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Molecular Simulations of Dodecyl-β-maltoside Micelles in Water: Influence of the Headgroup Conformation and Force field Parameters

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Abstract

This paper deals with the development and validation of new potential parameter sets, based on the CHARMM36 and GLYCAM06 force fields, to simulate micelles of the two anomeric forms (α and β) of *N*-Dodecyl-ß-maltoside ($C_{12}G_2$), a surfactant widely used in the extraction and purification of membrane proteins. In this context, properties such as size, shape, internal structure and hydration of the $C_{12}G_2$ anomer micelles were thoroughly investigated by molecular dynamics simulations and the results compared with experiments. Additional simulations were also performed with the older CHARMM22 force field for carbohydrates (Kuttel, M. *et al. J. Comp. Chem.* 2002, *23*, 1236-1243). We find that our CHARMM and GLYCAM parameter sets yields similar results in case of properties related to the micelle structure, but differ for other properties such as the headgroup conformation or the micelle hydration. In agreement with experiments, our results show that for all model potentials the β-$C_{12}G_2$ micelles have a more pronounced ellipsoidal shape than those containing **α** anomers. The computed radius of gyration is 20.2 Å and 25.4 Å for the α- and β-anomer micelles, respectively. Finally, we show that depending on the potential the water translational diffusion of the interfacial water is 7 - 11.5 times slower than that of bulk water due to the entrapment of the water in the micelle crevices. This retardation is independent of the headgroup in α- or β- anomers.

I. Introduction

Glycolipids (GLs) are glycosyl derivatives of lipids that belong to a large family of molecules known as glycoconjugates.[1] From a chemical point of view, GLs designate any molecule with surfactant properties containing a carbohydrate headgroup (with one or more monosaccharide unit) attached to a lipophilic tail. In particular, alkyl-glycosides are simple glycolipid molecules obtained, for instance, by condensation such as “Fischer glycosidation” of a sugar with a fatty alcohol.2 Their tension-active properties depend on the length of the

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Supporting information. Force field parameters, dihedral parameters for α- and β-anomer molecules and additional figures and tables. This information is available free of charge via the Internet at http://pubs.acs.org.

alkyl chain.3,4 Because they are highly effective, ecologic and non toxic, this class of surfactants has a wide range of applications in food, cosmetic and pharmaceutical industries.[5-7] Similar to other surfactants, GLs can form different mesophases in water, such as micelles, lamellae, vesicles, etc; depending on experimental conditions (see for instance refs. 3,8-15).

During the last decades, alkyl-glucosides have also attracted a great deal of interest in the context of membrane protein extraction16,17 given that they have a low critical micellar concentration (cmc) around 10^{-3}-10^{-4} $mol.1^{-1}$ (see Table 2 of ref.7 for data and references), form large aggregates and keep the protein structure and its activity intact.18,19 In particular, alkyl-glucosides have been successfully used for solubilization of large membrane protein complexes, such as rhodopsin20, cytochrome c oxydase[21,22] and protein channel.[23,24]

Among these detergents, *N*-Dodecyl-ß-maltoside ($C_{12}G_2$) (Figure 1) is one of the most used alkyl-glucosides in membrane protein extraction experiments.[17] Two anomers, α- and β-, exist for $C_{12}G_2$ due to two possible connectivities of the dodecane chain (DOD) and of the anomeric carbon (C_1') linking DOD to the maltose head. The β-isomer is in a linear conformation, whereas the α-isomer is in a right-angle bent formed between the maltose headgroup and the alkyl tail. The α-anomer is less soluble than the β[7,25] and is not commonly used in membrane protein studies, albeit with some notable exceptions. For instance, in the bacterial *E.Coli* Na^+/H^+ antiporter, it was reported recently [24] that the α-$C_{12}G_2$ surfactant is needed to obtain a crystallized protein in its native state. To explain this feature, it is generally assumed that the orientation of the maltose head in the surfactant leads to differences in sterical constraints (i.e. due to different packing parameters) and, possibly, in hydration behaviors. SANS and SAXS scattering experiments have shown that the α-anomer of $C_{12}G_2$ forms small quasi-spherical micelle, while the β- conformation forms large oblate aggregates.[13,26]

In the past few years, molecular dynamics simulations (MD) have been extensively used to study the structure and hydration of mono- and di-saccharides, in aqueous solutions (*e.g.*, refs 27,28,29,30,31,32,33,34,35, 36,37,38,39,40). MD with alkyl-glycosides (such as alkyl-*β*-*O*-glucoside (C_8Glc_1) or alkyl-β-*O*-galactoside (C_8Gal)) have been also performed in the past, involving bilayers,[41, 42, 43] micelles [44,45, 46, 47] or interacting with a plant protein.[48] In the studies of Bogusz *et al.* [44] and Chong *et al.* 47, the influence of the surfactant headgroup conformation on the micelle structure and hydration has been thoroughly examined. It was reported that despite the conformational changes in the headgroup, several properties remain nearly unchanged for the aggregates, in particular micelle shape, surfactant tail length and conformation. In contrast, other properties directly related to the interaction between the solvent and the headgroup (i.e. solvent accessible surface area, headgroup cluster structure, number of isolated water at the micelle surface) are significantly modified by the stereochemistry of the carbohydrate head.44,47 It was also noted that the sugar counterpart is responsible for strong perturbations of the water structure at the micelle surface and it affects the formation of a large hydrogen bond (HB) network at the micelle surface between water and the headgroups, and within the headgroups themselves (inter- and intra- HBs, respectively).41,47,49 This HB network may also explain the good thermal stability of the surfactants49 and cryoprotective effects.[36,50]

Despite their crucial role in membrane protein extractions, $C_{12}G_2$ micelles have been rarely studied by computational methods, and to our knowledge, only a single MD study has been performed on these systems in the past.[51] That investigation was mainly focused on the hydration properties of the micelles and used a thermodynamical approach to examine the micellisation behavior of surfactants with different chemical nature, and was compared with

experiments. To simplify the calculations, the simulations were carried out starting from a spherical aggregate of 45 β-$C_{12}G_2$. This aggregation number is far from that of 130, commonly accepted in the literature.[13,14,26] Moreover, the authors used the OPLS-AA force field not fully optimized for glycolipid molecules.[52] In absence of optimized parameters for the two $C_{12}G_2$ anomers for the widely used CHARMM and GLYCAM06 force fields, we have developed two sets of parameters compatible with these force fields for condensed-phase MD simulation studies. We expect that these new parameters will allow us to examine the influence of the headgroup stereochemistry in $C_{12}G_2$ micelle structures under experimental conditions. Our endeavour included the calculations of new RESP atomic charges for the current GLYCAM06 potential and an optimization of the dihedral angles for the acetal linkage between the maltose headgroup and the alkyl chain for both the α- and β-anomers compatible with the CHARMM36 force field (see next sections). These new CHARMM and GLYCAM parameters (named GLYCAM06 and CHARMM-Opt, respectively) have been tested and validated by performing different MD simulations of two realistic models of $C_{12}G_2$ micelles in explicit water. To compare our results with previous MD studies of glycolipid micelles,[44-46] we have also performed two simulations with the old CHARMM22 parameters taken from Kuttel *et al.*[53] and Reiling *et al.*[54], named throughout the paper with the acronym CHARMM-K.

This paper is organized as follows: in the next sections, we describe the procedures followed to derive RESP atomic charges as well as the optimization of the dihedral angles for the acetal linkage for the α-and β-anomers for the GLYCAM and CHARMM force fields. This is followed by sections covering MD simulations, the results, as well as the interpretations of these results.

II. Methods

1. RESP charge derivation for the α- and β-anomers of $C_{12}G_2$ for GLYCAM

RESP charge derivation for $C_{12}G_2$ GL for the GLYCAM force field was carried out using standard methods.[55-57] For this purpose, we have followed a similar approach than that described by Gouin *et al.*[39] Three molecules *i.e.* methyl α-*D*-glucopyranoside (AMG), methyl β-*D*-glucopyranoside (BMG) and 1-dodecanol (OH-DOD) were involved in charge derivation. For each glucose unit, two rotamers were selected for the ω (*i.e.* represented by the $O_6C_6C_5C_4$ and $O_6C_6C_5O_5$ rotational angles) in the *gauche-gauche* (*gg*, **ω** = -60°) and *gauche-trans* (*gt*, **ω** = +60°) conformations (see Figure S1 in the supplementary material) considering that they are the most populated in solution.[58] Optimized geometries presenting intramolecular HB were excluded from charge derivation to avoid over-polarization effect.[56] As a consequence, geometry optimization was carried out with dihedral angle constraints. The $HO_4'O_4'C_4H'_4$ dihedral angle of the glucosides AMG and BMG was constrained to 180°, whereas the HO_3-O_3-C_3-H_3 and HO_2-O_2-C_2-H_2 dihedrals of AMG and BMG were constrained to 180°, respectively. A single conformation for 1-dodecanol was considered in charge derivation, and the selected geometry was optimized in its extended conformation (*i.e.* "all *trans* dihedrals"). Indeed, it has been previously shown that the surfactant alkyl chain adopts mainly this conformation in the micelle core (see for instance refs.44،59،60). Frequencies were calculated for all the molecules, and transition state structures were excluded from the charge derivation procedure. Geometry optimization, frequency calculation and molecular electrostatic potential (MEP) computation were carried out using the Gaussian03 quantum mechanics (QM) package in the gas phase,61 whereas charge fitting was performed using the RESP program.55،56 The HF/6-31G** level of theory was used in the geometry optimization and frequency calculations62, while MEP computation was based on HF/6-31G* leading to implicit polarization required in condensed phase simulations when using the non-additive AMBER force field model.[55,56] The CHELPG algorithm was used to compute the grid of points involved in MEP computation.[63] The

molecular orientation of each optimized geometries was controlled using the rigid-body reorientation algorithm implemented in the R.E.D. program.[63] Four molecular orientations for each optimized geometry of AMG and BMG (based on the glucose atom names $C_1C_3C_5$, $C_5C_3C_1$, $C_2C_4O_5$ and $O_5C_4C_2$, see Figure S1) and for the alkyl chain (based on the 1-dodecanol atom names $C_1C_2C_3$,$C_3C_2C_1$, $C_1C_3C_5$ and $C_5C_3C_1$, see Figure S1) were generated before MEP computation, and involved in the charge fitting procedure to yield reproducible atomic charges. Charge fitting was performed using a single RESP stage with a hyperbolic constraint value of 0.01. Intra-molecular charge constraints between the methyl and the C4 hydroxyl groups of AMG and BMG and inter-molecular charge constraints between the methyl group of each methyl glucoside and the hydroxyl group of OH-DOD (Figure S1) were set to a value of zero during charge fitting allowing the definition of the molecular fragments and force field libraries required to build $C_{12}G_2$ GL. Each hydrogen atom bound to a sp3 carbon was also constrained to a target value of zero during charge fitting to ensure a compatibility with the GLYCAM force field.[64] The charge derivation procedure was automatically carried out using version IV of the R.E.D program.[63] RESP charges for the α– and β–anomers of $C_{12}G_2$ are reported in the supplementary information, and are freely available from R.E.DD.B. server (http://q4md-forcefieldtools.org/REDDB/)[65] with the accession code “F-72”.

