

Micelles, Rods, Liposomes, and Other Supramolecular Surfactant Aggregates: Computational Approaches

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Abstract Surfactants are an interesting class of compounds characterized by the segregation of polar and apolar domains in the same molecule. This peculiarity makes possible a whole series of microscopic and macroscopic effects. Among their features, their ability to segregate particles (fluids or entire domains) and to reduce the surface/interfacial tension is the utmost important. The interest in the chemistry of surfactants never weakened; instead, waves of increasing interest have occurred every time a new field of application of these molecules has been discovered. All these special characteristics depend largely on the ability of surfactants to self-assemble and constitute supramolecular structures where their chemical properties are amplified. The possibility to obtain structural and energy information and, above all, the possibility of forecast the self-organizing mechanisms of surfactants have had a significant boost via computational chemistry. The molecular dynamics models, initially coarse-grained and subsequently (with the increasing computer power) using more accurate models, allowed, over the years, to better understand different aspects of the processes of dispersion, self-assembly, segregation of surfactant. Moreover, several other aspects have been investigated as the effect of the counterions of many ionic surfactants in defining the final supramolecular structures, the mobility of side chains, and the capacity of some surfactant to envelope entire proteins.

This review constitutes a perspective/prospective view of these results. On the other hand, some comparison of *in silico* results with experimental information recently acquired through innovative analytical techniques such as ion mobility mass spectrometry which have been introduced.

Keywords Surfactants · Mass spectrometry · Micelles · Rods · Liposomes · Molecular dynamics

1 Introduction

Science's interest on surfactants has been recently further renewed [1]. Chemically, these molecules represent an interesting class of compounds characterized by the presence of both polar (head) and apolar (tails) domains that allow to define confined spaces (micelles) in liquid phase and in gas phase which can be used as molecular reactors [1]. Their ability to form micelles in condensed and gas phases has been exploited for different technological purposes such as the synthesis of porous materials or the production of personal care products (detergents and body washes), drug delivery systems, extraction agents for apolar substances, nanotechnologies, and their applications.

In aqueous solution, surfactant molecules partly spread in the fluid, but they particularly tend to adsorb at the liquid/air interface leading to a reduction of the surface tension. In this respect, a fundamental role is played by the relative strength of the polar–polar, polar–apolar, and apolar–apolar interactions that exist between surfactant molecules and the solvent. These interactions are quantitatively different being the strength order the following: $S_{\text{polar-polar}} \gg S_{\text{polar-apolar}} > S_{\text{apolar-apolar}}$. This leads to a strong anisotropy of surfactant–surfactant interactions and,

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as a consequence, to a tendency to accumulate surfactant molecules at the water/air interface oriented, so that head groups are dipped in water and the tails are laying on the water surface.

This behaviour is responsible of the noticeable dropping in surface tension, of some effects on the evaporation rate of solvent molecules, and of the spatial charge distribution at the water/air interface [2].

With increasing surfactant's concentration, an ongoing reduction of the surface tension and an increase of the amount of spread surfactant occur. Further increments in concentration lead to the growth of aggregates' number and size. Actually, the nature of surfactant molecules makes them inclined to self-assemble forming supramolecular structures such as micelles (Fig. 1a, d), vesicles (Fig. 1b), monolayers (Fig. 1c), emulsions, and liquid crystals [3].

The shape of the aggregates depends on several manageable factors such as surfactant structure, temperature, ionic strength, nature of the counter-ion, presence of other surfactants, and additives or solvents with a different nature. The concentration of the surfactant represents the key parameter for further transitions of surfactant aggregation state from micelles (spheroidal) to more exotic structures such as rods' bilayers [3], ring-like or thread-like micelles [4, 5], and cubic phases [6]. Instead, the nature of the surfactant determines the organization of the micelle showing the 'tails' confined internally and the 'heads' placed at the interface in the presence of a polar solvent (direct micelle Fig. 1a) or a reversed structure in which the heads are confined on the inside and the tails protrude outward when the bulk phase is represented by an apolar solvent (reverse micelle Fig. 1d) [7].

In the latter case, surfactant molecules do not show tendency to lay at the liquid/air interface but prefer to self-assemble in the bulk solvent forming the reverse micelles. In the areas of technology, the size of micellar cavities is a crucial parameter to check, since inside them, some reactions in confined space may be carried out. It is equally important to evaluate interfacial properties (effect of charge variation) that affect micellar reactivity [7]. In biochemistry, surfactants' aggregates have been exploited

as a model for biological membranes or for their ability in solvating proteins and enzymes. Micelles have been studied by various methods: mass spectrometry [7–10], ion mobility mass spectrometry (IM-MS) [12–15], NMR relaxation measurements [6, 16], neutron diffraction [17], infrared spectroscopy [18–20], electron paramagnetic resonance (EPR) [21–23], and light scattering [24]. Physico-chemical techniques are capable to give average values for diffusion coefficients and aggregate sizes [25, 26]; on the other hand, the aforementioned physical methods are used to determine complementary information.

In particular, mass spectrometry with the contribution of soft ionization techniques, such as MALDI and ESI, represents nowadays, one of the most powerful methods for the study of non-covalent charged aggregates. Through this technique, some information on the stability of different surfactant aggregates (cationic, anionic, and non-ionic), on their ability to self-assemble under adverse conditions (as the transition from the liquid to the gas phase), and on their capacity to form protection layers for protein macromolecules has been obtained [27]. NMR techniques [28] have been used to determine CMC, size, structure, and shape of micelles, ion binding, and inclusions of several guests within the micellar structures [29, 30] and interaction between surfactant and polymers. Neutron diffraction and light scattering techniques [17, 24] are mainly used to determine the sizes and shape of surfactant nanoparticles. EPR [21–23] allows to investigate cell membrane fluidity without interfering with the living organisms. On the other hand, infrared measurements in both condensed and gas phases (as Infrared Multi Photon Dissociation, IRMPD) give more detailed information on polar groups interactions that reflect on the functional groups vibration frequencies [19, 20]. The picture above implies that experimental measurements on surfactant aggregates allowed to determine various parameters, but no or limited information could be drawn as concern the mechanisms that lead to self-assembly or to dynamic processes that exist inside micelles or vice versa on the micelles' surfaces.

