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# Conformations of n-alkyl- $\alpha/\beta$ -D-glucopyranoside surfactants: impact on molecular properties

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## Abstract

Sugar-based surfactants are amphiphilic compounds bearing a head group derived from sugar. Such surfactants represent a good alternative to petroleum-based surfactants, because they can be prepared from bio-products and generally have a low toxicity. The conformational flexibility of sugars is well known and since they can form competitive intramolecular hydrogen bonding-like interactions, the most stable conformations are often non-trivial. Calculating molecular descriptors in the context of Quantitative Structure-Property Relationship (QSPR) studies require relevant conformations. To find such conformations and then develop QSPR models, in this study, we carried out a conformational analysis of two anomers, octyl  $\alpha$ -D-glucopyranoside and octyl  $\beta$ -D-glucopyranoside, to exhibit the main conformational parameters of glucopyranosides and their influence on some quantum chemical molecular descriptors that could be used in QSPR models of surfactants. From a starting set of 26 conformations for each anomer, optimized at B3LYP/6-31+G(d,p) level of Density Functional Theory, three most significant conformations, common for both glucopyranosides, generated by changing a single dihedral angle, were highlighted as the most significant conformations. The influence of solvent modeled by an implicit solvation model on conformations was discussed. Moreover, the influence of conformations on calculated molecular properties (partial charges, polarisability, and dipole moment) was discussed, for n-alkyl  $\alpha/\beta$ -D-glucopyranosides. It was shown that for the studied alkyl glucosides,

the dipole moment is influenced by the choice of conformations, but that the polarisability and the partial charges are less so.

**Keywords:** conformational analysis; sugar-based surfactants; density functional theory; alkyl glucopyranosides

## 1. Introduction

Surfactants are molecules presenting both hydrophilic and hydrophobic moieties. Thanks to these specific features, surfactants can self-assemble or adsorb at interfaces between phases [1]. This gives them particular functionalities for industrial and commercial applications, like cleaning products, cosmetics, or edible emulsions. Sugar-based surfactants are an important family of surfactants, in which the hydrophilic moiety is derived from sugar [2]. Although mostly containing only C, H, O, N and S atoms, they have quite diverse structures, as illustrated in Figure 1 for four important categories of sugar-based surfactants (alkylglycosides, sugar esters, amide-linked surfactants, and polyol derivatives).

Sugar-based surfactants are particularly studied nowadays as biobased compounds: sugar can be obtained from biorefinery-derived product, e. g. starch, and fatty alcohols or fatty acids, the starting material for hydrophobic moieties of many surfactants including sugar-based surfactants, can also be obtained from biorefinery [3]. So, no petroleum-based compounds are needed to prepare them, making them potential targets for green chemistry.

Moreover, these surfactants generally have a good biodegradation rate, and are therefore environmentally interesting. Their toxicity is low, notably against the skin [4, 5]. For these reasons, sugar-based surfactants have found various applications as personal care and detergent products [4]. Alkylglycosides are the most used sugar-based surfactants [4]. As can be seen from Figure 1, the sugar head and the alkyl chain of alkylglycosides are always connected through an ether linkage. The sugar head of alkylglycosides can be glucose, mannose, galactose, maltose or any other sugar unit. Although being still costly, their industrial use is growing [3]. For instance, decyl glucopyranoside and coco glucopyranoside (a mixture of octyl, decyl, dodecyl, tetradecyl, hexadecyl glucopyranosides) can be

found in the composition of many shampoos, cosmetics and laundry detergents. Other applications can be identified from current research. For example, octyl  $\beta$ -D-glucopyranoside [6] can be used for membrane protein purification.

Predicting amphiphilic properties of sugar-based surfactants is of interest, in order to further improve their existing applicative performances, or even to find new applications for them. Various methods have been proposed in the past to predict surfactant properties. These belong to three main categories: predictive thermodynamic frameworks [7, 8], molecular dynamics [9], and QSPR models [10]. Quantitative Structure Property Relationship (QSPR) modeling is a useful method to predict properties of molecules that consists of correlating experimental properties with molecular descriptors, characterizing the molecular structures of the target compounds [11]. QSPR enables to predict properties of existing molecules, or even properties of non-synthesized molecules. The *in silico* evaluation of the potential performances of new molecules may effectively direct the choice of synthesis pathways and reduce the experimental screening stage. QSPR have been widely used for various physico-chemical properties [12, 13]. Among them, amphiphilic properties were targeted, e.g. critical micelle concentration, its associated equilibrium surface tension, or Krafft temperature [10]. Notably, Behjatmanesh-Ardakani et al. [14] proposed QSPR models to predict critical micelle concentrations of anionic surfactants. In this study, two models were developed using quantum chemical descriptors calculated either in gas phase and in solvent using an implicit solvation model (CPCM). But no improvement of predictivity was observed with the CPCM-based model compared to the gas phase one.

Furthermore, such 3-dimensional descriptors also depend on the conformation on which they are calculated. So, to develop QSPR models for conformationally complex molecules like sugar-based surfactants, preliminary conformational analyses may be carried out. In this context, it is important to evaluate if such descriptors are, in practice, significantly conformation-dependent. Descriptors which are strongly dependent on conformations can introduce additional uncertainties in such models if erroneous conformations are used.

So far, no conformational analysis on surfactants, including sugar-based surfactants, was identified during our bibliographic survey. Only few previous Density Functional Theory (DFT) studies were conducted about sugar-based surfactants. Mosapour Kotena et al. [15, 16] focused on the intramolecular hydrogen bonds. In a first study, Mosapour Kotena et al. [15] concluded that octyl  $\beta$ -D-galactopyranoside forms one more intramolecular hydrogen bond than octyl  $\beta$ -D-glucopyranoside. In a second study [16], they concluded that octyl  $\beta$ -D-mannopyranoside forms one more intramolecular hydrogen bond than octyl  $\alpha$ -D-mannopyranoside. But no complete conformational analysis was performed.

In that context, conformational analyses have been performed to identify the key conformational parameters of octyl  $\alpha$ -D-glucopyranoside and octyl  $\beta$ -D-glucopyranoside and study their influence on molecular descriptors in the perspective of future QSPR models. In contrast with their corresponding sugars, the  $\alpha$  and  $\beta$  anomers of glucose, [17], alkyl  $\alpha$ -D-glucopyranosides and alkyl  $\beta$ -D-glucopyranosides are not in configurational equilibrium through mutarotation, and therefore can be isolated from each other even in solution [18]. Both anomeric series have been found to exhibit markedly different solid-state properties, the  $\alpha$ -anomers crystallizing more readily and being less water-soluble than the  $\beta$ -anomers [19]. Moreover, some differences were identified in self-assembly behavior, with e. g. octyl  $\alpha$ -D-glucopyranoside exhibiting a 2-fold lower critical micelle concentration than octyl  $\beta$ -D-glucopyranoside at 42°C [18]. It is therefore of interest to study the conformational flexibility of both anomeric series separately.