2. Optimization of the dihedral angle potentials for the acetal linkage in α- and β- $C_{12}G_2$ for CHARMM

Ethoxy tetrahydropyran (Et-THP) was used as a model compound to parameterize the acetal linkage in $C_{12}G_2$ GL. α- and β- substituted anomers were involved in the study (Figure S2). Tetrahydropyran (THP) parameters were those previously developed in the context of hexopyranoses.66 The bond, angle, dihedral, Lennard-Jones, and partial charge parameters involving the acetal group were transferred by analogy to methoxy-THP (Met-THP) parameters developed previously67 and existing linear ether parameters (Listing S1).68 The optimization of these transferred parameters was undertaken as follows. QM MP2/cc-pVTZ//MP2/6-31G* **Φ**/**Ψ** scans for both α- and β-anomers were performed (**Φ** = O_R-C_1-O_E-C_6, **Ψ** = C_1-O_E-C_6-C_7) at 15 degree increments, thus giving rise to 576 conformations as target data. Figure S3 shows that the transferred parameters serve as a good initial guess as they reproduce the QM energy surface satisfactorily. The dihedral parameters involving the exocyclic heavy atoms were directly fit using the MCSA automated dihedral fitting procedure [69] to the QM **Φ**/**Ψ** data, resulting in a marked improvement in the root mean square error (RMSE) from 2.01 (1.23) to 0.81 (0.83) kcal/mol for both α- and β- anomer. Figure S3 shows that the fit parameters reproduce well the QM **Φ**/**Ψ** potential energy surface for both anomers. Additionally, Figure S4 shows that the fit parameters reproduce the 1-D QM energy as a function of **Ψ** (**Φ** is kept constant at +/- 60 for α and β-anomer) much better than the transferred ones. Unconstrained MP2/6-31G* optimization of the molecules revealed the QM global minima for the α- anomer at values of (61.5°, 175.1°) and for the β-anomer at values of (-63.2°, -172°). These QM minima are correctly reproduced by our optimized dihedral parameters as seen in Table S2. We also notice that they also reproduce well the energy difference between the two anomers global minima, $\Delta E_{\alpha-\beta}$ ($\Delta E_{\alpha-\beta}$= -1.52 kcal/mol for QM and $\Delta E_{\alpha-\beta}$= -1.85kcal/molforMM).

The transferred partial charge on the ether oxygen atom (O_E) was validated by performing water pair interaction energy calculation as performed in previous studies.[66] This consists of optimizing the solute/water interaction distance at the HF/6-31G* level theory, with constraints on all other degrees of freedom. Table S3 shows that our parameters reproduce well the scaled QM interaction energies and adjusted distances,[66] thus validating the transfer of charges. These new sets of parameters are provided in the supplementary information in the CHARMM readable format (Listing S1).

3. Simulation Methods

To be consistent with the force fields developed in this study, we used an "all-atom" approach to model all micellar systems. RESP charges derived in the section II. 1 were involved in GLYCAM-based MD simulations with the bonded and non-bonded parameters taken from the GLYCAM06 force field version *f*.[64] The 1-4 van der Waals and electrostatic scaling factors were set to 1.0, in agreement with the developer recommendations.[64] In the case of the CHARMM-K simulations, we used two sets of parameters to model the sugar headgroup and the exocyclic atom connecting the maltose head and the alkyl chain. For the maltose head we used the parameters of Kuttel *et al.*[53] (a revision of the CHARMM22 force field for sugars of Ha *et al.*)[70] and for the acetal atom those of Reiling *et al.*[54], which is assigned to an ether oxygen atom type with a partial charge of -0.30 e. These two sets of parameters were previously employed by Bogusz *et al.*[44,45] and Konidala *et al.* [46] in MD simulations of C_8G_1 micelle in water. For the CHARMM-Opt simulations, we used the new set of parameters for hexopyranose[66] with optimized parameters for the $\mathbf{\Phi_H/\Psi_H}$ glycosidic dihedral angles which significantly improves the CHARMM force field for simulations of polysaccharides.[67] For the connection between the maltose head and the alkyl chain, we adopted the optimized parameter set for ethers by Lee *et al.*[71] combined with the optimized torsion parameters developed for Et-THP described in the previous section II.2. For all MDs performed with the CHARMM force fields, the alkyl chain of the surfactant was modeled with parameters developed by Klauda *et al.* for alkanes.[72] This contrasts with previous investigations[44,45] and the work of Konidala *et al.*[46] where for alkyl chain the parameters[73] were used. Finally, the TIP3P water model[73] was adopted to model the solvent for all the simulations.

4. Construction of the Micelles and Simulation Techniques

In this paper, we made the choice of using two *preassembled* micelles with 75 and 132 monomers of α- and β-$C_{12}G_2$ respectively. For the three different force fields studied in this work, the same approach was used to construct the six micelles and an identical protocol was applied in MD simulations. The aggregation numbers (N_{det}) was obtained by Dupuy *et al.*[13] by fitting the scattering curves from SAXS and SANS experiments at a temperature of 297 K and a concentration range between 20 and 100 mM for monodispersed micelles. We should emphasize that the N_{det} values may depend on the experimental methods and on the concentration. For example, the N_{det} value for the β-$C_{12}G_2$ micelle used here is higher than the value of 98 found by Rosevear *et al.*74 using gel filtration method, the value of 82 to 120 obtained by SAXS measurements[26] at 310 K, and the value of 111 ± 10 derived by Time Resolved Fluorescence Quenching (TRFQ) spectroscopy.[75] On the other hand, our N_{det} is well within the findings of others experiments, e.g. N_{det} = 125 ± 10 was reported using others TRFQ results at 4.89 - 19.6 mM, at 289 K - 333 K,[14] whereas N_{det} = 135-145 was found by Lipfert *et al.*[76] by SAXS at 298 K. In case of α-$C_{12}G_2$ micelle, only one aggregation number has been reported in the literature, N_{det}= 75.[13]

The starting configurations of the two aggregates were constructed using the Packmol program.[77] This program created an initial starting point for MD by packing in the sphere N_{det} $C_{12}G_2$ molecules in their extended conformation, with the first carbon atom (C_7) of the alkyl chain, near the headgroup at ~17 Å from the center of the micelle. This is larger than the total length (~14.0 Å) of the DOD chain in an extended conformation obtained with the DS Visualizer v2.0 (Accelrys Inc., San Diego) modeling program. In this way, the number of 'steric clashes' for the terminal ethyl groups of the $C_{12}G_2$ alkyl chain is reduced. To remove other inter- and intra-molecular overlaps, additional stages of conjugate gradient minimization followed by MD equilibration in vacuum with a small time step were carried out. Following this step, the headgroups were randomized by running MD simulation of the aggregates at 450 K for 300 ps, with the surfactant tail kept fixed to their minimized

conformation. From this point on, in all cases the systems were solvated by adding TIP3P water at standard density in a truncated octahedron cell, corresponding to a simple cubic primitive cell unit with parameters a=b=c and α=β=γ=109.472°. Given the two different N_{det} used in our study, we chose a=85 Å and a=95 Å for the simulations of the α- and β-anomers, respectively. These box sizes were chosen to ensure that all the molecular systems were within the experimental L_1 phase (*i.e.* < 45% in weight concentration),[75] and that there was a sufficient distance (~15 Å) between the micelle surface and the edge of the box to minimize interactions with periodic images.[78] As shown in Table 1, where we provide the composition of the two simulated systems, the simulated concentrations of the detergent are near 0.3 M and 0.40 M for the α- and β-$C_{12}G_2$ anomers, respectively. This is higher than the surfactant concentration used in the experimental study of Dupuy *et al.* [13] (0.02 - 0.04 $mol{\cdot}L^{-1}$) and higher than the critical micelle concentration (cmc) for the α- and for β-$C_{12}G_2$ (~$1.5.10^{-4}$ $mol.L^{-1}$ and ~$2.0.10^{-4}$ $mol.L^{-1}$, respectively) 13،75 at temperature 298 K. Indeed, simulations near the cmc would require about 2000 times more water in the simulation system leading to a dramatic increase of the calculation time. Furthermore, in order to equilibrate the solvent molecules, the systems were run for 300 ps at 450 K, with the ensemble of the micelles atoms fixed to their initial positions. Then, the constrained micelle atoms were released and the system slowly heated from 0 K to 297 K in 300 ps as described in ref.79 Finally, the resulting conformations were simulated in the NPT ensemble (T = 297 K and P = 0.1 MPa) for 14 ns after discarding the initial 300 ps. MD snapshots were saved every 240 fs for subsequent analysis.

5. Molecular Dynamics

For all the simulations and analysis performed in this study, a serial and parallel versions of the ORAC code were used.80 To simulate in the NPT ensemble, ORAC uses a method based on the extended system approach by adding extra (virtual) coordinates and momenta in the system to control the temperature and the pressure.81¯85 To integrate the equation of motion, a five time step r-RESPA integration scheme with a Liouvillean separation in three non-bonded shells, was used.86 The procedure combines a Smooth Particle Mesh Ewald (SPME) to handle electrostatic interactions,87 and the method of constraints to keep the covalent bonds involving hydrogen's at their equilibrium length.88 The SPME parameters were chosen to maintain a relative error of less than 0.1 % on the electrostatic interactions for all the micelles. For this purpose, a convergence parameter α = 0.43 $Å^{-1}$, a fifth-order B-spline and a 96 grid point in each cartesian direction to take care of the SPME charge interpolation for each simulated system was used.

