydrogen bonds were too weak to be analysed by AIM. The molecular graphs (indicating critical points and bond paths) in solvent phase for furanoside and acyclic forms are shown in Figure 4. The positions of the bond critical points (BCP) strongly depend on the electronegativity of bonded atoms.[52] Table 3 includes topological parameters for the intramolecular hydrogen bonding in acyclic form and furanoside isomers. The hydrogen bonds are characterised by two main parameters,

![Figure 3](image-url)  (colour online) Optimised pentahydrated octyl-β-D-xylopyranoside complex at B3LYP D2/def2-SVZ level.

| Table 2. Hydrogen bond lengths (Å) for α/β-xylopyranoside and octyl-α/β-xylopyranoside in solvent phase at the B3LYP/6-31 + G(d,p) level. |
|-----------------|-----------------|-----------------|-----------------|-----------------|
|                 | α-Xylose 1a     | β-Xylose 2a     |                 |
| OₓHₓ⋯O₁         | 2.46            | 2.47            | 2.48            | 2.48            |
| OₓHₓ⋯O₂         | 2.57            | 2.57            | 2.54            | 2.55            |
| O₂Hₓ⋯O₁         | 2.26            | 2.25            | 2.58            | 2.54            |


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Fi was introduced by Cremer and Essén as an indicator of the extent of covalency. A negative value for \( H(r) \) implies a dominating potential energy density \( V(r) \) over the kinetic energy density \( G(r) \), indicative of a stabilising covalent interaction.

Thus, the \( H(r) \) negative sign for the BCP of \( \text{O}_3\text{H} \cdots \text{O}_3 \) in isomer 3, \( \text{O}_3\text{H} \cdots \text{O}_2 \) and \( \text{O}_2\text{H} \cdots \text{O}_1 \) in isomer 4 suggests that these hydrogen bonds are partially covalent and classified as strong hydrogen bonds (Table 3). Another important parameter to evaluate the hydrogen bonding stability is the ellipticity (\( \varepsilon \)); the higher the \( \varepsilon \) value, the lower the hydrogen bond stability.[55,56] Thus, according to the \( \varepsilon \) values from Table 3, \( \text{O}_3\text{H} \cdots \text{O}_3 \) is slightly more stable in 3 than in 4; and \( \text{O}_2\text{H} \cdots \text{O}_1 \) in 3 is very unstable compared to other hydrogen bonds.

We also applied the NBO analysis for the furanoside and acyclic isomers (molecules 3, 4 and 5) to investigate the electronic interaction effect on the reactivity and behaviours of these molecules.[29] Table 5 displays the second-order perturbation stabilisation energies of donor–acceptor interactions in the NBO basis. This analysis is carried out by examining all possible interactions between donor and acceptor NBOs. The formation of hydrogen bonds suggests that certain amounts of electronic charge are transferred from the lone pair to the antibonding orbital. For the studied molecules, electronic charge is transferred from the \( n \) (O) lone electron pair orbital atom in donor fragment to the \( \sigma^*(\text{O} \cdots \text{H}) \) antibond orbital of the acceptor fragment. This interaction is estimated by second-order perturbation energy \( (E^{(2)}) \),[29] which is expressed as follow:

\[
E^{(2)} = q_i \frac{F(i,j)^2}{\varepsilon_j - \varepsilon_i},
\]

where \( q_i \) is the donor orbital occupancy, \( \varepsilon_i, \varepsilon_j \) the diagonal elements (orbital energies) and \( F(i,j) \) the off-diagonal NBO element. A quick comparison between the stabilisation energies of \( E^{(2)} \) corresponding to the most important charge transfer interaction (donor→acceptor, i.e. \( n(\text{O}) \rightarrow \sigma^*(\text{O} \cdots \text{H}) \)) shows that the

![Figure 4](image1.png)

**Figure 4.** (colour online) Molecular graph of intramolecular hydrogen bonding in solvent phase.

namely the Laplacian of the charge density \( (\nabla^2 \rho(r)) \) and the total electron energy density \( (H(r)) \) at the BCP. Bader and Essén suggested that a negative value of \( \nabla^2 \rho(r) \) implies a local charge concentration, which is linked with the covalency and shared-shell interaction.[53] Conversely, a positive \( \nabla^2 \rho(r) \) indicates a local charge depletion associated with ionic bonding or weak interatomic interactions such as hydrogen bonding. As it can be shown from Table 3, \( \nabla^2 \rho(r) > 0 \), which is in agreement with the type of the studied bond type (i.e. hydrogen bonds). The local total electronic energy density \( H(r) = G(r) + V(r) \) was introduced by Cremer and Kraka as an indicator of the extent of covalency. [54] This interaction is estimated by second-order perturbation energy \( (E^{(2)}) \),[29] which is expressed as follow:

| H bond (Å) | \( \rho(r) \) | \( \nabla^2 \rho(r) \) | Ellipticity (\( \varepsilon \)) | \( V(r) \) | \( G(r) \) | \( H(r) \) |
|-----------|------------|----------------|-----------------|-------|------|------|
| 3         | \( \text{O}_3\text{H} \cdots \text{O}_3 \) (2.04 Å) | 0.0222 | 0.072 | 0.0344 | −11.62 | 11.47 | −0.15 |
| 4         | \( \text{O}_3\text{H} \cdots \text{O}_2 \) (2.16 Å) | 0.0189 | 0.076 | 0.7011 | −10.36 | 11.12 | 0.77 |
| 5         | \( \text{O}_2\text{H} \cdots \text{O}_1 \) (1.87 Å) | 0.0212 | 0.071 | 0.0397 | −11.12 | 11.14 | 0.02 |
|           | \( \text{O}_2\text{H} \cdots \text{O}_1 \) (2.28 Å) | 0.0297 | 0.091 | 0.0378 | −15.00 | 14.65 | −0.36 |

Table 3. Topological parameters in solvent phase of octyl-\( \alpha/\beta \)-xylofuranoside (3 and 4) and acyclic-xyloside (5); the H bond length (Å), the electron density at BCP \( (\rho(r)) \), its Laplacian \( (\nabla^2 \rho(r)) \), the ellipticity (\( \varepsilon \)), the potential electron density \( (V(r)) \), the kinetic electron energy density \( (G(r)) \) and the total electron energy density at BCP \( (H(r)) \), in kcal\( \text{mol}^{-1} \).
value of $E^{(2)}$ for ($O_3\rightarrow\sigma^*O_5$–H) is higher than that of ($O_1\rightarrow\sigma^*O_2$–H) for the octyl-xylofuranoside (3) and $E^{(2)}$ of ($O_2\rightarrow\sigma^*O_4$–H) is higher than that of ($O_1\rightarrow\sigma^*O_2$–H) for the acyclic form (5). Furthermore, the lowest $E^{(2)}$ were observed in ($O_1\rightarrow\sigma^*O_2$–H) for 3 and 5. Hence, the strength of hydrogen bond in ($O_1\rightarrow\sigma^*O_2$–H) is weaker than that of ($O_3\rightarrow\sigma^*O_2$–H) and ($O_4\rightarrow\sigma^*O_2$–H), which is in agreement with the lengths of these hydrogen bonds of 2.04 and 2.16 Å for $H_2O\ldots O_1$ and $H_2O\ldots O_3$, and 1.87 and 2.28 Å in $O_2H\ldots O_2$ and $H_2O\ldots O_1$ for 3 and 5, respectively. Similarly, the $H_2O\ldots O_3$ length of 2.04 Å for both 3 and 4 would suggest that this hydrogen bond has the same strength in both isomers, which is confirmed by data from Table 4 that show very similar $E^{(2)}$ values for both 3 and 4. Thus, relying on the hydrogen bond distance is enough to estimate the strength of interaction but other topological parameters, such as those reported in Tables 3 and 4 are important to be included to explain the strength of such interactions.

Consequently, the role of the –CH$_2$OH group is crucial in stabilising hydrogen bonding. We showed that for the xylopyranosides where this hydroxymethyl group is absent, the hydrogen bond strengths are rather weak. However, the structures of xylofuranoside and acyclic isomers include a hydroxymethyl group and, as a result, hydrogen bonds are much stronger. Likewise, the hydrogen bond strength in, e.g. the octyl glucopyranoside [51] that has the hydroxymethyl (CH$_2$OH) group, is higher than the octyl xylopyranoside.