Octyl  $\beta$ -D-glucopyranoside has been widely studied in experimental literature [2], and previously modeled by Mosapour Kotena et al. [15]. Therefore, octyl  $\alpha$ -D-glucopyranoside and octyl  $\beta$ -D-glucopyranoside have been chosen as reference systems (cf. Figure 2). Corchado et al. [20], Csonka et al. [21] and Miura et al. [22] identified various conformational parameters for glucose. Since this configuration of glucose corresponds to the polar head of octyl  $\alpha$ -D-glucopyranoside and octyl  $\beta$ -D-glucopyranoside, these conformational parameters were used as a basis for our conformational analyses.

Then, the alkyl chain length was changed and the relative proportions of the most significant conformations was studied. Finally, the influence of conformations on various molecular properties that could be found in future QSPR models was analyzed.

## 2. Computational details

All molecular structures were fully optimized using DFT with the Gaussian09 [23] suite of programs. The B3LYP functional [24], including the Becke 88 [25] 3-parameter exchange functional and the Lee-Yang-Parr [26] correlation functional, was used since it already proved to be relevant for the theoretical study of carbohydrates [20, 27, 28] and sugar-based surfactants [15, 16]. Vibrational frequencies were calculated to ensure all stationary points (i. e. conformations) presented no imaginary frequency. Various Pople basis sets [29] were used from 6-31G to 6-311++G(2df,2pd).

Partial charge distributions were computed based on Natural Population Analysis (NPA) by using NBO 3.1 program as implemented in Gaussian09. [30]

The relative weight of each conformation was estimated based on the Boltzmann weighted populations, calculated using eq. 1 [29].

$$p_i = \frac{\exp\left(\frac{\Delta G_i}{RT}\right)}{\sum_i \exp\left(\frac{\Delta G_i}{RT}\right)} \times 100 \quad (1)$$

In this equation,  $p_i$  is the Boltzmann weighted population of the conformation  $i$ ,  $\Delta G_i$  is the relative Gibbs free energy of conformation  $i$  with respect to the most stable conformation,  $R$  is the ideal gas constant, and  $T$  is the temperature. Because sugar-based surfactants are mostly used at room temperature [31], for this study, the temperature was chosen at  $T = 298$  K.

Most part of this study has been conducted in gas phase but additional calculations have been performed in aqueous phase for the main conformations based on the COSMO Polarizable Continuum Model (CPCM) as implemented in Gaussian 09.

### 3. Results and discussions

To investigate the conformational space of n-alkyl glucopyranosides, octyl  $\alpha$ -D-glucopyranoside and octyl  $\beta$ -D-glucopyranoside were first studied as reference systems, as discussed in the introduction. Then, the influence of alkyl chain length on conformations was studied, from no alkyl chain ( $\alpha$ -D-glucose and  $\beta$ -D-glucose) to a C12 alkyl chain (dodecyl  $\alpha$ -D-glucopyranoside and dodecyl  $\beta$ -D-glucopyranoside). Finally, the influence of the conformation on partial charges, dipole moment and polarisability was examined, for the series of studied n-alkyl glucopyranosides.

#### 3.1. Conformational analysis of octyl- $\alpha$ -D-glucopyranoside

A good representation of the conformational space of the studied molecules is needed for conformational analyses.

No conformational analysis has been performed up to date on sugar-based surfactants. So, we used existing knowledge on glucopyranose which is the base of our target surfactants and for which several possible conformations were highlighted by Corchado et al. [20], Csonka et al. [21] and Miura et al. [22]. Based on these last studies, three critical structural parameters were identified. These parameters were considered (and systematically studied) for the present conformational analysis on octyl  $\alpha$ -D-glucopyranoside (and octyl  $\beta$ -D-glucopyranoside in the following section)

At first, 3 different staggered positions of the hydroxymethyl (noted gg, gt or tg), and the corresponding 3 eclipsed conformations (noted gg ecl, gt ecl or tg ecl) can be defined, as shown in the Newman representations displayed in Figure 3. Although eclipsed conformations are, in principle, unstable [18], we investigated them since Mosapour Kotena et al. [15] found and studied a stable eclipsed conformation (cc-tg ecl).

The network of hydrogen-bonding like interactions built between the OH groups of the sugar head can also have two different orientations: clockwise (c) or counter-clockwise (cc). At last, two different cycle conformations can be considered,  ${}^4C_1$  chair and  ${}^1C_4$  chair (as proposed by Csonka et al. [21]), as shown in Figure 3.

It has to be noticed that, in the  ${}^1C_4$  chair, additional possible hydrogen-bonding like interactions were identified, resulting in two different starting conformations, named “same” and “opp”. “same” means that O2-H2...O4-H4 and O3-H3...O6-H6, or H2-O2...H4-O4 and H3-O3...H6-O6 are oriented in the same direction. “opp” means that they are oriented towards opposite directions.

The alkyl chain was kept extended in a zig-zag form since this chain conformation minimizes the sterical hindrance between hydrogens in gas phase [32]. Besides, such extended conformation has been observed in crystal structures of alkyl glycopyranosides [33]. The higher stability of zig-zag forms has been further evidenced by comparison with gauche configurations for octyl  $\alpha$ -D-glucopyranoside (in Supporting Information, Figure S1).

Finally, 26 starting structures were optimized by DFT calculations at B3LYP/6-31+G(d,p) level.

Some of the starting structures converged to the same optimized conformation, thus reducing the starting set of 26 structures to 17 final conformations. The energetic levels and Boltzmann weighted populations of the 18 optimized conformations obtained for octyl  $\alpha$ -D-glucopyranoside are listed in Table 1. Pictures and cartesian coordinates of the tridimensional molecular structures are provided in Supporting Information.

First of all, in line with computational studies for glucose [21],  ${}^1C_4$  conformations, characterized by  $D(O_5-C_1-C_2-C_3)$  of about  $-60^\circ$  (between  $-55.7^\circ$  and  $-66.8^\circ$  for  ${}^1C_4$  conformations), are predicted to be less stable than  ${}^4C_1$  conformations, characterized by  $D(O_5-C_1-C_2-C_3)$  of about  $60^\circ$  (between  $50.5^\circ$  and  $57.8^\circ$  for the  ${}^4C_1$  conformations), by a difference in  $\Delta G$  of 6-13 kcal/mol.  ${}^1C_4$  conformations were not among the most stable conformations of of n-octyl- $\alpha/\beta$ -glucopyranosides, in agreement with Csonka et al. [21] for glucose. Such difference in stability between  ${}^1C_4$  and  ${}^4C_1$  conformations may be attributed to the sterical hindrance within  ${}^1C_4$  conformations than in  ${}^4C_1$  conformations, as proposed by Csonka et al. [21]

Also in line with computational studies for glucose [20], the counterclockwise (cc) network of hydrogen-bonding like interactions is favored with respect to the clockwise one. This may be due to the intramolecular hydrogen bond between the anomeric oxygen and the hydrogen of the alcohol in the

2nd position of the carbohydrate cycle ( $d_{O...H} = 2.51 \text{ \AA}$  for the  ${}^4C_1$  cc-tg conformation, as illustrated in Figure 4), which can only occur with the counter-clockwise hydrogen-bonding network. Once again, the alkyl chain does not seem to impact the network of hydrogen-bonding like interactions for the most stable conformation.