III. Results

First, we consider the general structure of the α- and β-$C_{12}G_2$ aggregates at different simulation times: t_{sim}≈ 0 fs, t_{sim}= 7.0 ns and t_{sim}=14.0 ns of the production period. Figure 2 (a-f) provides three snapshots for each type of $C_{12}G_2$ micelles taken from the CHARMM-Opt simulations; these results are representative of the other simulations described in this paper. Visual inspection of the figures shows that at the beginning of the run, the micelles have rougher surfaces with some glycolipid protrusions (see Figures 2(a) and 2(d)). Thus, the micelles present large solvent-exposed surfaces where the alkyl chains of the surfactant are exposed to the solvent (see below). However, after typically 2-3 ns of production, Figs. 2(b-c) and 2(d-e), the surfactants arrange themselves to form compact aggregates where a major part of the alkyl tails are buried and the surface is covered with the glycolipid headgroups. These pictures also show that the α- and β-$C_{12}G_2$ micelles are not perfectly spherical and that β-$C_{12}G_2$ micelle is more ellipsoidal than α-one (see below). This finding has been observed in the various MD simulations performed in this study, regardless of the force field. Finally, in contrast with previous simulations 46،47 of octyl-β-glucoside

micelles, the integrity of the micelles studied with the GLYCAM and CHARMM force fields is maintained all along our simulation time window (14 ns), and no surfactant molecules escaped from the micelle. This is consistent with previous experimental results obtained for alkyl-maltoside micelles where it was found that monomer exchange between micelle and the solvent is in the order of 0.1 to 1.2 μs.89

A. Size of the micelles

To examine the stability and to measure the dimensions of the micelle in the six runs, we have computed their instantaneous radii of gyration, R_g, over the course of the simulations (Fig. 3) using the following expression:

$$R_g^2 = \sum_i m_i (r_i - r_{cm})^2 / \sum_i m_i \quad (1)$$

Where m_i is the mass of the atom *i* of the micelle at the distance r_i from the center of mass r_{cm}. For all the micelles studied here, the R_g values are stable after typically ~3 ns of production. As indicated previously, during the beginning of the productive run (*i.e.* between ~ 0 and 3 ns time period), local arrangements and compaction of the surfactants on the micelle surfaces are observed. This feature was also observed in previous glycolipid micelle simulations.[47]

The instantaneous R_g values for the α-$C_{12}G_2$ micelle in the three runs stabilizes after ~ 3 ns around ~20 -21 Å until the end of the trajectory. The average R_g values, $\langle R_g \rangle$, of the α-$C_{12}G_2$ micelles, computed from the last 11 ns of CHARMM-K, CHARMM-Opt and GLYCAM06 runs (20.5 ± 0.1 Å, 20.2 + 0.1 Å and R_g= 20.0 ± 0.1 Å, respectively) are close to the R_g experimental value (18.6 ± 0.6 Å[13] calculated from the semi-axis lengths of the micelle a_M, b_M and c_M and the expression $R_g^2=(a_M^2+b_M^2+c_M^2)/5$ for an ellipsoid with an uniform density.[79] In the case of the β-$C_{12}G_2$ micelles, R_g reached stable values after ~2.5–3 ns depending the force field used. In contrast to the α-$C_{12}G_2$ simulations, the three force fields lead to significant differences (up to 1.0 Å) for the instantaneous and averaged R_g, especially for the two CHARMM force fields versions. For β-$C_{12}G_2$, the $\langle R_g \rangle$'s are equal to 26.4 ± 0.1 Å, 25.4 ± 0.1 Å and 25.1 ± 0.1 Å, for the aggregates simulated with the CHARMM-K, CHARMM-Opt and GLYCAM06, respectively. The $\langle R_g \rangle$'s obtained with the CHARMM-Opt and GLYCAM06 parameters are closer to the experimental value of 23.3 ± 0.6 Å.[13]

B. Shape of the Micelles

The micelle shape can be characterized by computing the instantaneous ellipsoidal axis ratio between the micelle major (a_M) and minor (c_M) semi-axis lengths, or a_M/c_M, obtained from the inertia tensors (see ref.79 for details). As shown in Figure 4, the six micelles present a stable ellipsoidal shape (*i.e.* $a_M/c_M > 1.0$) after typically ~4.0 ns. For the α-$C_{12}G_2$ micelles, their shapes do not depend significantly on the force field. This contrasts with the behaviors of the β-$C_{12}G_2$ micelles where the ratio a_M/c_M shows a much larger fluctuations. To be consistent with the calculation of the R_g, the initial 3 ns of each trajectory were discarded in the calculation of a_M/c_M. The average values of the ratio, $\langle a_M/c_M \rangle$, are reported in the 7th column of Table 2 for the different micelles studied. In our calculation, both α- and β-$C_{12}G_2$ are ellipsoidal, but α-$C_{12}G_2$ is the closest to the shape of a sphere. In the case of β-$C_{12}G_2$ aggregates, the instantaneous a_M/c_M values stabilize around ~1.40 at the end of the simulations independently of the considered force field and the $\langle a_M/c_M \rangle$ values are close for the three micelles: 1.38 ± 0.03, 1.43 ± 0.01 and 1.38 ± 0.04 for CHARMM-K,

CHARMM-Opt and GLYCAM06, respectively. In contrast, β-$C_{12}G_2$ micelles have a pronounced *oblate* shape ($a_M > b_M \approx c_M$), which agrees well with the experimental observations.[13,26,75]

However, we can underline that the $\langle a_M/c_M \rangle$ values for the β-$C_{12}G_2$ micelles remain, depending the force field between lower than the estimated experimental values (*i.e.* a_M/c_M =1.70 from Dupuy *et al.*).[13] The instantaneous length values of the semi-axis of each micelle hydrophobic core (*i.e.* a_{HC}, b_{HC} and c_{HC}) have been also computed by including only the contributions from the surfactant hydrophobic chain in the calculations of the inertia tensors. The average values of the three semi-axes, ($\langle a_{HC} \rangle$, $\langle b_{HC} \rangle$ and $\langle c_{HC} \rangle$), are reported in the 8th, 9th and 10th columns of Table 2. We find that the average major and minor semi-axis lengths $\langle a_{HC} \rangle$ and $\langle c_{HC} \rangle$ are in relative agreement with experimental values for α-$C_{12}G_2$ and β-$C_{12}G_2$ (*i.e.* $\langle a_{HC} \rangle$ = $\langle c_{HC} \rangle$ = 18.6 Å ± 1.0 Å) and $\langle a_{HC} \rangle$ = 28.2 ± 1.0 Å and $\langle c_{HC}$ ⟨ = 14.1 ± 1.0 Å, respectively).[13] The average thickness of the polar outer layer, or $\langle 1_{pl} \rangle$, computed by subtracting the semi-axis length of the hydrophobic core from those of the whole micelle ($\langle a_M \rangle$, $\langle b_M \rangle$ and $\langle c_M \rangle$), does not change significantly with the force field and is 6.7 ± 0.3 Å for the α-anomer of the $C_{12}G_2$ and increase up to 7.3 ± 0.4 Å for the β-anomer. Due to the partial folding of the maltose head, these values are 39.1 % and 33.4 % smaller than the calculated length of the maltose in its extended configuration (~11.0 Å). The larger $\langle 1_{pl} \rangle$ value for β-$C_{12}G_2$ is consistent with the fact that the β- anomer is linear and extends in the solvent, whereas α- is more folded, hence constrained on the micelle surface. In all cases, the $\langle 1_{pl} \rangle$ values are within 1 Å of the experimental values estimated from SAXS and SANS experiments, *i.e.* 5.4 ± 0.1 Å and 6.2 ± 0.1 Å for α-$C_{12}G_2$ and β-$C_{12}G_2$, respectively.[13,76]

C. Density profiles of the Micelles

To compare the spatial extent of the most relevant atomic group components of the micelles, we have computed their average radial mass density profiles $\rho(r)$ as a function of the distance, *r*, of the group from center of mass (COM) of the micelle.[79] We discuss here the $\rho(r)$ values obtained for the entire micelle (Micelle), the maltose headgroup (Maltose), the dodecane tail (DOD), the two maltose glucose rings (GlcA and GlcB), and the hydration water (H_2O). As previously discussed,[79] the non-spherical nature of the micelles will affect ρ(r) value to a certain extent, causing the broadening of these functions. ρ(r) values, averaged over the last 11 ns of each trajectory, are shown in Figure 5(a-b). The hydrophobic core ρ(r) profiles extend from 0 to ~19.0 Å from the micelle COM, and present similar shapes regardless of the force field. For the hydrophilic maltose head, the ρ(r)'s present a strong peak with density maxima at 21.0 ± 0.5 Å and 25.0 ± 0.5 Å for the α- and β-$C_{12}G_2$ micelles, respectively. These values are close to those obtained previously for $\langle R_g \rangle$. We notice that the position of the main peaks for the GlcA and GlcB density profiles depend more strongly on the force field than that of the other groups studied here. Considering all the results, GlcA ρ(r)'s extend from 15.0 Å to 25.0 Å and from 18.0 Å to 28.0 Å for α- and β-$C_{12}G_2$ micelles, respectively. Larger values, of 1 to 2 Å, are found for all GlcB ρ(r) values. The water density profile in Fig. 5 shows that water molecules deeply penetrate into the micelle headgroup and solvates the maltose heads to a different degree with a preference for the outermost glucose ring (GlcA). We can also emphasize that water shares significant contact with the micelle hydrophobic core as seen by the intercepts of the water and DOD ρ(r) curves. Finally, the water ρ(r) curves reach their bulk density value (~1.0 g/cm^3) near the edge of the box at 35 Å (α-$C_{12}G_2$) and 38 Å (β-$C_{12}G_2$) from the micelle COM.