**Electronic properties**

Quantum chemical calculations provided valuable insights to rationalise electronic properties of molecules. In order to estimate electron delocalisation in MOs of these investigated compounds, we performed DFT optimisation of the ground-state geometries using the B3LYP/6–31 + G(d,p) level of theory. The MOs were studied within the TD-DFT, using the same B3LYP/6–31 + G(d,p) level. The corresponding schematic diagram of the MOs is sketched for all studied isomers in Figure 5. Corresponding Table 5 gathers the electro-molecular properties of the different investigated isomers. Highest occupied molecular orbital–lowest unoccupied molecular orbital (HOMO–LUMO) analysis is an essential part of quantum chemistry as these frontier orbitals represent the main orbitals involved in the chemical stability and chemical reactivity.[57] HOMO and LUMO are frontier orbitals due to their existence at the outermost boundaries of the molecule electrons, where the HOMO represents the ability to donate an electron, while the LUMO represents the ability to accept an electron. The molecular reactivity is measured in terms of the energy gap ($E_{gap}$), i.e. the transition energy from HOMO to LUMO. $E_{gap}$ is directly correlated to the measure of the excitability of molecules; the smaller energy gap in a molecule, the easier its excitation, and vice versa. Moreover, the lower $E_{gap}$ value would exhibit the eventual charge-transfer interaction, which is generally responsible for the molecular bioactivity. However, larger $E_{gap}$ provides lower chemical reactivity as adding electrons to a high LUMO and to removing electrons from a low HOMO is quite energetically unfavourable.[57] The results gathered in Table 5 show that the energy gap of the 1a and 2a are larger than those of 4 and 5. Obviously, the relatively less stable isomer (5), which is the acyclic form, is more reactive than the other isomers. This electronic transition corresponds to the transition from the ground to the first excited state and is mainly described by an electron excitation from HOMO to LUMO. IP and A represent the ionisation potential and the electron affinity, respectively; a molecule having high IP or high A does not lose or accept electron easily. From the present results, the acyclic form has the higher A. $\mu_p$, $\eta$ and S are the chemical potential, hardness and softness, respectively, and collectively are known as global reactivity descriptors. For instance, the resistance to change of the electron cloud of the chemical system can be understood from the values of hardness ($\eta$), softness (S), and the stability of chemical species can be associated with its $\eta$, i.e. hard molecules have a large $E_{gap}$ and vice versa. The electrophilicity ($\omega$) is an index to quantify the global electrophilic nature of a molecule and measure the stabilisation in energy when the system acquires an additional electronic charge; the smaller the ($\omega$) value, the stronger the molecule stability.[58–60] One can readily see from Table 5 that isomer 5, which is relatively the less stable, has the higher electrophilicity. All other isomers have similar stability. Additionally, isomer 5 is softer than other studied isomers. Inversely, cyclic isomers are harder than the acyclic form.

**Table 4.** Second-order perturbation theory analysis of Fock matrix in NBO basis; the second-order perturbation energies $E^{(2)}$; the orbital energies $(\epsilon_j – \epsilon_i)$ and the off-diagonal element $F(i,j)$; all at the B3LYP/6–31 + G(d,p) level in solvent phase.

| Donor NBO(i) n(O) | Acceptor NBO(j) $\sigma^*(O\cdot H)$ | $E^{(2)}$ kcal mol$^{-1}$ | $\epsilon_j – \epsilon_i$, a.u. | $F(i,j)$ a.u. |
|------------------|-------------------------------------|---------------------------|---------------------------------|--------------|
| 3 LP(2) O$_3$    | BD*(1) O$_2H$⋯O$_2$               | 4.57                      | 0.87                            | 0.057        |
| LP(1) O$_1$      | BD*(1) O$_2H$⋯O$_2$               | 1.72                      | 1.04                            | 0.038        |
| 4 LP(1) O$_3$    | BD*(1) O$_2H$⋯O$_2$               | 4.60                      | 1.07                            | 0.063        |
| 5 LP(2) O$_2$    | BD*(1) O$_2H$⋯O$_2$               | 9.43                      | 0.93                            | 0.084        |
| LP(2) O$_1$      | BD*(1) O$_2H$⋯O$_2$               | 1.03                      | 0.78                            | 0.026        |
MEPs have been also applied to study electronic properties of the investigated molecules. MEPs are generally used, e.g. to investigate intermolecular association and molecular characteristics of tiny molecules and to elucidate the mode of actions of drugs and biological molecules.\cite{60,61} They display reactivity maps of most probable regions for the electrophilic attacks of charged points. The MEP values are coloured as follows: the red, green and blue colours represent the most negative, the zero potential and the most positive MES regions, respectively. These potentials in the MEP increase in the order of red, orange, yellow, green and blue. The negative MEP (red colour) corresponds to an attraction of protons or cations by the concentrated electron density in the molecule, while the positive MEP (blue colour) corresponds to the repulsion of protons or cations by atomic nuclei in low electron density and shielded nuclear charge regions. The MEP arrays and maps of the investigated isomers are shown in Figure 6.