To address this point, a more theoretical approach has been applied and several molecular dynamics studies of

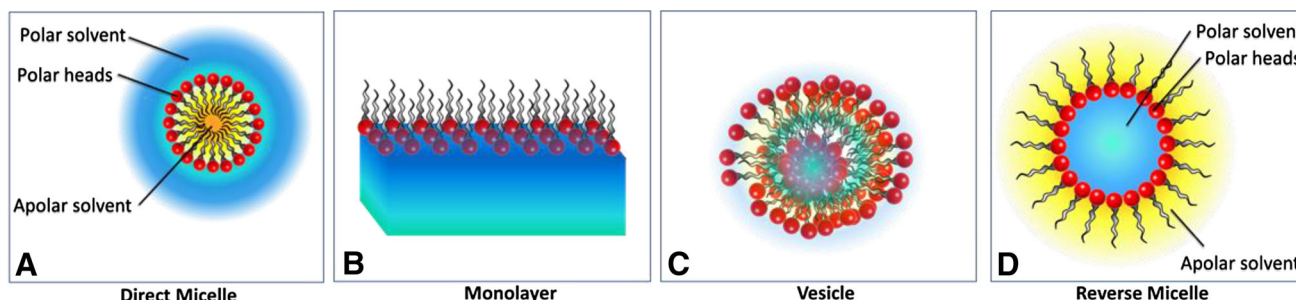


Fig. 1 Schematic representation structures obtained from surfactants: **a** direct micelle, **b** monolayer, **c** vesicle, and **d** reverse micelle. *Red spheres* represent the polar heads and *gray stripes* represent the hydrophobic tails

micelles provided a more detailed picture of their dynamics. In particular, anionic [12, 15, 31–34], cationic [35], reversed-anionic [36], and zwitterionic micelles [37, 38] have been investigated. Molecular dynamics has been and continues to be a very useful tool for biological systems as proteins, receptors, membrane receptors, and nucleic acids [39–49] but in the last years revealed a complementary support in the study of supramolecular aggregates.

More recent works tried to enlighten the transition mechanisms that lead to formation of more complex micelles (rod-like) and or to better describe even larger aggregates as liposomes [50].

In this review, we report the results obtained through a computational approach concerning the structure-related parameters (such as shape, size, counter-ion distribution, etc.) and dynamic properties (such as permeability, partition, and rheology) of the surfactants aggregates in condensed and gas phases. When and where possible these results are compared to some recent experimental results. Tables 1, 2 report the molecular structures of the surfactants and the categorization of the computational approaches object of this review, respectively.

2 Aggregates' Formation and Surfactant Concentration Effect on Micelle Formation in Condensed Phase

Different topics about surfactants' and micelles' formation have been deepened in the last years. In the following, we will briefly summarize and describe how Molecular dynamics (MD) has been adopted to explore several aspects of the micelle formation and the geometry adopted by the different components.

One of the main aspects studied with MD is about how surfactants concentration could affect the micelle formation. We will describe this effect on micelles with particular attention to the different MD approaches adopted.

Looking at the literature, it is possible to find out two main methods used: before 2011, researchers were focused on the classic MD to explore micelles' formation and after 2011, thanks to the MD algorithms evolution, coarse-grained (CG) technique for MD [51] has been adopted to deepen the behaviour of micelles.

In 2000, Marrink et al. published a work focused on the use of MD for the observation of spontaneous aggregation of the surfactants into single micelles, starting from the random distribution of molecules [52]. In their study, they found out that considering periodic boundary conditions, the quantity of surfactant is related to the free energy status reached by the micelle and this determines the final aggregate behaviour. In the same year, Bogusz et al. simulated octyl glucoside micelles to observe their structural

properties related to the number of lipids included within the micelle formation [53]. They observed that micelles consisting of five lipids molecules were unstable, while the ones containing ten or more molecules remained stable during 4 ns of MD simulation. Moreover, they observed that micelle size-affected surface properties may be because of the area-to-volume ratio variation, whereas internal properties (tail length, dihedral angle distribution, and isomerisation rate) are not significantly affected by the aggregate size.

Dodecylphosphocholine (DPC) micelles were the main focus of a study conducted by Tieleman, van der Spoel, and Berendsen [54]. In this study, the authors compared the structure and dynamics of the lipid tails of three different micelles containing 40 (M40), 54 (M54), and 65 (M65) DPC molecules with those of decane and dipalmitoylphosphatidylcholine (DPPC). These resulted comparable even if the dihedral transition rate resulted notably slower in the micelles than in decane and DPPC. The simulations were conducted in water for 15 ns. They observed that M54 and M60 presented a similar and spherical shape, whereas the M40 assumed an ellipsoid shape with an extended hydrophobic solvent accessible area and a restricted lipid packing.

In 2013, a very interesting first quantitative study on micelle/water partition coefficient and aggregates radius related to energy profiles has been published. In this study, MD was adopted as a starting point to collect variables of aggregates and calculate energy profiles [55]. Another high impact work on the use of MD to study molecular aggregates has been published in 2014 by Tang et al. [56]. In their study, it is noteworthy the comparison of different force fields (FF) on different aggregates of sodium dodecyl sulphate (SDS). In this study, GROMOS, CHARMM36, OPLS-AA, and OPLS-UA force fields are compared to observe the effect on the aggregates' formation. They observed that for small micelles (aggregation number 60–100), there were no significant differences in aggregates changing FF. In bigger aggregates (300 or higher units), the effect of force field used is stronger and influences aggregates' shape.