D. Hydration of the headgroup

As discussed in the previous section, radial mass density profiles show significant interaction between water and the $C_{12}G_2$ surfactant headgroups. To gain insights on this

aspect, we provide in the Table 3 some surface area (SA) properties of the micelles computed from the last 11 ns of the simulations. We first compare the instantaneous value of the SA per surfactant headgroup (SA_{HG}^{C12G2}) with the results of Dupuy *et al.*[13] obtained from SAXS and SANS experiments assuming that the α- and β-micelles are spherical. As described by these authors SA_{HC}^{C12G2}, the surface of the hydrophobic core of a sphere of radius $\bar{R}^{HC}$ was calculated. The average ellipsoid semi-axis of the micelle hydrophobic core $\langle a_{HC} \rangle$, $\langle b_{HC} \rangle$ and $\langle c_{HC} \rangle$ were used to calculate $\bar{R}^{HC}$with the expression: $\bar{R}^{HC} = (\langle a_{HC} \rangle \langle b_{HC} \rangle \langle c_{HC} \rangle)^{1/3}$. The average values of SA_{HG}^{C12G2} ($\left\langle SA_{HG}^{C12G2} \right\rangle$ are reported in the third column of the Table 3. We found that the $\left\langle SA_{HG}^{C12G2} \right\rangle$ values are in the range of 60.3 to 61.1 Å^2 and 55.5 to 65.1 Å^2 for the $C_{12}G_2$ α- and β-anomers, respectively. Values obtained with CHARMM-Opt and GLYCAM06 agree well with the experimental values (58 Å^2 and 52 Å^2 for the $C_{12}G_2$ α- and β-anomers, respectively), whereas the CHARMM-K results are further away.

In the 4th and 5th columns of the Table 3 are reported the average surface areas (SA) for the whole micelles $\left\langle SA_v^{C12G2} \right\rangle$ and $\left\langle SA_e^{C12G2} \right\rangle$, respectively. The SA_v^{C12G2} values were obtained from the Voronoi construction[90] by adding up the surface area of each Voronoi polyhedron shared between all surfactant atoms and water.[91] Instead, $\left\langle SA_e^{C12G2} \right\rangle$ was the ellipsoidal surface of the micelle obtained from the average semi-axis lengths ($\langle a_M \rangle$, $\langle b_M \rangle$ and $\langle c_M \rangle$) computed in section II.B. Comparison of the two values confirms that the micelle interfaces are corrugated (as also shown in Figure 1). Indeed, the surface rugosity factors $f_s = SA_v^{C12G2}/SA_e^{C12G2}$ was calculated between 1.7 and 2.1 and between 1.64 and 2.0 for the α- and β-anomers, respectively.

In the 6th column of Table 3, we also provide the average $C_{12}G_2$ surface alkyl chain ratio of the micelles, $\langle f_{tail} \rangle$ in contact with the solvent. The $\langle f_{tail} \rangle$ values were calculated with the SA_v^{C12G2} and the surface area of the alkyl chain atoms, SA_v^{C12}. $\langle f_{tail} \rangle$ values for all the micelles decrease by ~1.0 % when the surfactant head changes from the α- to the β-anomer and are calculated between 9.8 and 11.1 % and between 9.3 and 10 % for the α- and β-anomers, respectively. The lower $\langle f_{tail} \rangle$ values of GLYCAM06 indicate that for those micelles the surfactant alkyl chains of the micelle are more protected from the solvent than those obtained in the simulations with the CHARMM force fields. In comparison, the $\langle f_{tail} \rangle$ values reported in this work are lower than those found by Stephenson *et al.*[51] for a micelle with 45 β-$C_{12}G_2$ (~17.0 %), and also lower than for micelles with 27 octyl-β-galactose[47] (~30%) and 92 octyl-β-glucose monomers (20%).46 The latter is probably due to the smaller size of the headgroup in those micelles, which shields less the micelle hydrophobic core from water.

The average number of water molecules, $\langle n_w \rangle$, in the first solvation shell of each surfactant, or hydration number, were also computed during the last 11 ns of each run. They are presented in Table 4. For each configuration, the hydration water molecules were selected using a simple cutoff radius criterion, as described in ref.92. Briefly, a water molecule is considered near the micelle surface if its distance with any of the detergent atoms is less than $R_{cut} = f(R_w + R_{C12G2})$, where R_w and R_{C12G2} are the force field van der Waals radii of the water and of the $C_{12}G_2$ atoms, respectively, f is a parameter set arbitrarily to 1.1 in our calculations.[92] Five hydration numbers were calculated here: for the whole $C_{12}G_2$ molecule ($\left\langle n_w^{C12G2} \right\rangle$), for the headgroup ($\left\langle n_w^{G2} \right\rangle$), for the GlcA ($\left\langle n_w^{GlcA} \right\rangle$) and GlcB ($\left\langle n_w^{GlcB} \right\rangle$) units and for the alkyl chain ($\left\langle n_w^{C12} \right\rangle$). For all $\langle n_w \rangle$'s, higher values are found for the simulations obtained with CHARMM-K, whereas the $\langle n_w \rangle$'s of CHARMM-Opt and GLYCAM06 simulations are

close to one another. The $\langle n_w^{G2} \rangle$ value for CHARMM-Opt and GLYCAM06 are computed around 8.2 - 7.2, respectively, and compare well with the estimation of $\langle n_w^{C12G2} \rangle$ obtained from SANS, SAXS (8.0)[13] or TRFQ experiments for β-$C_{12}G_2$ micelle (7.9).[75] The bent conformation of the α-$C_{12}G_2$ slightly increases the headgroup hydration by 0.4 - 0.6 waters for the micelles simulated with the CHARMM-Opt and GLYCAM06 parameters, whereas for CHARMM-K the $\langle n_w^{G2} \rangle$ decreases by 0.3 units. For maltose molecules in water, hydration numbers between 5.7 and 22.6 are estimated by experimental studies, whereas values within 6.5 - 14.5 are obtained from computer simulations (see Table 3 of ref.33 and references therein). The validity of these results depends on the experimental techniques or the force field considered. Comparison of the hydration of the glucose rings GlcA and GlcB show that the number of water molecule around GlcB, connected to the alkyl chain, is, on average, ~2.6 units lower than for GlcA. This is independent of the force field employed and the conformation of the headgroup. Finally, the low values for $\langle n_w^{C12} \rangle$ (< 1.0 water) confirm that the micelle hydrophobic core have only sporadic contacts with the solvent consistently with the $\langle f_{tail} \rangle$ value calculated in this work.

To further examine the headgroup hydration, in Table 5 we provide the average number of nearest water for each maltose-oxygen, or $\langle n_{Ox-Ow} \rangle$, obtained from the computed radial pair density functions (RDF) of the maltose-oxygen ($O_{1\text{-}10}$) and water-oxygen (O_w) atoms. To obtain $\langle n_{Ox-Ow} \rangle$ the RDF functions were integrated until the first minimum at r ≈ 3.5 Å after the first peak. The $\langle n_{Ox-Ow} \rangle$ results indicate that water molecules solvate primarily the hydroxyl oxygen atoms (O_1, O_2, O_3, O_4,O_6, O_8, O_9 and O_{11}) of the maltose headgroup. This is consistent with previous simulation studies performed on other glycolipid micelles.[44,46,47] The number of water molecules in the first shell of these atoms are found between 1.9 and 3.7 as a function of the oxygen localization on the headgroup. These values vary little with the force field employed and the surfactant conformation. In general, the higher $\langle n_{Ox-Ow} \rangle$ values are obtained for the oxygen atoms O_3 (2.9 - 3.4) and for O_6 (3.2 - 2.4), the most the atoms are exposed to the solvent in GlcA. As an example, the hydroxyl oxygen O_{11} in GlcB has about one water molecule in its first shell that the equivalent atom O_6 in GlcA. The hydration of the ring oxygen atoms O_5 and O_{10} of GlcA and GlcB does not change much (~0.3 water) when the surfactant conformation changes from the α- to β-anomer. Finally, for the oxygen atoms involved in the glycosidic bond (O_1) and the link between the headgroup and alkyl chain (O_7), present low $\langle n_{Ox-Ow} \rangle$ values (< 0.8 and < 0.5) indicating that these oxygens are shielded from the solvent. This result is also consistent with another study, [46] where a $\langle n_{Ox-Ow} \rangle$ value close to 0.2 – 0.3 for O_7 was observed.

Considering the strong interaction between the $C_{12}G_2$ headgroup atoms and water, it is clear that the headgroup oxygen atoms will form an extended network of hydrogen bonds with water molecules and with donor groups of the detergent themselves.[93] The average number of HB between water molecules and the maltose headgroup (WHB) and within the surfactant headgroups (HHB), were computed for the last 11 ns of the simulations, using the following geometrical criterion: a HB was considered if the oxygen-oxygen distance equals or is smaller than 3.5 Å and the angle O-H…O was between 120 and 180°.[94] These values are reported in Tables S4, S5 and S6 of the supplementary information. We observed that each α-$C_{12}G_2$ molecule presents 0.5 - 1.0 more WHB than the β-anomer. These values vary only slightly with the force fields, CHARMM-K having the largest number of HB in α-$C_{12}G_2$ followed by CHARMM-Opt and GLYCAM06. This result is in agreement with small variations of hydration water in the first shell of the $C_{12}G_2$ headgroup and the decrease of $\langle n_{Ox-Ow} \rangle$ reported in the previous paragraph. We found that each $C_{12}G_2$ headgroup makes, on average, ~1.5 times more in the establishment of HB as an acceptor (~7.0) than as a donor (~5). This is consistent with previous computer simulations studies of C_8G_1 and

C_8Gal in water.[47] As also expected the total number of WHB obtained in this work is lower than the total WHB found for maltose in TIP3P water where the number of WHB (~15.9 and 22.4).[27,32] Further analysis of the individual HB donors and acceptors shows that the O_3 and O_6 (GlcA) and O_8 and O_9 (GlcB) hydroxyl oxygens make about one additional HB with water than the other oxygens. For these same oxygens, the number of WHB decreases by ~0.2 when the headgroup changes from the α- to the β-anomer. Finally, due to the strong entanglement of the maltose head at the micelle surface and to the low hydration of some of the hydroxyl oxygen atoms, it is expected that a large network of inter- and intra- headgroup donor/acceptor HB (INHB and INTHB, respectively) will be favored. Several inter-headgroup HB have been computed (among these previously examined by Chong *et al.*47) and are reported in the 5th to 9th columns in Tables S4, S5 and S6 in the supplementary information. The number of INHB is found to be much lower than the number of solvent-headgroup HB. On average, there are ~0.10 and ~0.25 HB per lipid for structures obtained from the CHARMM and GLYCAM force field simulations, respectively. The number of INHB is greater in β-$C_{12}G_2$ micelles and is due to the O_6-H…O_4, O_8-H…O_{10} and O_8-H…O_9 HB. Furthermore, three other INTHB were previously observed (O_6H_6…O_5 and $O_{11}H_{11}$…O_{10} in the first and second glucose rings and O_2H_2…O_9 between GlcA and GlcB).[27,28,94] These HB are correlated with the rotational freedom of the **ω** torsion angles and the **α**(l→4) glycosidic linkage flexibility. Our calculations indicate that these HB types exist during all of the simulations. In particular, O_2H_2…O_9 is present during approximately 70 - 80 % of the simulation times, whereas the two others INTHB only ~30 - 40 % of the time.