It has to be noted that most of the eclipsed starting conformations for the hydroxymethyl group tended to become staggered during the optimization. Therefore, it seems that even if intramolecular hydrogen-bonding occurs between the hydroxymethyl group and the neighbouring hydrogen donors/acceptors, eclipsed conformations are not favored.

To the end, it can be seen that, in line with NMR measurements in solution for glucose [34], three conformations, varying only by rotation of the hydroxymethyl side chain, are predicted in significant amounts based on the Boltzmann weighted populations calculated on the basis of Gibbs free energy differences ( $\Delta G$ ). The critical geometrical parameter associated with this is the dihedral angle  $D(H_5-C_5-C_6-O_6)$ . These three counterclockwise  ${}^4C_1$  conformations (gg, gt, tg) are associated, respectively, with  $D(H_5-C_5-C_6-O_6)$  about  $180^\circ$ ,  $-60^\circ$ , and  $60^\circ$ , as shown in Figure 5. For all these conformations, the hydroxymethyl hydrogen forms an intramolecular hydrogen bond with either the cyclic oxygen (for gg and gt conformation) or the  $O_4$  (for tg conformation). The  $d_{O...H-O}$  are, respectively,  $2.37 \text{ \AA}$  for the  ${}^4C_1$ -cc-gg conformation,  $2.39 \text{ \AA}$  for the  ${}^4C_1$ -cc-gt conformation, and  $2.08 \text{ \AA}$  for the  ${}^4C_1$ -cc-tg conformation.

To check that the basis set 6-31+G(d,p) was relevant for these systems, the 6-31G to 6-311++G(2df,2pd) basis sets were also used to compute the three most stable conformations, i. e.  ${}^4C_1$ -cc-gg,  ${}^4C_1$ -cc-gt, and  ${}^4C_1$ -cc-tg (presented in Figure 5). The best compromise was determined as the basis set to which additional basis functions, diffuse functions, or polarisation functions would not result in significant variation of the calculated Boltzmann weighted population. So, from Figure 6, the 6-31+G(d,p) basis can be considered as relevant.

### 3.2. Conformational analysis of octyl $\beta$ -D-glucopyranoside

The studied conformational parameters for octyl  $\beta$ -D-glucopyranoside were identical to those studied for octyl- $\alpha$ -D-glucopyranoside. These are the hydroxymethyl rotation, network of hydrogen-bonding

like interactions, and the ring conformation. As for octyl  $\alpha$ -D-glucopyranoside and on the basis of the same arguments, the alkyl chain was kept extended.

Once again, some of the 26 starting conformations converged to the same optimized conformation thus reducing the final set to 20 conformations. Pictures and details of the tridimensional molecular structures are provided in Supporting Information.

The results obtained for octyl  $\beta$ -D-glucopyranoside are very similar to those obtained for octyl- $\alpha$ -D-glucopyranoside. Indeed, the  ${}^4C_1$  conformations, the counter-clockwise network of hydrogen-bonding like interactions, and staggered hydroxymethyl conformations (D(H<sub>5</sub>-C<sub>5</sub>-C<sub>6</sub>-O<sub>6</sub>) about 180°, -60° and 60°) are favored as for octyl- $\alpha$ -D-glucopyranoside. The intramolecular hydrogen bonds involving the hydroxymethyl hydrogen are also comparable: gg and gt conformations include a hydrogen bond with the cyclic oxygen, whereas tg conformation includes a hydrogen bond with O<sub>4</sub> ( $d_{O\cdots H-O} = 2.36 \text{ \AA}$ ,  $2.41 \text{ \AA}$ , and  $2.07 \text{ \AA}$  for gg, gt and tg conformations, respectively).

As shown in Table 2, the three most stable conformations (depicted in Figure 6) are the same than those for octyl- $\alpha$ -D-glucopyranoside, although the cc-tg conformation is predicted in smaller proportions.

At last, the method described in §3.1. for octyl  $\alpha$ -D-glucopyranoside was also used to check that the basis set used in the calculations for alkyl  $\beta$ -D-glucopyranosides (6-31+G(d,p)) remains relevant, as shown in Figure 6. It has also to be noticed that we observed only a weak influence of the solvation on the relative stability of main conformations of octyl  $\alpha/\beta$ -D-glucopyranosides as shown in Supporting Information (Table S2).

### 3.3. Influence of alkyl chain length

The alkyl chain length is a critical structural parameter for surfactants in general, and sugar-based surfactants in particular. [1] Indeed, it has demonstrated to strongly influence surfactant properties such as critical micelle concentration, efficiency, or Krafft temperature. [2] For this reason, its influence on head conformations of alkyl glucopyranosides has been studied.

These theoretical results indicate that head conformations are not influenced by alkyl chain length or anomeric orientation, as characterized by the stability of their  $D(H_5-C_5-C_6-O_6)$  values (provided in Supporting Information, Table S2).

The relative proportions of the most significant conformations was determined by increasing the alkyl chain length from no carbon (i. e. glucose) to 12 carbons for the  $\alpha$  and  $\beta$ -type alkyl glucopyranosides. As shown in Figure 7, increasing the length of the carbon chain revealed nearly no influence on the predicted relative stability of the 3 most stable conformations.

From Figure 7, it can be suggested that the alkyl chain length is not a critical parameter for the conformational equilibrium of sugar-based surfactants in gas phase.

### **3.4. Influence on the molecular properties**

Since molecular properties can be correlated to macroscopic properties, e. g. through the use of QSPR models [13], it is interesting to evaluate if conformations influence the values of some calculated molecular properties to evidence the variation level that can be introduced by the conformational choice. We chose to study partial charges on key points of the surfactants, dipole moment, and polarisability, since these electrostatic properties can reflect the asymmetry of charge distribution in polar head and alkyl chains of surfactants, which is a typical behavior of surfactants. It has to be noticed that none of the investigated descriptors revealed significant changes with the alkyl chain conformation (see Supporting Information, table S1).

#### **3.4.1. Charge distribution**

Surfactants have in general well-differentiated hydrophilic and hydrophobic fragments. This is the case for n-alkyl glucopyranosides, as illustrated in Figure 8.

In Figure 8, we can see that the hydrophilic head has electron-acceptor (blue) and electron-donor (red) parts, and that the hydrophobic tail show an almost neutral surface. The hydrophilic head can withdraw or give electrons to the alkyl chain, as previously shown for ionic surfactants. [35, 36] It is

of interest to examine such phenomena in non-ionic surfactants. Thus, the partial charge along the alkyl chain and the partial charge of the sugar head were studied.

### 3.4.2. Partial charges

Moreover, the NPA partial charges along the alkyl chain and on the sugar head were also studied. As previously mentioned, the alkyl chain length (i.e., for linear tails, the number of methylene units) has a profound influence on amphiphilic properties of surfactants in general [1], including sugar-based surfactants. [2].