With the optimisation of coarse-grained method for MD [51], researchers have started to adopt this approach to better explore aggregates' formation. Velinova et al. published a work focused on coarse-grained MD to describe how different concentrations of pentaethylene glycol monododecyl ether ($C_{12}E_5$) can affect the micellar assembly [3]. They observed that starting from a low concentration of molecules and increasing it, one can observe a transition of shape from spherical to rod-like (Fig. 2).

Phase transition in model lung surfactant monolayers has been deeply studied with MARTINI CG [57] MD by

Table 1 Molecular structures of the surfactants

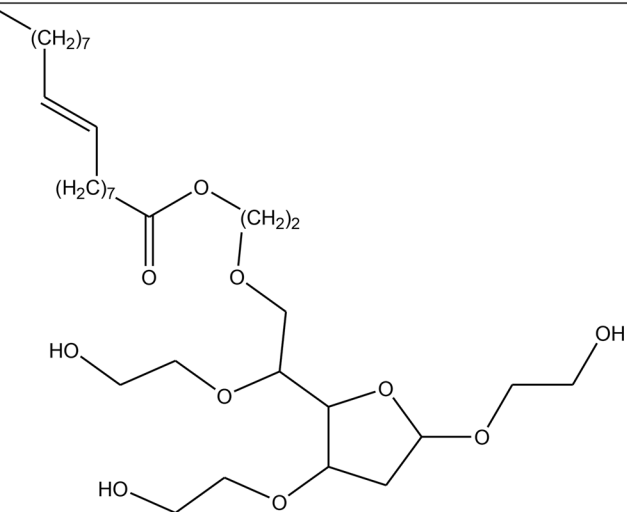
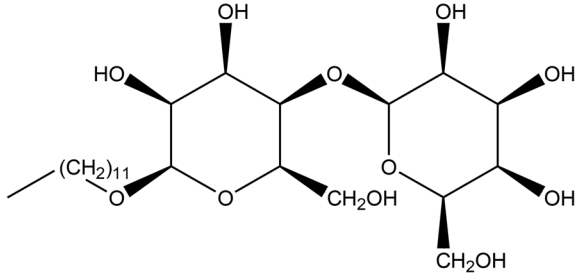
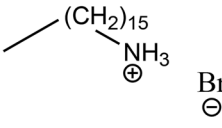
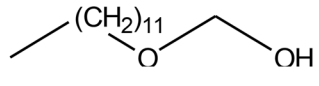
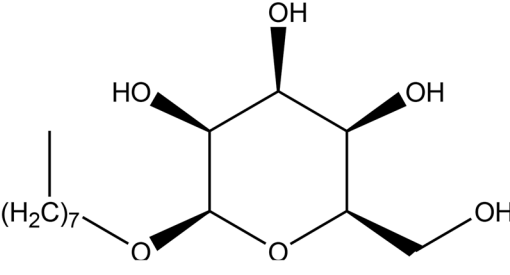
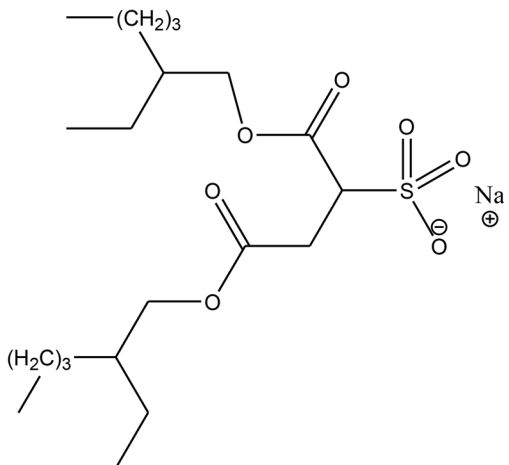
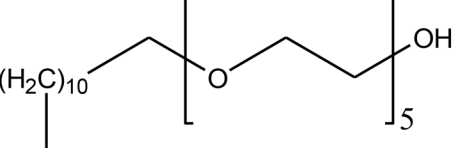
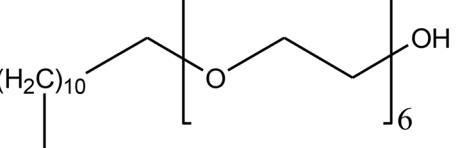
 <p style="text-align: center;">Tween 80</p>	 <p style="text-align: center;">Dodecylmaltoside</p>
 <p style="text-align: center;">CTAB</p>	 <p style="text-align: center;">BRIJ35</p>
 <p style="text-align: center;">Octylglucoside</p>	 <p style="text-align: center;">NaAOT</p>
 <p style="text-align: center;">C12E5</p>	 <p style="text-align: center;">C12E6</p>

