Conformation, orientation and dynamics of dodecylphosphocholine in micellar aggregate: A 3.2 ns molecular dynamics simulation study

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A dodecylphosphocholine micelle of 86 monomers with 5776 water molecules has been simulated under NPT conditions for 3.2 ns using GROMACS2.0. The micelle was found to be very dynamic. Some of the C-C bonds, independent of their position in the DPC monomer, adopt gauche conformation and the trans → gauche transitions are quite frequent. An average of about 11% of the C-C bonds in the micelle are observed to be in the gauche conformation (i.e., dihedral angle < 120°). The terminal methyl groups are randomly distributed all over the micelle whereas the nitrogen atom of phosphocholine headgroup atoms is restricted to the interface region. Some of the monomers were found to lie on the surface. The shape of micelle, influenced by the packing considerations, shows deviations from spherical shape. The phosphocholine headgroup is well solvated and there is no water penetration into the micelle core. The overall features of the micelle of 86 DPC monomers conforms to the lattice model of micelle proposed by Dill and Flory [Dill K A, Flory P J (1981) Proc Natl Acad Sci USA 78, 676-680] and is similar to DPC micelles of smaller aggregate sizes except for the positional preference of the C-C bonds for the gauche conformation and the trans→gauche transition times [Tieleman D P, van der Spoel D, Berendsen H J C (2000) J Phys Chem B 104, 6380-6388; Wymore T, Gao X F, Wong T C (1999) J Mol Struct (Theochem) 485-486, 195-210]. It appears that packing considerations play a predominant role in determining the shape and dynamics of the micelle.

Micelles, especially those of dodecylphosphocholine (DPC), are being increasingly used as model systems to mimic bilayers in various experimental studies. This, together with improvements in methodology and computational resources, has led to an increasing number of molecular dynamics (MD) simulations to address issues related to the dynamic properties of lipid aggregates in aqueous media. Recently, MD simulation studies on the structure and dynamics of DPC micelles of varying aggregation sizes have been reported. In these studies, a DPC micelle of 54 monomers was simulated for 15.4 ns (referred to as M54 simulation henceforth); the length of the simulation for the other three aggregate sizes is 1.06 ns for micelles of 40 and 65 monomers (M40 and M65 simulations) and 1.2 ns for the micelle of 60 monomers (M60 simulation). A recent MD study of octylglucoside micelles of different aggregate sizes showed that the structural aspects of the micelles are strongly influenced by the structure of the amphiphile. It was also observed from this MD study on octylglucoside micelles that the accessible surface area (ASA) per lipid decreases with an increase in the aggregate size; in particular, the ASA for the hydrocarbon tail in the micelle of 75 monomers (largest aggregate size simulated by Bogusz et al.) was very close to the corresponding value for a bilayer.

The aggregation number of micelle has been shown to be influenced by impurities, temperature, nature and length of hydrocarbon chains, nature of the headgroup, salt concentration and the association of other molecules. It has also been suggested that micelles do not have one definite size but comprise a large range of aggregation numbers with a concentration maximum around a mean aggregation number. Although the aggregation number for pure DCP micelles has been found to be 56±5 at 20°C, for dodecyl detergent micelles in general, the aggregation number has been observed to range from 50 to 90 at 25°C. In this background, the present MD simulation study was undertaken to investigate, in atomic detail, the structure and dynamics of DPC micelle containing 86 monomers in presence of explicit water molecules. The results from the 3.2 ns MD study show that the overall dynamic features and the orientation and shape of the 86-monomers micelle is very similar to those of smaller aggregate size DPC.
micelles and GM1 embedded DPC micelle. Thus, within the range of 50 to 90 monomers per micelle observed for dodecyl detergent, the micellar dynamics seems to be fairly similar.

Methods

Standard values of bond lengths and bond angles were used for generating the coordinates of the atoms in the hydrocarbon tail of DPC; for generating the coordinates of the atoms in the phosphocholine moiety, the relevant values were taken from the single crystal structure of lysophosphatidylcholine analog (Fig. 1). DPC was taken initially to be in the all-trans conformation. The coordinates for the micelle were generated using the Euler’s rigid body rotation method as described earlier. Briefly, a molecule of DPC was oriented such that the terminal methyl group was offset by 5 Å from the origin and the hydrocarbon tail was along the X-axis in the XY-plane. Using this as template, fourteen DPC molecules were generated in the XY-plane by rotations around the Z-axis (angle $\phi$). This was accomplished by varying $\phi$ from 10 to 340 in increments of 25. In the next step, treating this set of 14 DPC molecules as a rigid body, rotations were performed around the X-axis by varying from 0 to 150 in increments of 25. This resulted in a micelle of 98 monomers. From this, 12 monomers were deleted by visual inspection to reduce crowding along positive and negative X-directions. The resulting micelle with 86 monomers was considered as the starting conformation for the simulation.