The MEPs confirm that the electron density is larger at the outer edges near to the electronegative atoms (i.e. O atoms) than the inner surfaces of the cyclic ring and the alkyl chain. Both MEP arrays and maps provide a visual representation of the electronic distribution for the acyclic and cyclic forms including pyranoside and furanoside isomers. The difference of electronic distribution of molecules implies a difference on their amphiphilicities and so on their liquid crystal behaviours. In fact, the \textit{Fd3m} cubic phase contains at least two lipid components, of different amphiphilicities. Logically, the more polar lipid component would

Table 5. Calculated (B3LYP/6-31 + G(d,p)) electro-molecular characteristics of the different isomers in solvent phase.

|     | $\varepsilon_{\text{HOMO}}$ | $\varepsilon_{\text{LUMO}}$ | $E_{\text{gap}}$ | $\eta$ | $\mu_p$ | $\omega$ | $S$ |
|-----|---------------------|---------------------|-----------------|-----|------|------|-----|
| 1a  | $-7.44$             | $-0.05$             | $7.40$          | $0.05$ | $3.70$ | $3.80$ | $0.27$ |
| 1b  | $-7.39$             | $-0.08$             | $7.30$          | $0.08$ | $3.65$ | $3.74$ | $0.27$ |
| 2a  | $-7.47$             | $-0.06$             | $7.41$          | $0.06$ | $3.70$ | $3.83$ | $0.27$ |
| 2b  | $-7.42$             | $-0.08$             | $7.34$          | $0.08$ | $3.67$ | $3.75$ | $0.27$ |
| 3   | $-7.33$             | $-0.09$             | $7.24$          | $0.09$ | $3.62$ | $3.71$ | $0.28$ |
| 4   | $-7.34$             | $-0.12$             | $7.22$          | $0.12$ | $3.61$ | $3.73$ | $0.28$ |
| 5   | $-7.43$             | $-1.60$             | $5.83$          | $1.60$ | $2.92$ | $4.51$ | $0.34$ |

$\varepsilon_{\text{HOMO}}, \varepsilon_{\text{LUMO}}$ (eV): energies of the frontier MOs; $E_{\text{gap}}$ (eV): energy gap; $\eta$ (eV): ionisation potential; $\mu_p$ (eV): electron affinity; $\omega$ (eV): hardness; $\mu_p$ (eV): chemical potential; $S$ (eV$^{-1}$): softness.

**Figure 5.** (colour online) MOs diagram of octyl-D-xyoside isomers in solvent phase.
be preferentially located into the larger inverse micelles (less curved), and inversely, the less polar component into the smaller (more curved) inverse micelles. This MEPS results also highlight the heterogeneity nature of these xylolipids. This heterogeneity is related to the sugar amphoterism, which is inherited in the lipid self-assembly and reflected in many biological functions of the membrane such as the delivery of nutrients and drugs.[62]

**Conclusion**

Quantum chemical calculations have provided a detailed investigation of the electro-molecular properties of the octyl-\(D\)-xylosides, including geometrical optimisation and stability predictions. Calculations were carried out in both gas and solvent phases for comparative purposes and solvent-effect investigations. We showed that the inclusion of solvent even implicitly (i.e. PCM) stabilises all investigated systems. The xylose ring differs from glucose only in that the hydroxymethyl (\(-\text{CH}_2\text{OH}\)) group on C5 carbon atom of glucose is replaced by a proton, thus reducing the headgroup volume and also making it less hydrophilic. This structural modification involving replacement of the \(-\text{CH}_2\text{OH}\) group by a proton has an impact on stabilising hydrogen bonds and more interestingly on rendering these molecules more favourable to inverse micellar cubic phase formation. By investigating only single molecule, we explained how the xylose headgroup is able to adopt different conformations, which in a water/lipid system could lead to two different effective headgroup hydrophilicities hence behaving more like a ternary system and may provide some explanation to the formation of two non-equivalent inverse micelles present in the cubic phase identified by x-ray to have the \(Fd\overline{3}m\) space group. Interestingly, inverse micellar cubic phases provide a wide range of important applications, including biomedical and chemical uses.[63] Although the current results allow understanding the electro-molecular features for a single molecule, rationalising intermolecular interactions including intermolecular hydrogen bonding is essential towards establishing a full glycolipids property/structure relationship and understanding glycolipids self-assemblies. Results from such studies will be revealed in due course.

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**Disclosure statement**

No potential conflict of interest was reported by the authors.

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