Table 1 continued

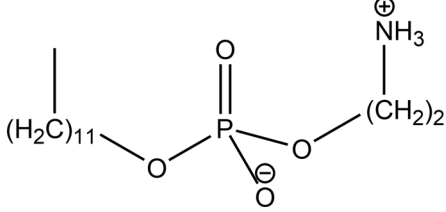
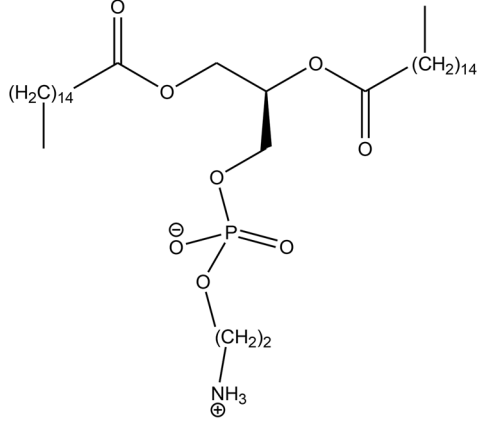
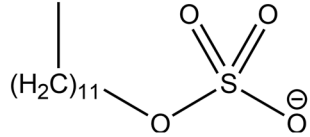
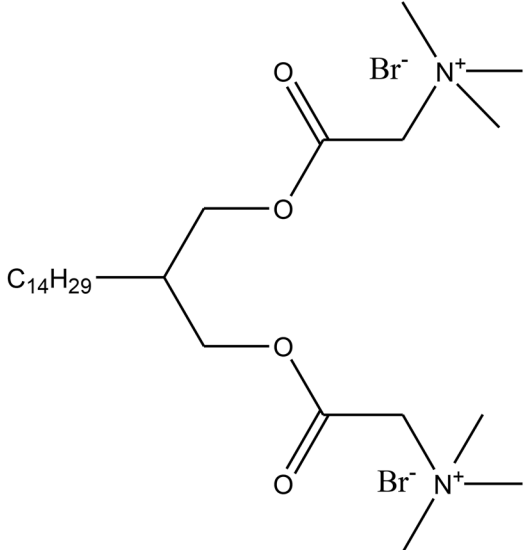
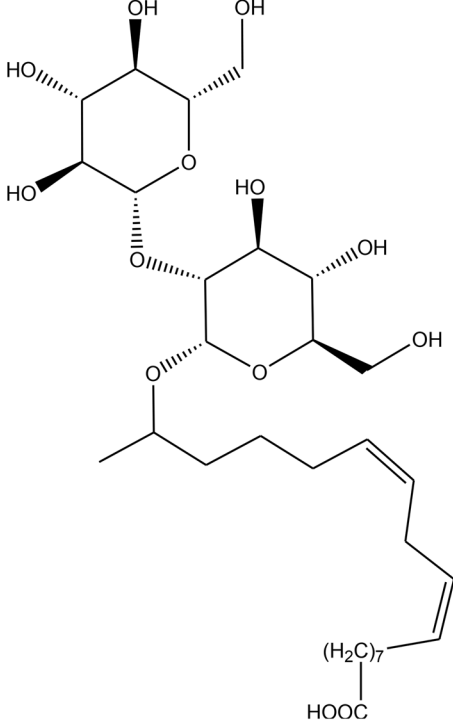
 <p style="text-align: center;">DPC</p>	 <p style="text-align: center;">DPPC</p>
 <p style="text-align: center;">SDS</p>	<p style="text-align: center;">$C_sH_{2s}-\alpha,\omega$-bis($C_mH_{2m}N^+(CH_3)_2Cl^-$)</p> <p style="text-align: center;">Gemini</p>
 <p style="text-align: center;">Bolaamphiphilic</p>	 <p style="text-align: center;">Sophorolipide</p>

Table 2 Categorization of the computational approaches

Surfactant	MD force field	Conditions	Simulation time	Ensemble	Phase	References
Sodium dodecyl sulfate	CHARMM	PBC	120 ps	NPT	Water TIP3P	[31]
Sodium dodecyl sulfate			182 ps	NPT	Water	[33]
Sodium dodecyl sulfate	CHARMM36	PBC	400 ns	NVT/NPT	Water CHARMM TIP3P	[55]
Sodium dodecyl sulfate	GROMOS, CHARMM36, OPLS-AA, OPLS-UA	PBC	20–30 ns	NPT	Water SPC, TIP3P, TIP4P	[56]
Sodium dodecyl sulfate	Dry Martini-CG-MD	PBC	12 μ s	NVT	CG water beads	[60]
Sodium dodecyl sulfate	AMBER6/parm98 FF	PBC	5 ns	NPT	TIP3P	[64]
Sodium dodecyl sulfate	CHARMM	PBC	1 ns	NPT	TIP4P	[69]
DPC	GROMOS	PBC	6–50 ns	NPT	Water SPC	[52]
DPC	GROMOS	PBC	50 ns	NPT	Water SPC	[67]
DPC	GROMOS	PBC	15 ns	NPT	Water SPC	[54]
Octylglucoside	CHARMM	PBC	4 ns	NPT	Water TIP3P	[53]
CTAB	CHARMM36	PBC	100 ns	NVT/NPT	Water CHARMM TIP3P	[55]
CTAB/Myoglobin	GROMOS96 43A1	PBC/Non PBC	20 ns	NPT	Water SPC/vacuum	[89]
C ₁₂ E ₅ PEO and PEG	Martini-CG-MD	PBC	900 ns–2.5 μ s	NPT	CG water beads	[3]
DPPC	Martini-CG-MD	PBC	1 μ s	NPT	CG water beads	[58]
SDS, SHS, SNS	Martini-CG-MD	PBC	2 μ s	NVT	CG water beads	[59]
NaAOT	Linse-Halle method	Non PBC	2 ns	NPT	Water SPC/E	[7]
NaAOT	Linse-Halle method	Non PBC	300 ps	NPT	Water SPC/E	[62]
NaAOT	CHARMM	PBC	6 ns	NPT	Water SPC/E	[63]
NaAOT	In house method	Non PBC	–	–	In vacuum	[1]
NaAOT	AMBER	Non PBC	100 ns	NPT	In vacuum	[84]
NaAOT	AMBER	PBC/Non PBC	1 ns/1 ns	NVT/NPT	Water TIP3P/vacuum	[85]
NaAOT	AMBER	Non PBC	50 ns	NVT	vacuum	[86]
NaAOT	AMBER	Non PBC	50 ns	NVT	vacuum	[87]
MeAOT	Linse-Halle method	Non PBC	250 ps	NPT	Water SPC/E	[65]
C ₁₂ E ₆	OPLS	PBC	3.5 ns	NVT	Water SPC	[68]
Brij35	CHARMM	PBC	200 ns	NVT/NPT	Water TIP3P	[71]
Brij35/CTAB	CHARMM	PBC	200 ns	NVT/NPT	Water TIP3P	[71]
Brij35/SDS	CHARMM	PBC	200 ns	NVT/NPT	Water TIP3P	[71]
Tween80	GROMOS53A6 _{OXY+D}	PBC	100–240 ns	NVT/NAPzT	Water SPC	[72]
Dodecyl Maltoside/proteins	OPLS-AA	Non PBC	16 ns		vacuum	[27]
Multihead cationic surfactant	CG-MD	PBC	1 μ s	NPT	CG water beads	[75]
Bolaamphiphilic Sphorolipids	GROMOS9653a6	PBC	300 ns	NPT	Water SPC	[79]
Gemini Dimeric	–	PBC	–	NPT	Water	[73]
Gemini dimeric	CG-MD	PBC	1 μ s	NPT	CG water beads	[74]
12-s-12 gemini surf.	CHARMM	PBC	10–17 ns	NVT	Vacuum/water TIP3P	[77]
Gemini cationic bis-quaternary ammonium 12-2-12	CVFF	PBC	2 ns	NPT	Water	[76]