In particular, the NPA partial charge of each  $\text{CH}_x$  ( $x = 2$  or  $3$ ) units of the alkyl chain was investigated as a function of its position for octyl  $\alpha$ -D-glucopyranoside and octyl  $\beta$ -D-glucopyranoside, as illustrated in Figure 9. For both anomers (i. e.  $\alpha$  and  $\beta$ ), while there is a significant NPA partial charge on the first methylene of the alkyl chain, the NPA partial charge is close to zero for all other  $\text{CH}_x$  units of the alkyl chain.

This suggests that electron withdrawing from the tail to the head occurs in non-ionic surfactants. If no previous work on this phenomenon was identified for non-ionic surfactants, Huibers [35] found the partial charges of the first methylene to be significant for four ionic (anionic, cationic and amphoteric) surfactants on the basis of semiempirical computations (AM1, PM3, MNDO/d). In contrast, Minisini [36], who studied partial charges calculated from Hartree-Fock or DFT methods, found that positive partial charges were distributed throughout the chain of dodecyltrimethylammonium, a cationic surfactant.

Electron withdrawing from the tail to the head was observed for all conformers and for both the  $\alpha$  and  $\beta$  anomers of the whole series of the studied alkyl-D-glucopyranosides. Moreover, such charge transfer seems only to affect the first methylene significantly.

Besides, the NPA partial charges on the sugar head are neither significantly influenced by conformations, as shown in Figure 10.

NPA partial charges of the sugar head are negative for both  $\alpha$ -D-glucopyranosides and  $\beta$ -D-glucopyranosides. They only increase after replacing the anomeric hydrogen of glucose by a  $\text{CH}_3$ . Then, adding new methylenes does not have a significant effect on NPA partial charges of the sugar head, which are around -0.30 for all alkyl glucopyranosides. This indicates that electron withdrawing from apolar tail to polar head is practically independent from alkyl chain length and anomeric orientation.

As partial charges on the sugar head and along the alkyl chain revealed not dependent on the 3 most relevant conformers, calculating the Boltzmann average of the partial charge of the sugar head did not change the values from the ones of the most stable conformer.

### 3.4.3. Dipole moment

The dipole moment is an important electrostatic property of molecules that represents the asymmetry of charge distribution in molecules. Since, as shown in Figure 8, surfactants have an asymmetric distribution of electronic charges, the dipole moment of surfactants is an interesting characteristic quantity. Moreover, some existing QSPR models dedicated to surfactants already included it. [14, 37-43] Thus, we studied the influence of the conformation on dipole moments of alkyl glucopyranosides.

The dipole moment can vary significantly from one conformation to another: it is higher for cc-gg conformations than for cc-gt and cc-tg conformations, as illustrated in Figure S6. For example, in the case of octyl  $\alpha$ -D-glucopyranoside, the dipole moment  $\mu$  is of 4.5 D for cc-gg conformation and only 3.3 D for cc-gt conformation. Similarly,  $\mu = 4.3$  D and 3.8 D for the cc-gg and cc-gt conformations of octyl  $\beta$ -D-glucopyranoside, respectively.

It might be because the hydroxymethyl is not aligned to the carbohydrate cycle for cc-gg conformations. As a consequence, the distance between barycenters of positive and negative charges may be increased along  $\text{C}_4\text{-C}_1$  axis of the polar head for octyl- $\alpha$ -D-glucopyranoside, and orthogonally with respect to the  $\text{C}_4\text{-C}_1$  axis of the polar head for octyl  $\beta$ -D-glucopyranoside.

It has to be noticed that, for both alkyl- $\alpha$ -D-glucopyranosides and alkyl  $\beta$ -D-glucopyranosides and for a given conformation, its dependency to alkyl chain length is limited to short alkyl chain lengths (up to 3C).

#### 3.4.4. Polarisability

The polarisability is another important electrostatic property of molecules that measures the linear response of the electronic cloud to a weak external field. [44] This property accounts for the propensity of the molecule to be polarised by an external field, and can be interesting to characterize surfactants, since a salient feature of this class of molecules is to be constituted by a polar head and a non-polar tail.

The polarisability linearly increases with alkyl chain length whatever the conformation, as shown in Figure 12. The linear dependency to alkyl chain length can be expected, since polarisability is generally proportional to the volume of the molecule [45, 46], and the volume of the molecule linearly increase by each addition of a new CH<sub>2</sub>. The weak dependency of polarisability to conformations may be explained by its high correlation with the molecular volume as just mentioned, the molecular volume being itself weakly influenced by conformations since it can be estimated by summing contributions from each atom in the molecule [47].

#### Conclusion

A Density Functional Theory study has been carried out to investigate the influence of conformations on the molecular properties of n-alkyl glucopyranosides. Considering gas phase structures with an extended alkyl chain, the most critical conformational parameter has been found to be the hydroxymethyl group. The most stable conformations consist in <sup>4</sup>C<sub>1</sub> cycles with counter-clockwise networks of hydrogen-bonding like interactions and the hydroxymethyl in the three possible staggered configurations, gg, gt, and tg. The conformers presenting <sup>1</sup>C<sub>4</sub> cycles, with clockwise networks of hydrogen-bonding like interactions, and with eclipsed hydroxymethyl configurations revealed less stable (with less than 5% in Boltzmann distribution). Overall, the obtained results were consistent with experimental work and computational evidences reported in literature on glucose, indicating that the

presence of an alkyl chain does not seem to influence significantly the main conformational parameter of the sugar moiety for glucose-based surfactants.

The analysis of molecular properties revealed that dipole moments are dependent on the orientation of the hydroxymethyl group. Other molecular descriptors like partial charges or polarisability do not seem to be significantly influenced.

Moreover, similar tendencies were obtained when calculating the molecular properties as an average over significant conformations or by using the most stable conformation, when looking at the influence of the alkyl chain length on molecular properties.

In this context, the results obtained here constitute a help for the molecular modeling of these molecules, in particular to compute geometrical and quantum-chemical descriptors in QSPR studies. Indeed, the studied set of conformational parameters (chair conformation, network of hydrogen-bonding like interactions, hydroxymethyl orientation) keeps relevant for similar sugar-based surfactants, for which  ${}^4C_1$  conformations with counter-clockwise networks of hydrogen-bonding like interactions can be considered as the most stable structures. The relative stability of conformations issued from the rotation of hydroxymethyl remains the key conformational parameter for the extended zig-zag form of n-alkyl glycosides.

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**Table 1.** Calculated relative free energies and B3LYP/6-31+G(d,p) Boltzmann weighted populations for octyl- $\alpha$ -D-glucoopyranoside.

Chair form	Conformation	$\Delta G$ (kcal/mol)	p (%)
${}^4C_1$	cc-tg	0.0	41
	cc-gt	0.1	35
	cc-gg	0.4	21
	cc-tg ecl	1.8	2
	c-gg	2.7	0
	c-tg	3.1	0
	c-gt	3.9	0
	cc-gg	6.3	0
	cc-gt	7.0	0
	cc-tg	7.1	0
${}^1C_4$	cc-tg2	8.5	0
	cc-tg ecl same	8.8	0
	c-gt	11.7	0
	c-tg	11.9	0
	c-tg2	12.8	0
	c-gg	13.2	0
	c-tg ecl opp	13.4	0

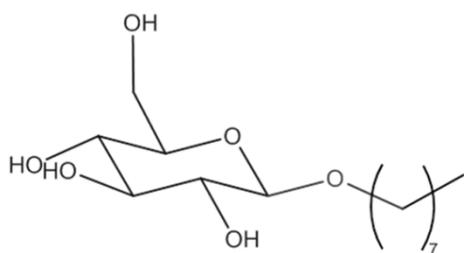
**Table 2.** B3LYP/6-31+G(d,p) relative free energies and Boltzmann weighted populations for octyl  $\beta$ -D-glucopyranoside.