Berendsen and co-workers have simulated a DPC micelle of 54 monomers for 15.4 ns using GROMACS2.0 software and GROMOS96 force field. The relaxation behaviour of the lipid tail carbon atoms derived from this study was found to agree well with experimental observations. In the present study also, the GROMOS96 force field was used except for the fractional charges for the phosphocholine moiety, which are from Chiu et al. The simulations were run on Origin200 compute-servers using GROMACS2.0 (ref. 18, 19). The dielectric constant was set to 1. The steepest descent algorithm was chosen for energy minimization. The energy-minimized solute was placed in the center of a rectangular box of SPC water corresponding to a density of 1.03 g/cm$^3$. The final system for MD simulation had a micelle of 86 DPC monomers (1978 atoms) surrounded by 5776 water molecules in a rectangular box of size 6.12 x 5.97 x5.96 nm. The solvated system was energy minimized without constraints for 400 steps to remove close contacts of water molecules with solute. This was followed by a 1 ps equilibration run by position-restraining the solute atoms to relax the water molecules. The solute restraints were removed by further equilibrating the system under NVT conditions for 50 ps followed by 3150 ps of NPT run; this was run as jobs of 200 ps duration. Coordinates and velocities were saved at 2

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**Fig. 1**—Schematic showing the nomenclature used for the atoms of dodecylphosphocholine. Partial atomic charges (in e.u. from ref. 17) are also shown and are underlined. The atoms of choline moiety have been prefixed with a C to distinguish them from those of the dodecyl chain. CM1, CM2 and CM3 refer to methyl groups. The atoms enclosed in the dotted line constitute a charge group.
ps intervals. The equations of motion were integrated using Verlet’s leapfrog algorithm with a 2 fs time step and constraining all the bond lengths. Initial velocities were assigned from Maxwellian distribution corresponding to a temperature of 300 K using a random number generator. Temperature was maintained by separately coupling the solute and the solvent to a 300 K bath by weak coupling method ($\tau_T = 0.1$ ps). Pressure was maintained at 1 bar using isotropic pressure coupling ($\tau_P = 1.0$ ps). Periodic boundary conditions were applied and non-bonded interactions were calculated using a 1.5 nm neighbour list cut-off. The non-bonded atom list was updated after every 50 steps.

**Results and Discussion**

**Energy minimization and initial equilibration of the DPC micelle**

According to the lattice model of micelle proposed by Dill and Flory,$^{20}$ the terminal methyl groups are widely distributed in the micelle and some of the C–C bonds are in the gauche conformation. However, the positions of the terminal methyl groups in a micelle of 86 DPC monomers and of the gauche C–C bonds in the dodecyl chain are not known a priori. It is also not known how many of these C–C bonds are in the gauche conformation. Hence, the micelle was initially generated as radially symmetric with all the C–C bonds in the trans conformation. This micelle model was subjected to 400 steps of in vacuo energy minimization using GROMOS96 to relieve steric clashes, present mainly in the core of the micelle. The force constant $K_{\text{sn}}$ of the dihedral angle term was set to zero to facilitate free rotations around the C–C bonds. The innumerable steric clashes that were seen in the initial structure were observed to be relieved at the end of energy minimization. From visual inspection, it was also observed that some dihedral angles were no longer trans. However, several bond angles showed large deviations from the equilibrium values.

When the energy-minimized micelle was solvated, it was found that 6 water molecules were present within 12 Å from the center of mass of the micelle. This solvated micellar system was equilibrated restoring the $K_{\text{sn}}$ of the C–C bonds to its original value (i.e., $1.4 \text{ kCal.mol}^{-1}$). At the end of 200 ps of initial equilibration, the deviations in bond angles from the equilibrium values were found to be minimal (RMS deviation of 5.075 over 2322 bond angles) and 14% of the C–C bonds were found to be in the gauche conformation (i.e., $|\text{dihedral angle}| < 120^\circ$). At this stage of equilibration, 7 atoms were found within 5 Å from the center of mass. Thus, the core of the micelle, which was empty in the initial model due to the 5 Å offset, is no longer void; this points to the tendency of the micelle to pack its interior. Penetration of the water molecules into the micelle was also checked; it was found that the water molecule nearest to the center of mass is at 12 Å.

Subsequent to the initial 200 ps equilibration, simulation was continued for another 3 ns. However, to ensure that the properties of the micelle inferred from the simulation are accurate, trajectory information from only the final 500 ps (2.7 to 3.2 ns) was considered for analysis. The simulation for the remaining 2.5 ns duration (0.2 to 2.7 ns) was considered as an extended equilibration run.

**Analysis of the trajectory for the last 500 ps of the simulation**

**Conformation around the C–C bonds**

There are 774 C–C bonds in the micelle model considered in the present study (9 bonds per monomer and 86 monomers per micelle). These C–C bonds showed frequent transitions between the trans, gauche$^+$ and gauche$^-$ conformations. The percentage of these C–C bonds in the gauche conformation (i.e., $|\text{dihedral angle}| \leq 120^\circ$) varied between 8 and 12 (Fig. 2; average 10% with RMSD 0.92). It was found that all the C–C bonds, irrespective of whether they are towards the termini or are in the middle of the dodecyl chain, adopt the gauche conformation to almost the same extent (data not shown). However, the C–C bonds adjacent to the phosphocholine

![Fig. 2](image-url)

Fig. 2.—The percentage of the 774 C–C bonds in the micelle that are found in the gauche conformation plotted as a function of time.
headgroup show a marginally higher gauche population than those in the middle of the dodecyl chain.