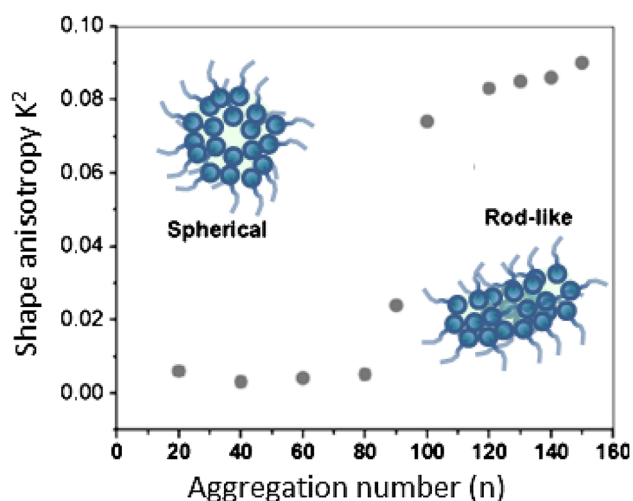


Fig. 2 Relative shape anisotropy against aggregation number of pentaethylene glycol monododecyl ether ($C_{12}E_5$). Adapted from reference 3

Susan L. Duncan research group. In their work, Duncan et al. focused on the role of single surfactant component in liquid-condensed and liquid-expanded phase transition [58].

Yang and Sun in 2014 studied the surface-bulk partition for three ionic surfactants using coarse-grained MD [59]. Accordingly, to experimental data, they found that for short chain, surfactant stable oligomers were formed before micelles were assembled.

In 2015, Wang et Larson published a work based on the sodium dodecyl sulphate micelle fission and fusion under a dry MARTINI force field [60].

3 Water Molecules Properties in Micelle Structures

Many researchers have focused their attention on the role and disposition of water molecules inside the micelles. In the proposed references, classic MD approach has been adopted to study these phenomena. In 2000, Faeder and Ladanyi published a work on reverse micelles to deepen the composition and behaviour of the aqueous component [7]. To set up the study, a simple point charge extended (SPC/E) water model [61] was used and all the parameters to simulate the surfactant sodium bis(2-ethylhexyl)-sulfo-succinate known as Aerosol OT (NaAOT) micelle composition were taken from experimental data. The simulations showed an interesting attitude of water molecules. It seems in fact that in such a kind of aggregates, water is likely to be trapped in the ionic interfacial layer, reducing its translational and rotational motions, as demonstrated by a wide range of experiments [61].

Rosenfeld and Schmuttenmaer in 2006 published their work on reverse micelles' water molecules' distribution [62]. In their simulations, the authors proposed a comparative explorative study on reverse micelles presenting a size range measured as radius from 10 to 23 Å. Through the simulations, a series of hydrogen bonding profiles and spatial distribution of molecules are presented. NaAOT reverse micelles as model to outline water role in aggregates' formation have been deeply studied also by Chowdhary and Landanyi in 2009 [63]. In this study, different micelle sizes are investigated to deepen the role and disposition of water molecules. In the observed examples, the water molecules exist primarily in the interior of the reverse micelles, and when water/surfactant ratio (also known as water content or w_o) is about 7.5, they exhibit bulk-like properties. Some of the water molecules have also been found in the inter-sulphonate head group region interacting with the NaAOT carbonyl groups.

4 Counterions' Effects on Surfactant Assembly

One of the most important MD study on the counter-ion role in micelles' assembly for sure is the one published by Bruce et al. [64]. In their paper, they describe an all-atom 5 ns simulation of micelles containing 60 sodium dodecyl sulphate monomers [64]. The results published underline the stability of the aggregates during the whole simulation. Particular attention is given to the structure and motion of the sodium counterions. They found that a stable distribution of ions requires a long equilibration time (about 1 ns). Another interesting aspect retrieved from their simulations is that for the entire simulation, about 25% of the sodium ions are located in the first shell and 50% stay in the first two shells of the assembly.

The water mobility related to counterions' effect was also analysed in another important paper published by Harpham et al. [65]. In their work, the authors evaluate the mobility and the structure of water molecules in NaAOT. Particularly, they investigated reverse micelles with water content $w_o = 5$ and Na^+ , K^+ , and Cs^+ ions to evaluate the self-intermediate scattering function of water hydrogen atoms. From their experiments, authors found that water molecule interfacial mobility is quite different depending to the three different counter-ion types, whereas the core mobility is not strictly bound to the ion used. In 2013, Ladanyi published review collecting works about how counterions can affect surfactant assembly [66]. In particular, he analysed the behaviour of different systems such as normal micelles, monolayers at the air/aqueous solution interface, and reverse micelles. In this review, the author reports, for example, how the presence of Na^+ and Ca^{2+} can affect the interfacial structure depending on a balance

between counterion-water and counterion-head group interactions in dimethyl propionic acid (DMPA) monolayers. For reverse micelles, the author points out how counterions have an important role in the assembly process, especially on the changes in aggregate shape.

5 Surfactants Role in Micelle Formation

Some researches mainly focus on the surfactant molecules behaviour and their role in forming micelle aggregates. One interesting aspect studied by Bond et al. is the spontaneous assembly of dodecylphosphocholine micelles around two different membrane proteins [67]. The main focus of the work is the kinetics of aggregates' formation, measured as radius of gyration variation. They first observed the formation of small micelle-like aggregates where the detergent molecules fused to protein molecules. Then, these small micelles fused together with other small ones to generate bigger ones. The fusion process is observed thanks to head-to-head interactions of the detergent molecules. In 2005, Chanda and Bandyopadhyay investigated the properties of a monolayer of monododecyl hexaethylene glycol (C12E6) adsorbed at the air/water interface [68].