Chair form	Conformation	$\Delta G$ (kcal/mol)	p (%)
${}^4C_1$	cc-gg	0.0	52
	cc-gt	0.2	35
	cc-tg	0.9	11
	cc-tg ecl	2.3	1
	c-gg	2.5	1
	c-tg	3.5	0
	c-gt	4.8	0
	cc-gg	8.3	0
	c-gt	8.6	0
	c-tg opp	8.9	0
${}^1C_4$	c-gt ecl	9.4	0
	cc-gt	9.9	0
	cc-gt2	10.1	0
	c-gt2	10.4	0
	c-gg	10.9	0
	cc-tg opp	11.0	0
	cc-gg opp	11.3	0
	c-gg	12.1	0
	c-tg same	12.1	0
	cc-tg	12.3	0

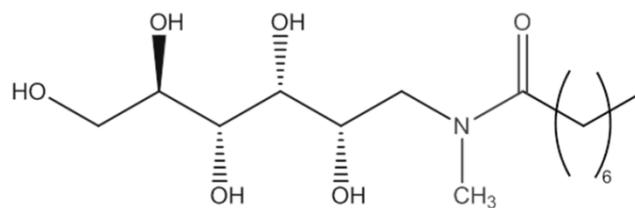
**Table 3.** H<sub>5</sub>-C<sub>5</sub>-C<sub>6</sub>-O<sub>6</sub> dihedral angles (in degrees) of the most significant conformations of octyl  $\alpha$ -D-glucopyranoside and octyl  $\beta$ -D-glucopyranoside, (B3LYP/6-31+G(d,p) level of theory)

conformation	<sup>4</sup> C <sub>1</sub> -cc-gg	<sup>4</sup> C <sub>1</sub> -cc-gt	<sup>4</sup> C <sub>1</sub> -cc-tg
octyl $\alpha$ -D-glucopyranoside	-175.3	-57.7	47.3
octyl $\beta$ -D-glucopyranoside	-175.6	-57.4	47.5

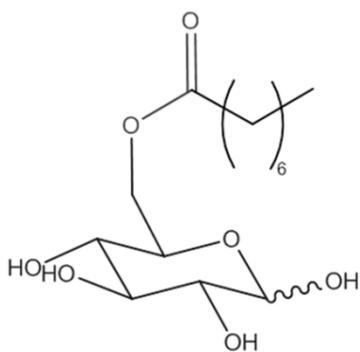
**Figure 1.** Examples of structures for four important categories of sugar-based surfactants.