E. Conformation of the Surfactant

To examine in more detail the hydration differences of the micelles, we have studied the surfactant conformation by computing the main peak of the average end-to-end distance probability distributions P(r). Specifically, we have computed the d_{C12} and d_{G2} by collecting from the trajectories the distances between the atoms C_7 and C_{19} of the alkyl chain and between the O_4 and O_{12} of the maltose head, respectively. Since the d_{C12} and d_{G2} end-to-end distances are strongly related to the conformations of the alkyl tail and headgroup of the surfactant, respectively, we have examined the conformation of several characteristics torsion angles of the tail (such as all the CCCC dihedral angles, the first $C_7C_8C_9C_{10}$, and last $C_{15}C_{16}C_{17}C_{18}$ dihedrals)[44], the torsion angles involved in the connection of the alkyl chain and the maltose head (*i.e.* $O_7C_7C_8C_9$ [44], $O_{10}C_1O_7C_7$[27,95], $C'_1O_7C_7C_8$28,96) and **ω**1 and **ω**2 angles (i.e. $O_6C_6C_5O_5$[95] and $O_{11}C_6C_5O_{10}$64) by computing the corresponding normalized dihedral angle distribution P(**ϕ**). These functions were computed and averaged over the last 11 ns of each run. The relative gauche^{+-} ($p_g{}^{+-}$) and *trans* (p_t) populations were also extracted and are presented in Table 6. P(r) functions for the two CHARMM simulations (not shown here) display similar shapes with a strong peak at d_{C12} ≈12.3 Å for all the micelles regardless of the surfactant headgroup anomer. This is ~10.9 % smaller than the value (~14.0 Å) calculated for an extended dodecane chain with the modeling program Discovery Studio Visualizer. In contrast to the CHARMM results, the alkyl tail P(r) functions for the two micelles simulated with GLYCAM06 parameters present two peaks at d_{C12} ≈ Å and d_{C12} ≈ 13.8 Å (figures not shown) indicating a coexistence of two populations for the alkyl chain length. In the literature, a smaller value for d_{C12} is strongly related to the partial folding of the hydrophobic chain in the micelle core and existence of "*gauche defaults*".[97,98] In this context, we found that the CCCC dihedral angles of the alkyl chain are mostly in their *trans* state with relative populations p_t close to 72.0 % and 84.6 % for the CHARMM and GLYCAM06 force fields, respectively. These results are consistent with previous simulations of micelles containing surfactant with a dodecane chain (see for instance refs 99, 100, 59). As for the CHARMM simulations, the peaks in P(r) peaks do not change much (< 1 %) when going from an axial (α-) to an equatorial (β-) conformation of the surfactant headgroup (see Table 6). Further investigation shows that the outermost and

innermost CCCC dihedral angles (i.e. $C_7C_8C_9C_{10}$ and $C_{15}C_{16}C_{17}C_{18}$) have a larger gauche^{+-} population, $p_{g+-} \approx 27$ %, than the others dihedrals in the alkyl chain, $p_{g+-} \approx 15$ %. Similar results were found in previous MD simulations of octyl-β-glucoside micelles[44], where the lower steric conflicts found at the extremities of the alkyl chains decrease the gauche conformation of the chain. Finally, we find only small differences, less than 12 % in p_t, in the CCCC angles between the CHARMM and GLYCAM06 simulations. Similar behaviors were obtained in simulations of LDAO micelles simulated with the CHARMM27 and AMBER94 force fields, $p_t \approx 71.0$ % and $p_t \approx 82.8$ %, respectively.[101]

In our simulations, the $O_7C_7C_8C_9$ dihedral angle remain in a *trans* state, in agreement with previous simulations of octyl-β-glucoside micelles.[44] Nevertheless, we found that CHARMM-Opt has a p_{g+-} 25 % smaller than that of CHARMM-K, closer to GLYCAM06 and in agreement with QM/MM calculations carried for the α- and β-anomers of maltose.[67] For the $O_{10}C_1'O_7C_7$ (**Φ**) dihedral angle we observed that for all the simulations, this angle is in gauche$^+$ (> ~ 90 %) for the α- and β-anomers. Also, our results show that for all the micelles the **Ψ** dihedral angle, $C_1'O_7C_7C_8$, is always found in a *trans* state. Compared to CHARMM-K, in CHARMM-Opt the p_t of this angle decreases by ~13 units to 18 % depending on the anomer, and is closer to the values obtained for the GLYCAM force field.

In the last two rows of Table 6, we have listed for all the simulations, the average relative population of the two **ω** dihedral angle in the reducing (GlcA) ($\boldsymbol{\omega}_1 = O_6C_6C_5O_5$) and non-reducing (GlcB) ($\boldsymbol{\omega}_2 = O_{11}C_6'C_5'O_{10}$) glucose units of the maltose head. In glucopyranose, due to rotational freedom of the **ω** dihedral angle, three stable conformers exist, defined by the position of the OH oxygen relative to oxygen ring atoms (here, O_5 and O_{10}), termed *gauche-gauche (gg)*, *gauche-trans (gt)*, and *trans-gauche (tg)* which correspond to **ω**= -60°, -60° and 180°.[102, 103,104] Computational results on maltose have shown that **ω** has a strong preference for gauche values.[58,105] This is due to steric repulsions between the hydroxyl groups in position 4 and 6, described as the "gauche effect".[106]

In contrast to maltose in vacuum, where the **ω** angle adopts preferentially a *gt* conformation, for maltose in solution, MD simulations performed in condensed phase[28,37] and experimental studies[107] have shown that the *gg* conformation is favored, Our results for CHARMM-K and CHARMM-Opt show a different behavior for **ω**, for which the conformation *gt* is favored with respect to *gg* (*gt*/*gg* ≈60:40). For GlcB, we find that these angles are mainly in its *gg* conformation except for the β- anomer where $\boldsymbol{\omega}_2$ highly similar *gg* and *gt* populations. These results, can be explained by the incomplete hydration of the maltose headgroup in the detergent and the existence of inter maltose HB.

Turning our attention to the maltose head linkage conformation, the P(r) functions (not shown here) present peaks at $d_{G2} \approx 8.8$ Å (α-anomer) and $d_{G2} \approx 9.8$ Å (β-anomer). These values change slightly (0.2 Å) with the potential employed and are smaller than the length for a maltose molecule in an elongated conformation (10.3 Å, with $\boldsymbol{\Phi}_H = \boldsymbol{\Psi}_H = 0.0°$). On Figure 6, we have plotted the distribution maps of the P($\boldsymbol{\Phi}_H$,$\boldsymbol{\Psi}_H$) glycosidic dihedral angles pair in population percentage for all simulations. We find that, except for the α-$C_{12}G_2$ micelle simulated with the new CHARMM potential, all of the P($\boldsymbol{\Phi}_H$,$\boldsymbol{\Psi}_H$) present a compact elliptic shape with a maximum point near (-40°, -25°) ± 10°. In the former system, instead, two areas are sampled, around (-25°; -20°) and (-65°; -50°), for 70 % and 30 % of the total simulation time, respectively. It is difficult to validate these results, as no experimental data exist in the literature for P($\boldsymbol{\Phi}_H$,$\boldsymbol{\Psi}_H$) of $C_{12}G_2$ micelles and these results differ for a maltose molecule in water where experimental (such as NMR[32,38,108,109 or optical rotation 110) and theoretical studies (such as QM[38,111,112 and MD 28,32,37,69,113) predicted two peaks for P($\boldsymbol{\Phi}_H$,$\boldsymbol{\Psi}_H$) around (-50°; -30°) ± 20° and (-40°; -30°) ± 20°.

F. Water Dynamics at the Micelle Surface

To examine the dynamic behavior of water molecules around the micelles, we have computed the mean square displacement (MSD) of the translational diffusion $\langle|r(t) - r(0)|^2\rangle$ for water molecules at the micelle surface. Water molecules included in this calculation were at a distance of less than 4.0 Å from any detergent molecule at a given time of the trajectory (details about the calculation are available in ref.47). For the different micelles studied in this work, the MSD functions are shown in Figure 6 and the translational diffusion parameters are reported in Table 7. MSD functions are compared with the results obtained from a NPT simulation (T = 297 K and P = 0.1 MPa) for 1000 TIP3 water molecules simulated in a cubic box for 1 ns. As shown previously for water molecules near protein surfaces [114,115], direct micelles[116,117] or reverse micelles[79,118] the water MSD presents a sub-diffusive regime and can be fitted with a power law (*i.e.* $\langle|r(t) - r(0)|^2\rangle \propto t^{\theta}$) rather than a linear dependence in time as observed in bulk water. This behavior is assumed to be the consequence of the geometric/energetic disorder found at the micelle and protein surfaces.[114] For all micelles, the fit to a power law leads to similar values for θ, around 0.34 and 0.40. These values are comparable to the θ values found previously by one of us (MM) for water around the $C_{12}E_6$ micelle surface (0.3 and 0.4 at T = 283 K and 318 K, respectively).[117] In this micellar system, it has been shown that the water interact with the long hydrophilic ethylene oxide $(EO)_6$ chain through a large hydrogen bonds network.[119] For a subdiffusive regime, it is useful to define a rough estimate of the water residence time, τ_w, as the time needed by a water molecule to cover a distance of 9 $Å^2$, i.e. corresponding to a path spanning a water molecular diameter.[120] The ratio, between τ_w and the residence time of the bulk water values (τ_w^b = 2.7 ps) are reported in the 4th and 5th rows in Table 7. We find that the τ_w values change significantly with the force field employed, but not with the surfactant headgroup conformation. τ_w values are calculated for all the simulations between 18.9 and 30.5 ps. In the GLYCAM06 simulations, water dynamic retardation, or τ_w^b/τ_w, are ~ 11.3 for the α- and 11.7 for the β-anomers. The differences obtained for water diffusion is probably the results of the headgroup conformation variations and the number of trapped water at the micelle interface for the six micelles.