The results showed the long polar head groups of the surfactants as tilted toward the aqueous layer interacting with water molecules. The surfactant monolayer showed a strong influence in the translational and rotational mobility of interfacial water molecules. Moreover, they observed that a small distance variation between water molecules and surfactant head groups caused a huge change in the dipolar reorientation motion of water molecules within the micelles.

Yoshi and Okazaki published a work based on the analysis of structure and dynamics of SDS molecules in micelles [69]. To get information on the surfactant assembly process, the authors assessed a 2D surface correlation function for the hydrophilic sulphur atoms and a bond analysis between the hydrophobic chains of molecules. They found that the hydrophobic molecules were simply packing in the micelle as forming “a soccer ball-like structure characterized by the coordination number of three” as the same authors stated.

In the first 100 ps of the simulations, they observed the formation of a hydrophobic bond between the surfactant molecules, but at about 1 ns, the same disappeared letting the molecules to diffuse.

The self-assembly and localization of nanoparticles (NPs) at fluid/fluid interfaces for aggregates' formation are the topic on a very interesting paper published by Ranatunga et al. [70]. In this work, authors tried to quantify the physical properties of NPs closed to a fluid interface. Thanks to the MD simulations, this study demonstrated that

the functionalization of the layer molecules could alter the interfacial behaviour of the NP and so the effect of this functionalizing process on the NP deformability. These experiment outcomes could be considered an important guide in the interpretation of NP contact angles. Mixed micelles have been studied by Storm et al. to evaluate how surfactant nature can influence the partition behaviour of different solutes [71]. The main focus of the work is based on the observation that ionic or non-ionic surfactant can extremely influence the solute disposition inside the aggregate. In their work, the authors start from the use of classical MD to assess the self-assembly of polyethylene glycol dodecyl ether (Brij35) and mixtures either with cethyl trimethyl ammonium bromide (CTAB) or with SDS at different concentrations. Once the micelles have been assembled, COSMOmic, a computationally efficient method is used to predict the partition behaviour of various solutes between micelle of different sizes and bulk water. The most important aspect of this work is, for the first time, the self-assembly of pure Brij35 and the mixtures of Brij35/CTAB and Brij35/SDS on atomistic scale. Moreover, it seems like the results retrieved in the simulations are in accord to the experimental data.

Recently, Tang et al. used a united-atom MD to simulate the behaviour of polyoxyethylene sorbitan oleate (Tween 80) isomers [72]. Particularly, they focused on two stereoisomers, three constitutional isomers, and three structures with one, two, and three tails to study the different behaviours of these molecules in the assembly process. From their study, the authors found that the distribution of tween tail and ethylene oxide head groups is affected by the length the four polyoxyethylene head groups, but it seems not to be sensitive to stereoisomerization. The outcomes represent a valid support for the improvement of the surface tension and other properties in the design of Tween 80.

An heavy impact on the micelle formation an mostly on their shape is observed in the case of gemini surfactant. These molecules that consists of two classical cationic surfactants (containing m carbon atoms) linked by a variable length spacer (containing s carbon atoms) are capable to form variously shaped micelle-like superstructures, depending on the size of the spacer. Investigations made by Karaborny et al. [73] on a simplified model, containing 32,000 particles periodically repeated in the three directions, were capable to evidence thread-like and three-like structures for such surfactants. The particles were of two types: water-like and oil-like. The former interacts by a Lennard-Jones (LJ) potential large enough to include volume effects and attractive forces, and the latter interacts with each other by way of LJ potential with a large cutoff and with water-like particles by way of small LJ potential to include no attractive forces.

These results were also obtained by Maiti et al. [74] evaluating single chain, dimeric (Gemini) and trimeric surfactants. The same coarse-grained computational approach by Samanta et al. [75] performed on surfactants with multiple polar heads, and gives more conventional ball-shaped micelles.

A more regular cylindrical micelle structure, verified by circular dichroism measurements, has been calculated by Oda et al. [76] using an all-atom approach based on a constant valence force field. In this case, the modeled initial structure was immersed in periodic box ($63 \times 60 \times 60 \text{ \AA}^3$) containing water. The structure was equilibrated running the dynamics at constant volume for 500 ps. It followed a constant pressure MD simulation (1500 ps long) that generated the final cylindrical micelle. A fully atomistic modeling was chosen by Khurana et al. [77] to follow the behaviour of a series of Gemini surfactant deposited along water surfaces in proximity and in correspondence of their CMC. The dynamics took advantage of the CHARMM force field, and the initial equilibrium was obtained by means of the SHAKE/RATTLE algorithm [78]. Final models obtained after 15–17 ns of dynamics evidenced some differences between the investigated Gemini surfactants, based on the spacer length. When the spacers were constituted by alkyl chains containing 3, 4, and 16 carbons, a clear formation of micelles inside the solvent was observed. Spacers containing 12 and 14 carbons resulted into a surfactant continuous distribution at the air/water interface.

Finally, recent studies on bolaamphiphilic surfactants by Dhasaiyan et al. [79] have evidenced the very promising formation of surfactant ribbons or giant vesicles. These supramolecular structures were obtained from the MD study of sophorolipids of oleic and linoleic acids, respectively. The all-atom approach exploited the GRO-MOS9653a6 force field and very long MD simulation (up 700 ns).

6 Gas-Phase Surfactant Behaviour: The NaAOT Model

One of the most studied surfactant in both gas and condensed phases is NaAOT. This chiral surfactant is characterized by an anionic sulfonate head connected by means of a succinate residue to two branched alkyl chains. The chemical properties of such a surfactant confer its capability to self-assemble to give reverse micelles and direct micelles in non-polar and polar solvents, respectively. For these reasons, this surfactant has been used as a model for a series of papers oriented to the gathering of information on surfactant behaviour in gas phase.