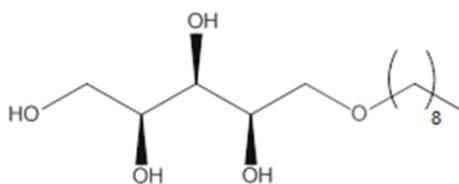
**Alkylglycosides**



**Amide-linked surfactants**



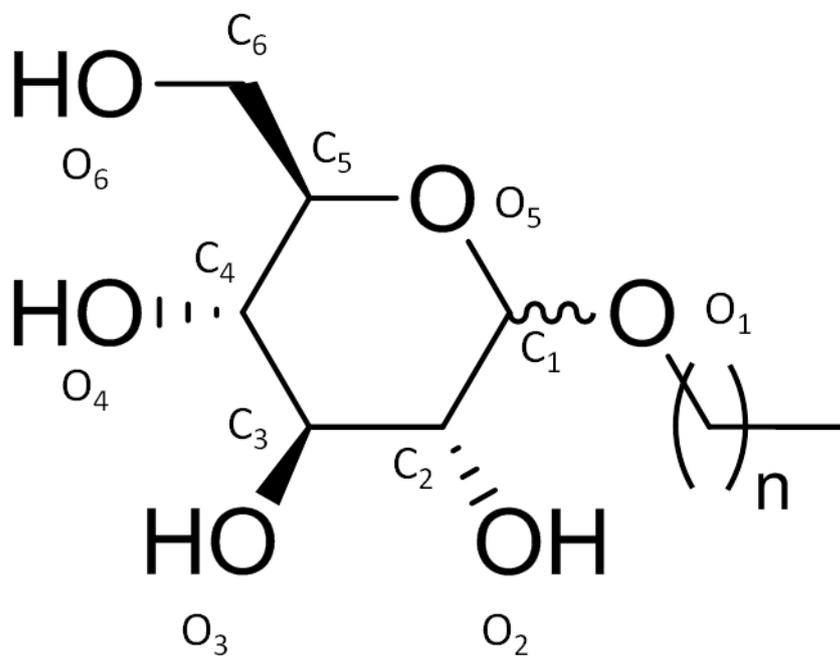
**Sugar esters**



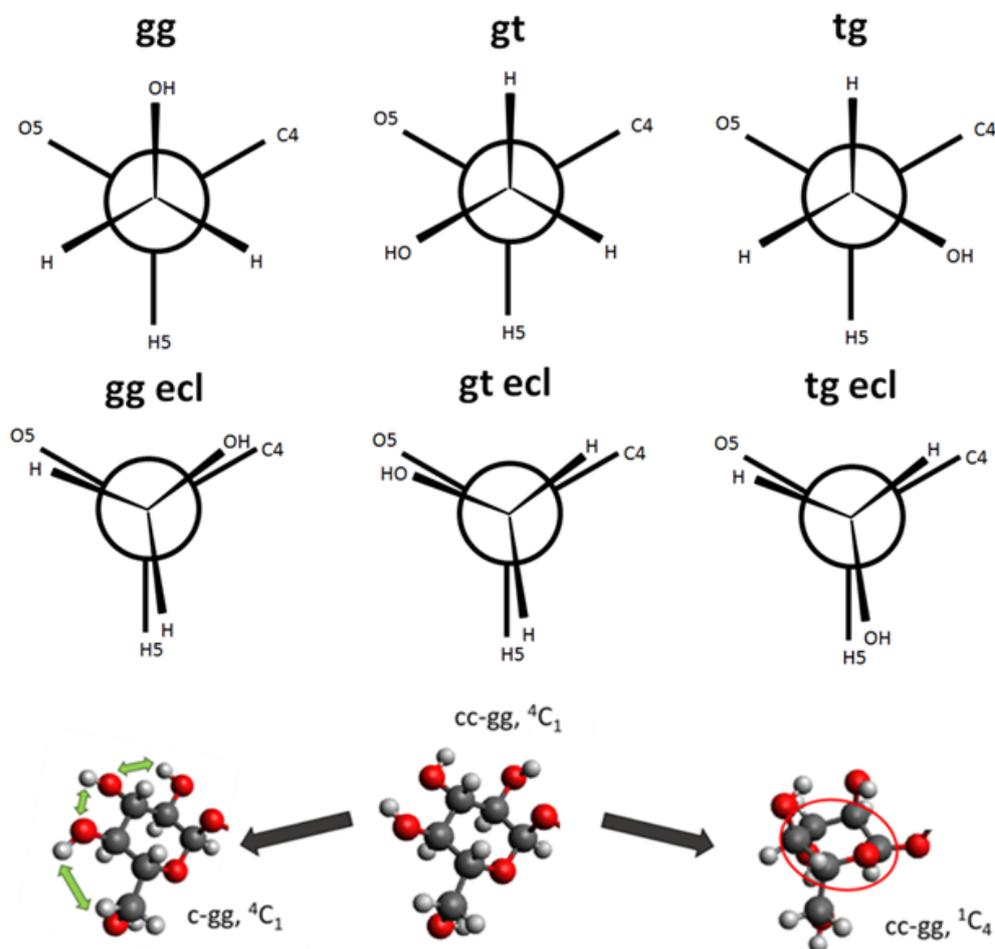
**Polyol derivatives**

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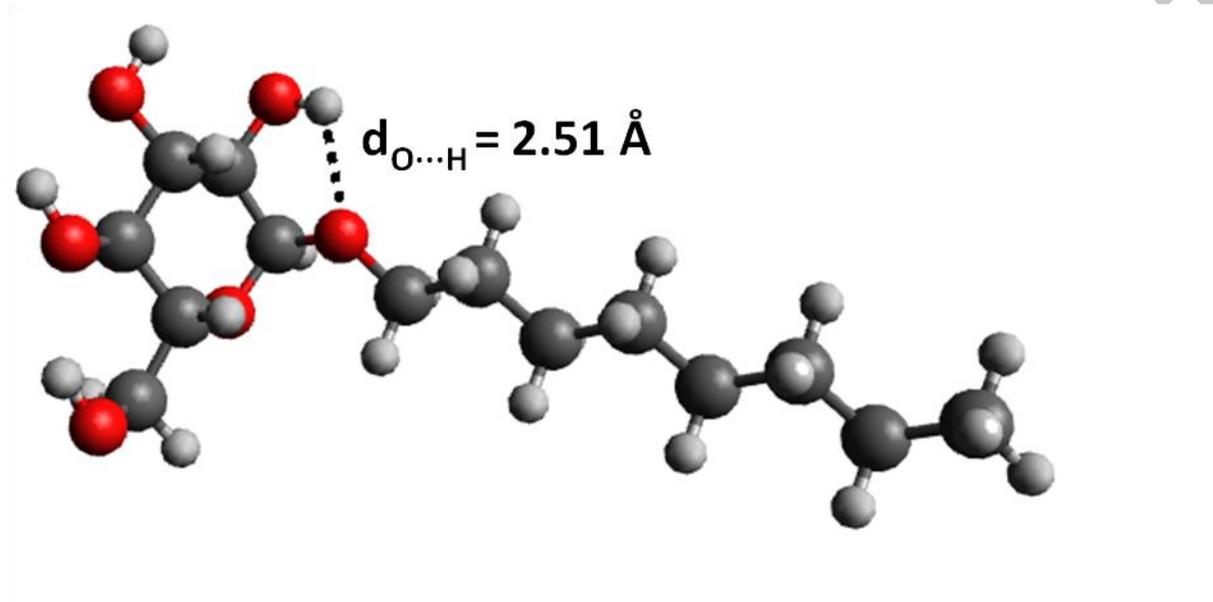
**Figure 2.** General structure of n-alkyl glucopyranosides. Hydrogen atoms are labeled like the heavy atom (such as C or O) to which they are bonded.



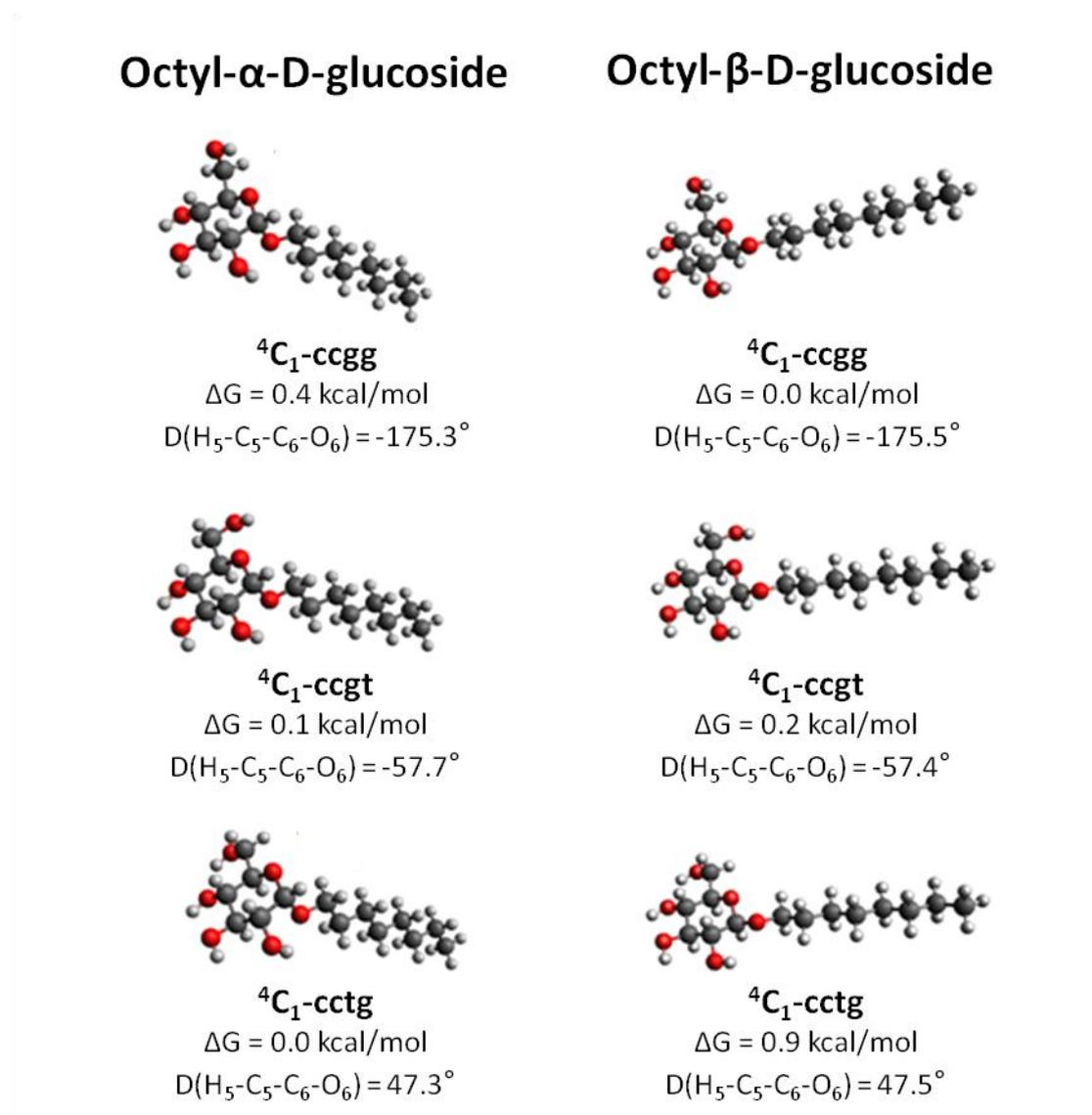
**Figure 3.** Top: the 3 staggered and the 3 eclipsed positions of the hydroxymethyl moiety. Bottom: networks of hydrogen bonding-like interactions and chair conformations studied, illustrated on a  $\alpha$ -D-glucopyranoside sugar head.