To the best of knowledge, no experimental data on water dynamics are available for $C_{12}G_2$ micelles. Notwithstanding, Chong *et al.*[47] have computed the residence time of water near each headgroup oxygen atoms for micelles of octyl-glucose (C_8G_1) and galactose (C_8Gal). The authors found that τ_w maximum values are between 41.0 - 164.0 ps (C_8G_1) and 28.4 ps - 88.0 ps (C_8Gal) depending the localization of the hydroxyl group in the headgroup and the cutoff employed. The largest τ_w values are found for water molecules trapped within the crevices and clefts at the micelle surface. Finally, the τ_w values obtained here largely exceed the average residence time found by MD for water in the first shell of maltose (~11.6 ps) in water [31] or in QENS experiments at 320 K (~3.4 ps).121

IV. Conclusion

In this paper, we have presented the development of two new potential models, based on the CHARMM36 and GLYCAM06 force fields, to be used in the molecular modeling of the α- and β-anomers of $C_{12}G_2$ GL. These surfactants are widely employed to extract and solubilize membrane proteins. To validate these potentials, we have investigated the structure of significant $C_{12}G_2$ micelles by MD simulations. In particular, we have studied the structural properties of the micelles with the two anomeric forms, and described the dynamical properties of water molecules at the micelle/water interface. The results obtained for the new potentials were also compared with those obtained with older parameters developed for carbohydrate for CHARMM22.

We found that the three force fields studied here lead to different results particularly for the properties related to the headgroup conformation and micelle hydration. In particular, our calculations show that the α- and β-$C_{12}G_2$ micelles have a $\langle R_g \rangle$ close to 20.2 Å and 25.4 Å, respectively. The computed $\langle R_g \rangle$'s agree reasonably well with SAXS and SANS experiments[13] when the micelles are simulated with the new parameters developed for CHARMM36 CHARMM and GLYCAM06.

Concerning the global shape of the micelles, we observed no significant differences between the three force fields and the different micelles studied. The α-$C_{12}G_2$ micelles have an average major-to minor semi-axis ratio $\langle a_M/c_M \rangle$ close to 1.20 whereas the β-$C_{12}G_2$ micelle has a more pronounced oblate shape with $\langle a_M/c_M \rangle$ values around 1.38 - 1.43, in qualitative agreement with published experimental observations.[13,26,75] The computed radial density profiles indicate that water penetrates deeply at the micelle headgroup and hydrates preferentially the outermost glucose ring (GlcA). Due to the difference in the surfactant headgroup conformations, we also observed slight differences in the headgroup hydration. Consistently with previous simulations carried out with others glycolipid systems,[44,46,47] we found that the micelle/water interfaces are highly corrugated with a rugosity factor values around 1.6 - 2.0. The average solvent surface area for the α- and β-$C_{12}G_2$ anomers simulated with CHARMM-Opt and GLYCAM06 are found to be around 60.6 $Å^2$ and 55.5 $Å^2$ per molecule, respectively, which is close to experimental values.[13]

Concerning micelle hydration, we found that the alkyl chains of $C_{12}G_2$ are in all the cases sturdily protected from the solvent, as less than ~10% of the water penetrate the micelle core. Due to the strong entanglement of the maltose head at the micelle surface, within each micelle we observed a large hydrogen bond network consisting in a complex combination of inter- and intra-HB between adjacent headgroups. HB between water and headgroups do not depend on the headgroup conformation, as we found a highly similar patterns for headgroup/water HB's for both α- and β-anomers (with only on average ~0.6 units of difference).

Finally, investigations of the dynamic behavior of the hydrating water for all the micelles show that the water translational diffusion is strongly retarded with respect to the bulk by a factor of 7.0 to 11.7, depending on the potential. Interestingly, the headgroup conformation does not affect the water diffusion for the three force fields examined here. In particular, water diffusion results near the micelle interface are similar for CHARMM-Opt and GLYCAM06 (~ 8.5 and ~ 11.7 smaller than for the bulk, respectively) and are ~1.5 time larger than the diffusion values obtained in CHARMM-K based simulations

In conclusion, the molecular modeling and simulation results reported in this paper are a first and necessary step to improve our atomic level knowledge of the $C_{12}G_2$ micelles. In addition, because our potential parameters are consistent with two major protein force fields (CHARMM and AMBER) they offer a solid starting point for further studies on the interaction and aggregation of membrane proteins with $C_{12}G_2$ detergents.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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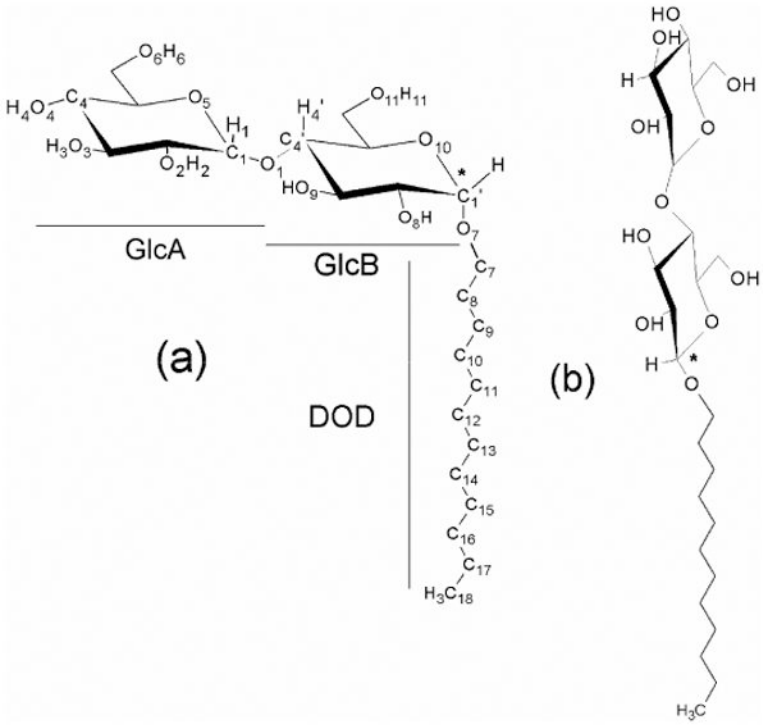

Figure 1.

The α- (a) and β-anomers (b) of $C_{12}G_2$ surfactants with the atom numbering scheme used in the paper. The anomeric center C_1' of the molecule is underlined with a star.

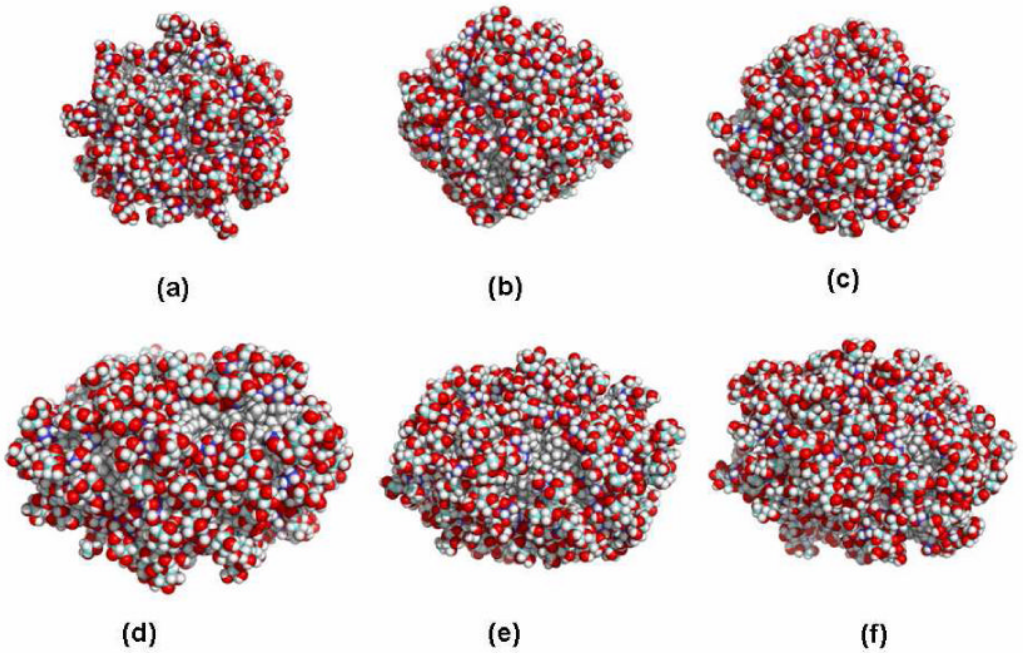

Figure 2.

Representative MD Snapshots of the α- (a-c) and β-anomers (d-f) of $C_{12}G_2$ micelles simulated with the CHARMM-Opt force field at t≈240 fs (a, d), t≈7.0 ns (b, e) and (c, f) and t ≈14 ns of the production period. Oxygen and hydrogen are in red, and white colors. Carbons in GlcA, GlcB and in the alkyl chain are blue, cyan and gray respectively. Water molecules are removed for visual clarity. Figures were produced with the PyMOL program.[122]

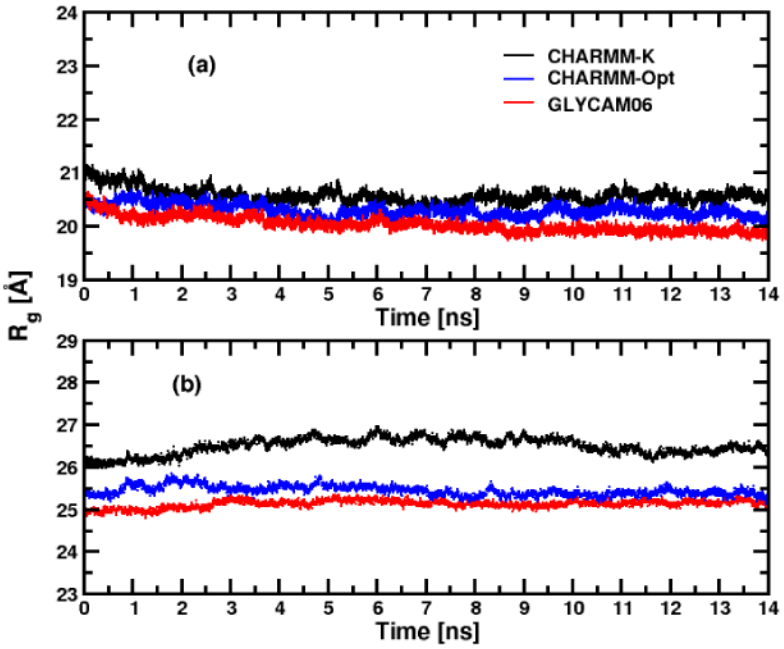

Figure 3.
Time evolution of the radius of gyration, R_g, for α- (a) and β-anomers (b) of $C_{12}G_2$ micelles.