One of the first works devoted to study anhydrous micelles formed by NaAOT in non-aqueous environment is that of Bulavchenko et al. [1]. In this paper, a simple model is proposed according to which ions are allowed to move over some closed surfaces in a vacuum at $T = 0 \text{ K}$, the charges are taken to be discrete and the modeled electrostatic field extends beyond the double electric layer. The shape of the resulting micelle is tracked as the cationic counterions penetrate the anionic layers and the most probable structure for a series of cations (Li^+ , Na^+ , Cs^+ , $[\text{Co}(\text{H}_2\text{O})_6]^{2+}$, and La^{3+}) has been prevised. The most interesting results of the approach are the finding that when the distances between anionic and cationic surfaces (d_{3-4}) are low, the electrostatic interaction favors the self-assembling of the surfactant molecules. Finally, a crystal-like structure has been predicated for the modeled reversed micelles, and several other papers will confirm this first speculation (Fig. 3).

A vast literature has been devoted to gather from MD structural and geometry information to couple to mass spectrometry measurements. From this point of view, computational chemistry and tandem (or energy resolved) mass spectrometry are very complementary techniques: the first gives both geometry and speculative energetic information, while the second produces experimental values. A synergistic approach provides very detailed results and can explain several features and dynamical behaviour of the investigated molecules.

A pioneering study of Bongiorno et al. [8] conducted on NaAOT showed a remarkable convergence of the mass spectrometry results and the Density Functional Theory (DFT) calculation. The geometry optimization was carried out on a trimer, using a 3-21G basis set through BP86 functional [80] along with a resolution-of-identity approximation (RI-DFT) [81, 82]. In addition, in the case, for the sulphur atoms, d-type functions with exponent 0.39

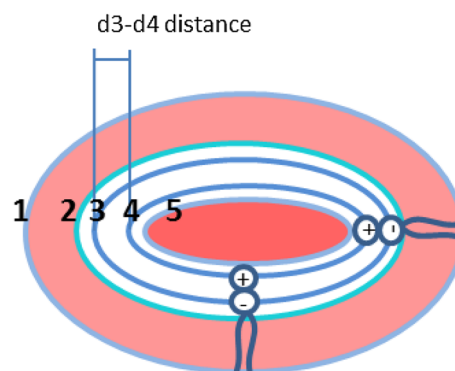
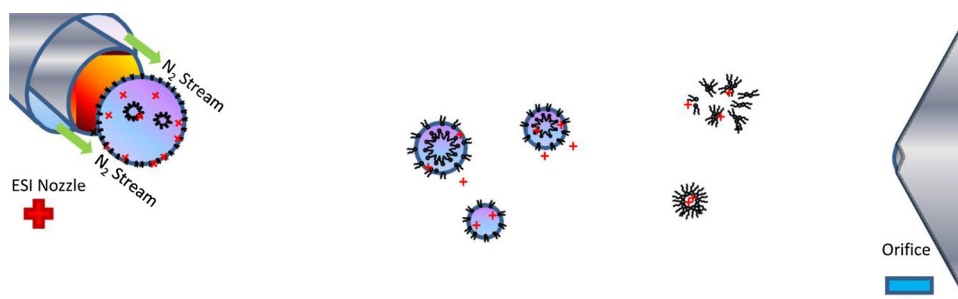


Fig. 3 Schematic presentation of the model of the reversed micelle of AOT adapted from reference 1: outer surface 1, surface separating the polar from non-polar part of molecule 2, potential-determining ions surface 3, layer of the counterions surface 4, central cavity surface: 5

Fig. 4 ESI ionization of surfactants, early stages: droplet formation and volume reduction



were added. Results evidenced a reverse micelle-like structure of the optimized aggregates with a crystal-like core were strong electrostatic interactions modulated the stability of the entire supramolecular aggregate. The stability order determined through DFT calculation indicated that the positively charged trimer was the most stable structure followed by neutral and lastly by negatively charged aggregate. In this work was also evidenced that (for this surfactant, in the gas phase) direct micelles geometries were energetically strongly disfavored.

Following this pathway, further studies performed [10, 11] on a series of alkane sulfonates evidenced the same trend: formation of aggregates (positively and negatively charged) characterized by a polar crystalline-like core and reversed micelle-like structure. Energy resolved mass spectrometry measures were instead used to get information about the role of the hydrophobic chain on the overall stability of the aggregates evidencing, for these moieties, negligible or no-influence. Another paper by Giorgi et al. [83] using both energy resolved mass spectrometry and DFT calculation evidenced the gas-phase formation and structural features of negatively charged NaAOT aggregates in the presence of alkyl halides. Calculations allowed to correlate mass spectrometry CID values with calculated energy changes accompanying the dissociation process $[AOT_2\text{-metal}]^- \rightarrow AOT^- + AOT\text{-metal}$ and showing good agreement between experimental and calculated values. The following reactivity order of metal cation as stabilizing moiety was also established: $Na > Li > K > Rb > Cs$.

A fully MD study *in vacuo* on aggregates constituted by AOT-metal (being the metals used: Li, K, and Cs) has been conducted in 2010 by Longhi et al. [84]. The computational approach started from the anion AOT^- structure obtained by an RHF/6-31G* level of theory optimization. The following dynamics study was performed using an all-atom general Amber force field. *In vacuo* MD simulation without a periodic box, as have also been evidenced elsewhere, [84–86] required a prior equilibration of the forming aggregate that was found necessary to avoid the formation of several small aggregates. Once stabilized, the generated structures were gradually heated up to 700 K to

allow the loss of the memory of the original conformation, and finally brought back to 300 K to perform the simulation. The information obtained evidenced an invariable preference for reverse micelle-like structures, while the stability order confirmed the trend of the previous studies made by DFT [8]. Change in the alkali metal showed that aggregation energy decreases with the increase of the size of the alkali ion, lastly an increasing deformation from sphere to ellipsoid of the whole structure has been observed on the increasing of the aggregate size. In a following study of the same group using the same computational approach [87] increased, the investigated aggregate size as well as the charges accommodated inside. It was deduced that the maximum number of extra charges that can be safely retained by each supramolecular aggregate increases with aggregation number but in a non-linear fashion (markedly for small aggregates). The charge state also influences the structure (becoming this latter more oblate with the charge increasing) and the stability (that steeply decrease on the increase of the charge state) of the aggregates. An evaluation of the fragmentation temperature has also been performed on singly charged aggregates, and has been evidenced that this temperature decreases on increasing the aggregation number. For multiply charged aggregates, the fragmentation temperature trend instead shows a maximum that probably results from a balance of multiple fragmentation pathways and electrostatic interactions.