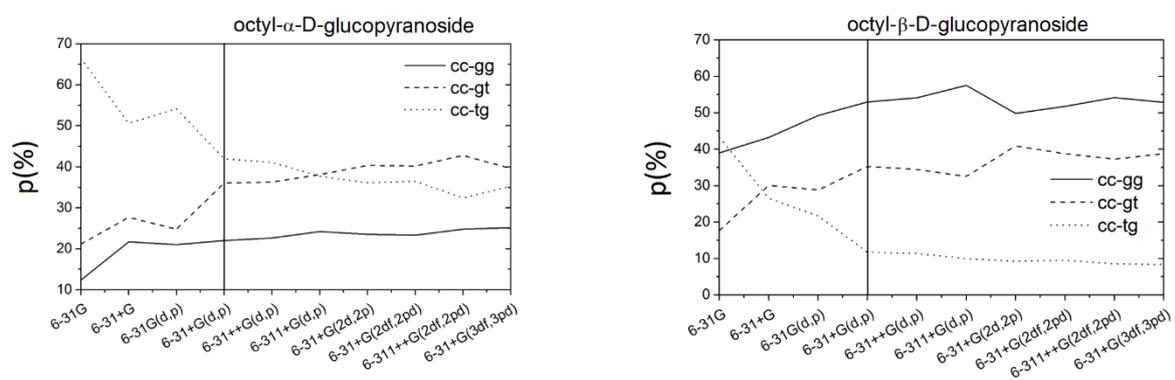
**Figure 4.** Intramolecular hydrogen bond characteristic of counter-clockwise (cc) conformations, represented by the dashed black line, for the  ${}^4C_1$  cc-tg conformation of octyl  $\alpha$ -D-glucopyranoside at B3LYP/6-31+G(d,p) level.



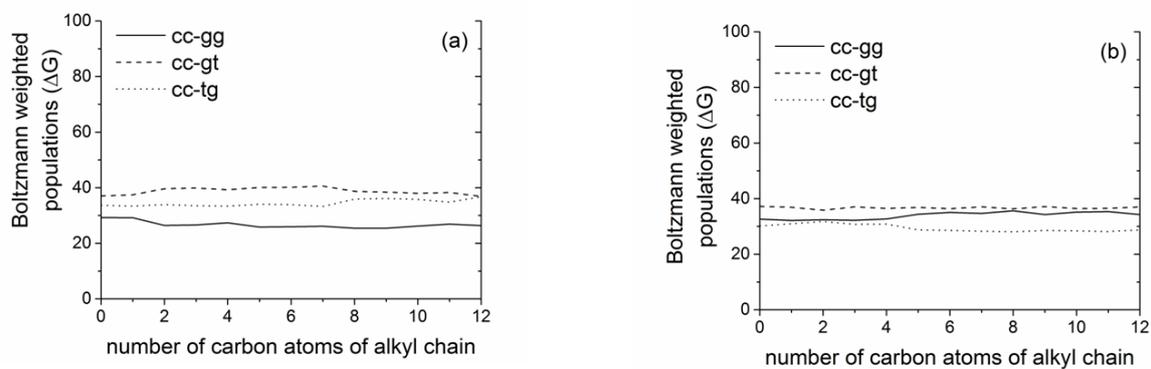
**Figure 5.** Most significant conformations of octyl  $\alpha$ -D-glucopyranoside and octyl  $\beta$ -D-glucopyranoside at B3LYP/6-31+G(d,p) level.



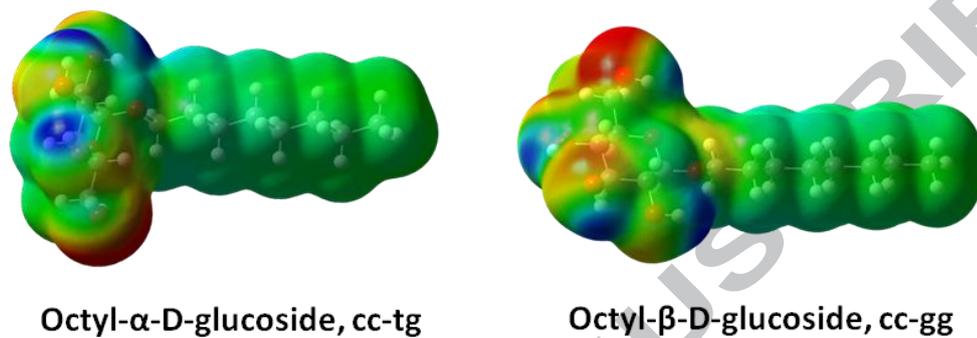
**Figure 6.** Boltzmann weighted populations  $p(\%)$  as a function of basis set, for octyl- $\alpha/\beta$ -D-glucopyranoside.



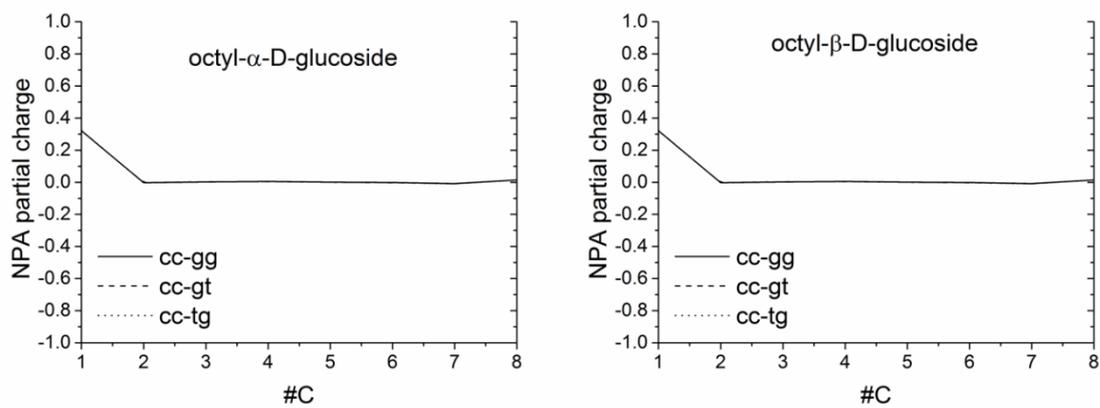
**Figure 7.** Influence of the chain length on the repartition of the three conformations (a) alkyl- $\alpha$ -D-glucopyranosides, (b) alkyl  $\beta$ -D-glucopyranosides.