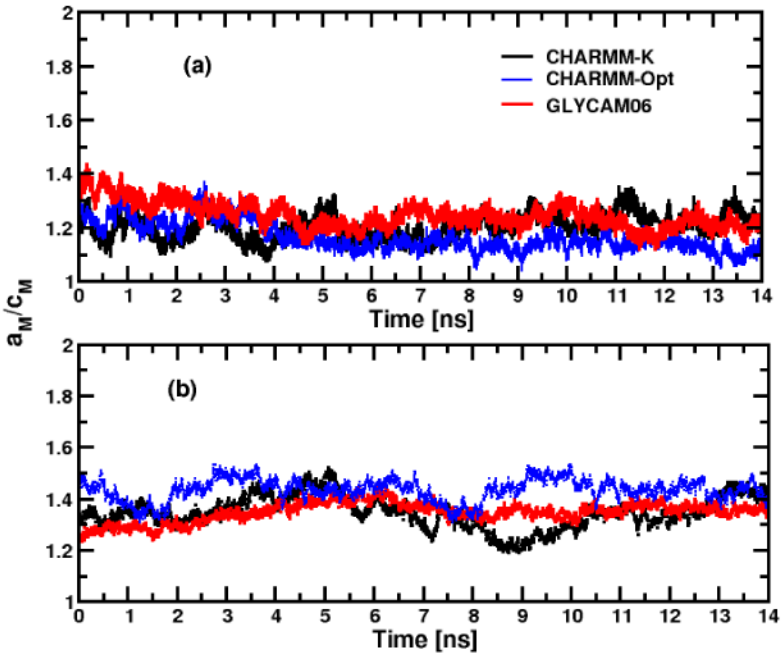

Figure 4.
Time evolution of the major and minor semi-axis of inertia ratio for α- (a) and β-anomers (b) of $C_{12}G_2$ micelles.

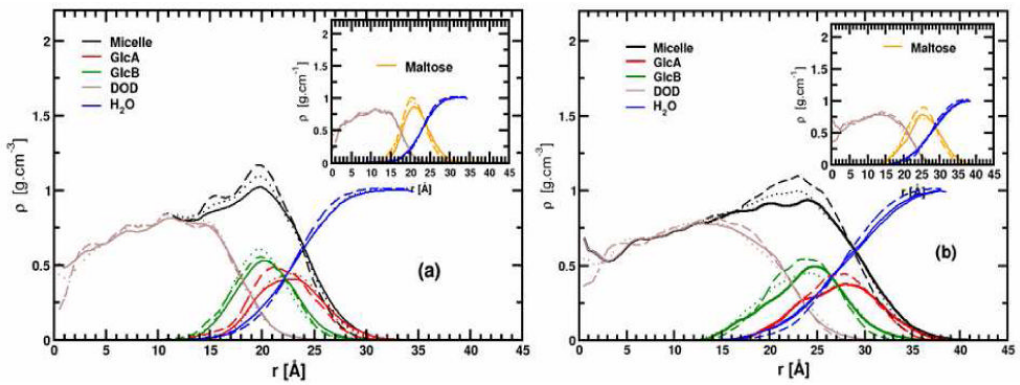

Figure 5.

Average radial density profiles with respect to the center of mass (r = 0 Å) for simulations performed with CHARMM-K (continuous line), CHARMM-Opt (dotted lines) and GLYCAM06 force fields (dashed line) for micelles α- (a) and β-anomers (b) of $C_{12}G_2$ micelles. In the inset, the radial profiles for the micelle hydrophobic core (maroon), the maltose headgroup (orange) and water (blue) are plotted. A 0.5 Å bin width was used for both figures.

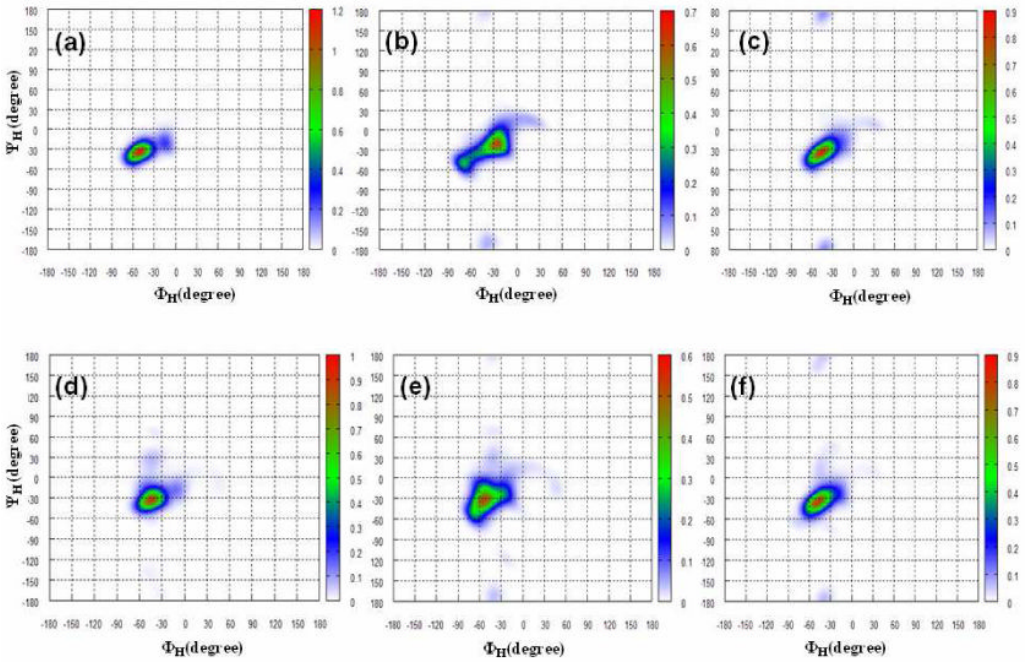

Figure 6.

Distribution map of the Φ_H/Ψ_H glycosidic dihedral angles pairs in population percentage for α- (a) and β-anomers (b) of $C_{12}G_2$ micelles for the CHARMM-K ((a) and (d)), CHARMM-Opt ((b) and (e)) and GLYCAM06 ((c) and (f)) force fields, respectively. The grid interval is 5.0° and contour lines are spaced every 0.2 %.

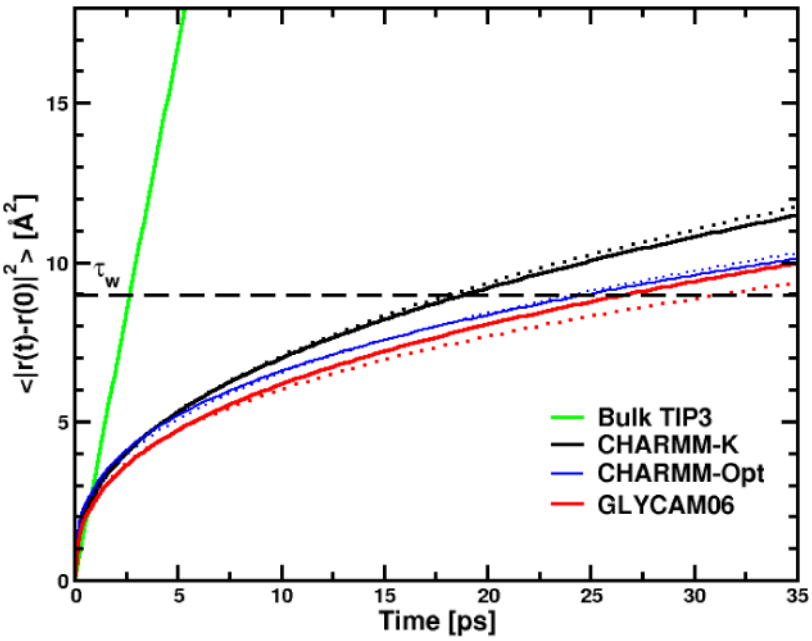

Figure 7.
Interfacial water mean square displacement (MSD) as function of time for α- (continuous line) and β-anomers (dotted line). The black dashed line gives the distance for computing the residence time τ_w (see the main text).

Table 1
Simulations parameters for the micelle simulations

N_{C12G2}, N_{H2O}, and N_{atm} are the numbers of *N*-dodecyl-ß-*D*-maltopyranoside monomers ($C_{12}G_2$), water and atoms composing the simulated systems. m_{C12G2}/m_{Tot} is the weight concentration (in %) of $C_{12}G_2$ in each system. t_{sim} is the simulation time (the 300 ps equilibration period was excluded from the analysis).

System	α-$C_{12}G_2$	β-$C_{12}G_2$
N_{C12G2}	75	132
N_{H2O}	13771	18389
N_{atm}	47388	65859
m_{C12G2}/m_{Tot}	13.4	16.9
T (K)	297	297
t_{sim} (ns)	14.0	14.0
ρ (g/cm^3)	1.02 ± 0.01	1.03 ± 0.01

Table 2

Average dimensions and shapes of the six micelles

$\langle ... \rangle$ stands for the ensemble average. Values with M and HC subscripts were computed by including all the micelle atoms and those of the hydrophobic core, respectively. The radii of gyration and the semi-axis lengths were computed using the inertia tensor (e.g. see ref. 79) and the main text for details. $\langle l_{pl} \rangle$ is the average polar layer thickness of the micelle in Å. The statistical errors (maximum errors) are always lower than 0.1 Å, 0.8 Å and 0.3 Å for the R_g, semi-axis lengths and polar layer thickness, respectively.