The frequency of occurrence of transitions between the trans, gauche⁺ and gauche⁻ conformations was also analyzed. It was found that the fastest transition was within 2 ps and the slowest, after 1284 ps. However, -53% of transitions occurred in the time scale of 0 to 10 ps suggesting that the hydrocarbon tails were very dynamic. The frequency of conformational transitions was found to be nearly the same whether the C-C bond was close to the headgroup or was towards the terminal methyl group.

The average distance per frame between the terminal methyl group (Cl2) and the phosphorus atom varied between 14.6 and 15.2 Å (data not shown). This distance, being dependent on the conformation around the intervening C-C bonds, was 15 Å in the initial model of the dodecyl chain wherein all the C-C bonds were in the trans conformation and all the bond angles were set to equilibrium values. The near-constancy of this distance suggests that the dodecyl chain assumes, overall, an extended conformation during the simulations.

**Orientation and dynamics of DPC monomers**

The orientation and dynamics of the DPC monomers in the micelle were analyzed using the distribution profiles of C12, C7 and N atoms. The distribution profile of C12 showed that the hydrocarbon chain termini were widely distributed throughout the micelle with a broad maximum between 6 to 15 Å from the center of mass (Fig. 3). This observation is in agreement with the lattice model of micelles. The C7 atoms were distributed between 12 and 17 Å. However, distribution of N was relatively narrower and peaks at around 22 Å. The distribution profiles of these three atoms together indicate that the monomer arrangement in the micelle is no longer radial and that some of the monomers completely lie on the surface of the micelle. The average values of \( I_1, I_2 \) and \( I_3 \) (principal moments of inertia along the X-, Y- and Z-directions) are 1.47, 1.71 and 1.67 (in the ratio 1.0:1.16:1.14) suggesting that the shape of the micelle is not spherical. The deviation from the spherical shape seems to increase gradually as can be seen from the plots of \( I_2/I_1 \) and \( I_3/I_1 \) as a function of time (Fig. 4).

A few of the nitrogen atoms also occur within 18 Å from the center of mass in some of the frames; such nitrogen atoms were found to be mainly surrounded by water molecules and to some extent, by atoms of the phosphocholine headgroup of other monomers. It was also found that it was not the nitrogen atom of the same monomer that was always closer to the center of mass; this suggests that some of the choline headgroups come closer to the center of mass in a dynamic fashion.

**Solvation**

The number of water molecules is 0 up to 10 Å from the center of mass (Fig. 5) indicating the absence of water penetration into the micelle core. Beyond this distance, however, the number of water molecules increases significantly. An average of 13-14 water molecules were found to be associated with the entire phosphocholine headgroup; this number is very similar to that found for the headgroup in DPPC. Despite the presence of water molecules close to the choline headgroup, no hydrogen bonding interactions were found because of the absence of hydrogen bond acceptor/donor groups in this moiety.

Solvation profile for only the nitrogen atom showed a
distinct peak that is absent in the profiles of P and CO1 (Fig. 6) suggesting that the N(CH3)+ group is on the surface whereas the phosphate group is relatively buried.

Comparison with DPC micelles of smaller aggregate sizes

The extent of penetration of water molecules into the 86-monomer micelle is found to be similar to that seen for micelles of 45, 54, 60 and 65 monomers. However, in the 86-monomer micelle, no positional preference is observed either for the gauche conformation or for the trans ↔ gauche transition time. In contrast, a distinct positional preference for the gauche conformation and for trans ↔ gauche transition time was observed for DPC micelles of 45, 54, 60 and 65 monomers. It was found that, in these micelles, the C–C bonds that are towards the termini had a higher gauche population than those bonds that were in the middle of the dodecyl chain. The distribution of C7 and N atoms was found to be different in the M54 micelle compared to that in the M60 micelle, and in the M86 micelle simulation reported herein (Fig. 3). The shape of the micelle also seemed to be different for micelles of different aggregate sizes (M60 and M54 micelle were found to be prolate and mostly spherical, respectively; Fig. 4). Overall, it can be concluded that within the aggregate size range of 50 to 90 monomers observed for dodecyl micelles, micellar dynamics is fairly similar and varying numbers of monomers can be accommodated in the micelle with minor changes.

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References

5 Hyvonen M T, Rantala T T & Ala-Korpela M (1997) Biochips J 73, 2903-2907
6 Woolf T B (1998) Biochips J 74, 115-131
11 Lauterwein J, Bosch C, Brown L R & Wuthrich K (1979) Biochips Biophys Acta 556, 244-264