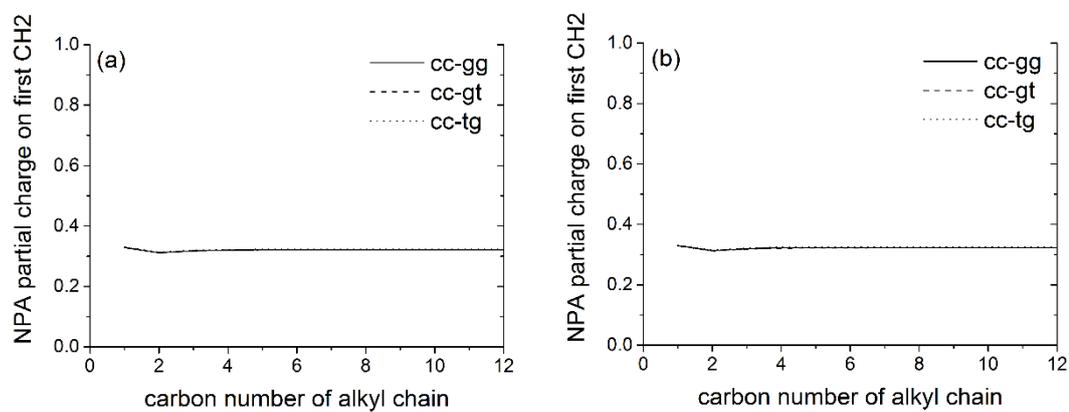
**Figure 8.** Electrostatic potential maps onto the electron density surface (isovalue of  $0.0004 \text{ e}/\text{\AA}^3$  and color-coding from  $-0.04$  to  $0.04 \text{ e}/\text{\AA}^2$ ) of the most stable conformations of octyl  $\alpha$ -D-glucopyranoside and octyl  $\beta$ -D-glucopyranoside



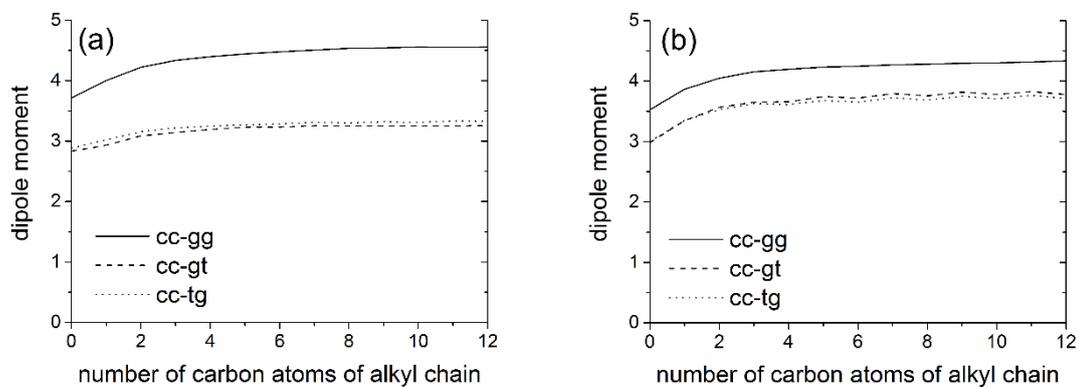
**Figure 9.** Partial charge of the  $\text{CH}_x$  ( $x = 2$  or  $3$ ) as a function of its position for octyl  $\alpha$ -D-glucopyranoside and octyl  $\beta$ -D-glucopyranoside at B3LYP/6-31+G(d,p) level.



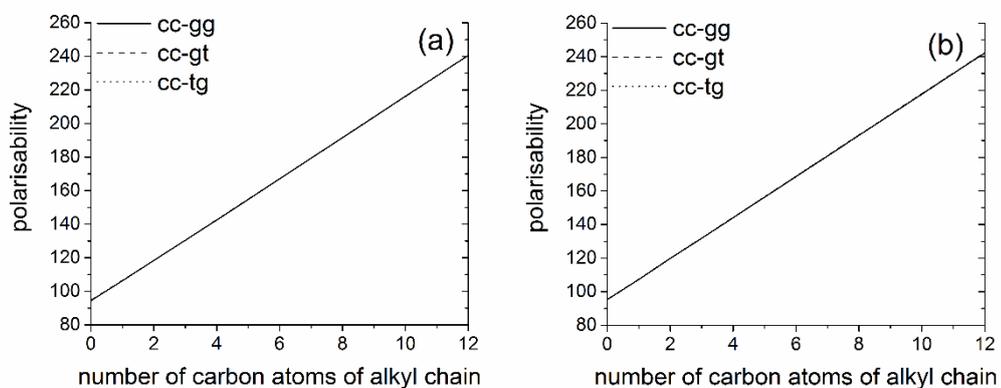
**Figure 10.** NPA partial charges of the sugar head as a function of alkyl chain length, (a) for alkyl- $\alpha$ -D-glucopyranosides (b) for alkyl  $\beta$ -D-glucopyranosides at B3LYP/6-31+G(d,p) level. NPA partial charges are provided for the individual conformations (cc-gg, cc-gt, cc-tg)



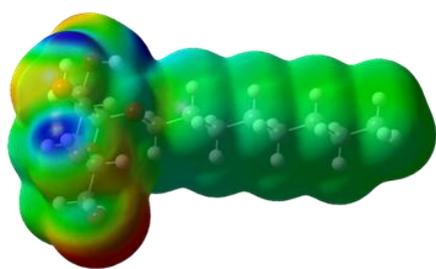
**Figure 11.** Dipole moment for both n-alkyl glucopyranosides as a function of alkyl chain length, (a) for alkyl- $\alpha$ -D-glucopyranosides (b) for alkyl  $\beta$ -D-glucopyranosides at B3LYP/6-31+G(d,p) level. Dipole moments are provided for the individual conformations (cc-gg, cc-gt, cc-tg).



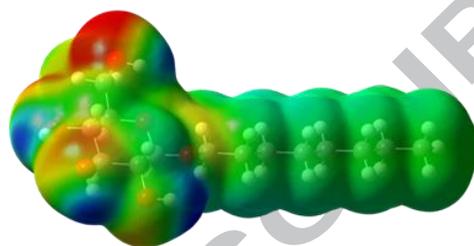
**Figure 12.** Polarisability for both n-alkyl glucopyranosides as a function of alkyl chain length, (a) for alkyl- $\alpha$ -D-glucopyranosides (b) for alkyl  $\beta$ -D-glucopyranosides at B3LYP/6-31+G(d,p) level. Dipole moments are provided for the individual conformations (cc-gg, cc-gt, cc-tg).



Graphical abstract



Octyl- $\alpha$ -D-glucoside, cc-tg



Octyl- $\beta$ -D-glucoside, cc-gg

- The conformations of sugar-based surfactants are studied.
- Rotation of hydroxymethyl group was identified as the main conformational parameter.
- Influence on a series molecular properties have been analyzed.

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