Force field	Micelle	$\langle R_g \rangle$	$\langle a_M \rangle$	$\langle b_M \rangle$	$\langle c_M \rangle$	$\langle a_M/c_M \rangle$	$\langle a_{HC} \rangle$	$\langle b_{HC} \rangle$	$\langle c_{HC} \rangle$	$\langle l_{pl} \rangle$
CHARMM-K	α-$C_{12}G_2$	20.5	28.4	25.6	23.8	1.20	22.1	19.1	16.5	6.7
	β-$C_{12}G_2$	26.4	38.8	34.7	28.1	1.38	33.1	27.3	20.0	7.2
CHARMM-Opt	α-$C_{12}G_2$	20.2	27.8	26.1	24.3	1.14	21.5	19.1	16.7	7.0
	β-$C_{12}G_2$	25.4	38.1	33.0	26.5	1.43	30.6	24.8	19.3	7.7
GLYCAM06	α-$C_{12}G_2$	20.0	28.4	25.5	23.1	1.23	22.3	18.6	16.5	6.5
	β-$C_{12}G_2$	25.2	37.2	32.0	30.1	1.38	30.1	24.4	19.2	7.2

Table 3

Surface properties of the micelles

$\langle ... \rangle$ stands for the ensemble average. SA_{HG}^{C12G2} (in $Å^2$) are the average surface area per headgroup computed using the micelle oil core radius. SA_v^{C12G2} and SA_e^{C12G2} are the average micelle surfaces computed with the Voronoi polyhedron, [90] assuming an ellipsoid-like geometry for the micelle. $\langle f_{tail} \rangle$ is the average surface fraction shared between the water and the $C_{12}G_2$ alkyl chain. The statistical errors (maximum errors) are always lower than 3.0 % and 0.2 % for the surfaces and $\langle f_{tail} \rangle$ values.

Force field	Micelle	$\langle SA_{HG}^{C12G2} \rangle$	$\langle SA_{V}^{C12G2} \rangle$	$\langle SA_{e}^{C12G2} \rangle$	$\langle f_{tail} \rangle$
CHARMM-K	α-$C_{12}G_2$	61.1	19425.0	9244.5	11.0
	β-$C_{12}G_2$	65.1	33237.6	16581.5	10.0
CHARMM-Opt	α-$C_{12}G_2$	60.4	17625.0	9013.2	10.9
	β-$C_{12}G_2$	56.8	29422.8	15894.6	9.3
GLYCAM06	α-$C_{12}G_2$	60.3	15675.0	9146.6	9.8
	β-$C_{12}G_2$	55.5	25726.8	15666.0	9.3

Table 4

Hydration numbers

$\langle ... \rangle$ stands for the ensemble average. $\langle n_w^{G2} \rangle$, $\langle n_w^{GlcA} \rangle$, $\langle n_w^{GlcB} \rangle$, $\langle n_w^{C12} \rangle$ and $\langle n_w^{C12G2} \rangle$ give the average number of water molecule at 4.0 Å of the maltose head, the outermost and innermost glucose rings and the alkyl chain, respectively. The statistical errors (maximum errors) are always lower than 0.1 %.

Force field	**CHARMM-K**		**CHARMM-Opt**		**GLYCAM06**	
System	α-$C_{12}G_2$	β-$C_{12}G_2$	α-$C_{12}G_2$	β-$C_{12}G_2$	α-$C_{12}G_2$	β-$C_{12}G_2$
$\langle n_w^{G2} \rangle$	8.3	8.6	8.2	7.6	7.6	7.2
$\langle n_w^{GlcA} \rangle$	5.2	5.6	5.2	5.1	4.7	4.9
$\langle n_w^{GlcB} \rangle$	3.1	3.0	3.0	2.5	2.9	2.3
$\langle n_w^{C12} \rangle$	0.8	0.8	0.8	0.7	0.6	0.6
$\langle n_w^{C12G2} \rangle$	9.1	9.4	9.0	8.3	8.2	7.8

Table 5

Nearest neighbors for the micelle oxygens

The micelle oxygen atoms are labeled as it followed: O_1 and O_7 are the acetalic oxygens, O_5 and O_{10} are the maltose ring oxygens and all the remaining are hydroxyl oxygens (see Figure 1). Also, $\Delta_{\beta-\alpha}$ is the difference in the average number of nearest neighbors between the β- and α-anomers. The values have been obtained by integrating the O_x-O_w pair correlation functions *g(r)* up to the first minimum at around r≈3.5 Å. Total GlcA and Total GlcB give the average nearest neighbors for the outermost and innermost glucose unit of the molecule, respectively.

Force field	**CHARMM-K**			**CHARMM-Opt**			**GLYCAM06**		
$\langle n_{Ox-Ow} \rangle$	α-$C_{12}G_2$	β-$C_{12}G_2$	$\Delta_{\alpha\rightarrow\beta}$	α-$C_{12}G_2$	β-$C_{12}G_2$	$\Delta_{\alpha\rightarrow\beta}$	α-$C_{12}G_2$	β-$C_{12}G_2$	$\Delta_{\alpha\rightarrow\beta}$
O_1-O_w	0.7	0.8	0.1	0.5	0.5	0.0	0.5	0.4	-0.1
O_2-O_w	2.3	2.7	0.4	2.5	2.3	-0.2	2.1	2.6	0.5
O_3-O_w	3.6	3.7	0.1	2.9	3.2	0.3	3.0	3.4	0.4
O_4-O_w	2.0	2.6	0.6	2.3	2.6	0.3	1.9	2.4	0.5
O_5-O_w	1.1	1.3	0.2	1.3	1.0	-0.3	1.3	1.0	-0.3
O_6-O_w	3.1	2.5	-0.6	2.6	2.3	-0.3	3.2	2.4	-0.8
Total GlcA	12.8	13.6	0.8	12.1	11.9	-0.2	12.0	12.2	+0.2
O_7-O_w	0.2	0.5	0.3	0.3	0.3	0.0	0.2	0.4	0.2
O_8-O_w	2.4	1.9	-0.5	1.9	1.6	-0.3	1.7	1.5	-0.2
O_9-O_w	2.4	2.0	-0.4	2.2	1.8	-0.4	2.2	1.6	-0.6
O_{10}-O_w	0.8	0.9	0.1	0.7	0.6	-0.1	0.6	0.8	0.2
O_{11}-O_w	2.0	1.7	-0.3	1.7	1.6	-0.1	1.8	1.3	-0.5
Total GlcB	7.8	7.0	-0.8	6.8	5.9	-0.9	6.5	5.6	-0.9

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Table 6

Trans and Gauche populations

Dihedral angles between -180° and -120°, between -120° and +120° and between +120° and +180° are defined as gauche$^+$ (p_g^+), trans (p_t) and gauche$^-$ (p_g^-), respectively. The exponents a, b and c are for ^{a}gauche^{+-}, ^{b}gauche$^+$ and ^{c}gauche$^-$, respectively. The statistical errors (maximum errors) are always lower than 0.3 %. See the main text for details.

Force field	**CHARMM-K**		**CHARMM-Opt**		**GLYCAM06**	
Micelle	α-$C_{12}G_2$	β-$C_{12}G_2$	α-$C_{12}G_2$	β-$C_{12}G_2$	α-$C_{12}G_2$	β-$C_{12}G_2$
CCCC	71.8, 28.2^a	72.0, 28.0^a	71.4, 28.6^a	72.1, 27.9^a	84.6, 15.4^a	84.7, 15.3^a
$C_7C_8C_9C_{10}$	67.4, 32.6^a	70.9, 28.1^a	66.7, 33.3^a	67.7, 32.3^a	82.0, 18.0^a	80.0, 20.0^a
$C_{15}C_{16}C_{17}C_{18}$	73.3, 26.7^a	75.4, 24.6^a	70.8, 29.2^a	68.5, 31.5^a	81.0, 19.0^a	82.8, 17.2^a
$O_7C_7C_8C_9$	80.5, 20.5^a	80.6, 20.4^a	54.4, 46.6^a	53.3, 47.7^a	61.8, 38.2^a)	63.0, 37.0^a
$O_{10}C'_1O_7C_7$	2.3, 97.7^b	0.1, 99.9^c	0.5, 99.5^b	4.9, 95.1^c	2.4, 97.6^b	6.7, 93.3^c
$C'_1O_7C_7C_8$	90.1, 8.9^a	89.1, 10.9^a	71.7, 28.3^a	76.4, 23.6^a	81.7, 18.3^a	78.1, 11.9^a
$O_6C_6C_5O_5$ (**ω**$_1$)	59.0^b, 43.7^c	59.3 ^{b}, 39.4^c	60.9^b 35.0^c	51.6^b, 39.3^c	51.7^b, 44.7^c	50.9^b, 44.5^c
$O_{11}C_6C_5O_{10}$ (**ω**$_2$)	24.5^c, 75.3^c	37.0 ^{b}, 54.4^c	36.7^b, 60.0^c	29.9^b, 26.7^c	30.9^b, 65.9^c	37.1^b, 53.9^c

Table 7

Translational diffusion of the hydration waters

θ is the dispersion regime parameter obtained by fitting the $\langle |r(t) - r(0)|^2 \rangle$ function to t^{θ}. τ_w is the water residence time, defined as the time (in ps) for a water to cover a distance equal to its own diameter (*i.e.* 3 Å) and $\tau_w/\tau_w{}^b$ is the retardation or the ratio between the water residence time in the micelle and the bulk.

Force field	**CHARMM-K**		**CHARMM-Opt**		**GLYCAM06**	
System	α-$C_{12}G_2$	β-$C_{12}G_2$	α-$C_{12}G_2$	β-$C_{12}G_2$	α-$C_{12}G_2$	β-$C_{12}G_2$
θ	0.39	0.40	0.34	0.36	0.38	0.35
τ_w (ps)	18.9	18.3	24.8	24.8	27.2	30.5
$\tau_w/\tau_w{}^b$	6.7	6.5	8.5	8.5	11.7	11.3