A recent paper published by Longhi et al. [85] followed NaAOT aggregation as early to the droplet containing the surfactant (Fig. 4).

This slightly different computational approach, which always took advantage of an “all-atom” algorithm based on AMBER, revisited the initial equilibration using periodic boundary condition to simulate a nanodroplet containing 1000 water molecules and a variable number of AOT^- anions and of Na^+ cations. The most striking information is the observation of the initial direct micelles’ organization of the NaAOT aggregates in the aqueous solution that rapidly reorganize, in ESI conditions, to give reverse micelle-like aggregates in ns timescale. Interestingly, it is also reported that the reorganization occurs, while water is still present in the nanodroplet. It is indeed observed that at

about $t = 0.5$ ns, hydrophobic tails firmly point outward the droplet structure, and this organization persists for the total endurance of the simulation. Longhi et al. also investigated the behaviour of the negatively charged supramolecular aggregates *in vacuo* for NaAOT aggregates containing up to 20 molecules of the anionic surfactant and charge state up to -5 . Similar to the previous paper [87], the reverse micelle-like structure is the favored one with a shape that increasingly becomes elongated on increasing the charge state and the aggregation number. The study evidenced that the temperature-induced aggregate fragmentation always proceeds through a bottleneck formed along the major axis of the elongated shape. This process involves formation of small aggregates through a charge separation mechanism.

The self-assembling and structural organization of only a few detergents (NaAOT and a series of *n*-alkyl trimethyl ammonium bromides) have been investigated in gas phase. Recently, Bongiorno et al. (in press) reported the breakdown curves and yields curves of charged aggregates of DMEB in the gas phase by ER-MS experiments, while structural organization has been prevised by MD simulations. MD simulation geometries showed a homogenous bromide distribution, while the ER-MS experimental findings evidence the unsymmetrical CS processes. Quantum mechanics calculations (DFT) on the structures evidence that, apart from the electrostatic interactions, the most determinant interactions are due to an OH–Br bonding. This latter is also involved in linking monomeric DMEB units and consequently on the growth of these ionic micellar systems. Furthermore, MD calculations confirm the occurrence of OH–Br bonding in positively and negatively charged bigger aggregates, and the MD simulation structures (in good agreement with experimental CCS) evidenced a less strict reverse micelle-like structure and a more spread bromine anion distribution with respect to other reverse micelle-like structures previously reported.

7 Surfactants–Protein Interaction

With the aim to elucidate the structural transitions that accompany the encapsulation and dehydration processes observed during the mass spectrometry experiments performed by Sharon et al. [88], Wang et al. [89] defined molecular dynamics experiments where horse myoglobin alone, in the presence of water and in the presence of various amounts of CTAB, was modeled. An MD simulation was conducted with an all-atom approach using the GROMACS application and the GROMOS96 43A1 force field. The computational approach implied the prior analysis of the two systems alone: CTAB micelles and protein, and the following study of the micelle protein complex

system. As also evidenced for NaAOT micelles, CTAB self-assembles into direct micelles in the water containing model, but rearranges into a stable dry reverse micelle-like structure once put in vacuum. However, different from NaAOT in this case, a three-layered onion structure is observed. The structure evidences hydrophobic core, an outer layer, and a hydrophilic middle layer consisting of the surfactant head groups and of the corresponding counter ion. The following analysis of myoglobin indicated that both in solution and in water, the overall structure is well preserved if a small thin water film is coating the macromolecule. Large deviations from original structure are observed when the water is completely removed. The simulation of the complex system formed by the protein and the surfactant evidenced that this latter does not form a reverse micelle structure coating the protein (at least in the 65 ns-long simulation in bulk water). Reducing the water content and using periodic boundary conditions, however, a reverse micelle formed around the protein structure. In these conditions, even in vacuum, the MD simulation of the aggregate showed minor variation of the protein structure with respect to the native one. This is a confirmation of the supposed surfactant mediated protection of the native protein structure. In a following article, van der Spoel et al. [90] conducted a study similar to that of Wang et al. [89] on a series of proteins (namely, CTF, insulin, lysozyme, ubiquitin, and myoglobin). It has been evidenced that during the transition from solution to gas phases, the overall native structure was largely maintained, once provided a low charge state. Incidentally, a slight increase of the hydrogen bonds with respect to condensed phase is observed. In the same work, the MD models evidenced that surfactant action is capable to reduce structural stress to the investigated proteins. This prospects the possibility to carry membrane proteins in gas phase with no or minor structure modification, theoretically allowing to study drug binding with a stoichiometric approach.

Last MD approach to enlighten surfactant protein relationship in gas phase is by Borisyk [27]. In this study, a protein–surfactant assembly has been studied by means of IM-MS and vacuum MD simulations. From the experimental point of view, the MD simulation was performed using the OPLS (all atoms) force field implemented in the GROMACS 4.6.7 package, but the restraints used to map the surfactant positions onto the protein surface were obtained by IM-MS experiments. At this point, unsurprisingly, an evidence for micellar inversion of dodecyl maltoside was shown by MD simulations. The inversion is thermally favored and finally results in an increased protein–surfactant head group interaction. The organization of protein–surfactant assemblies is unlikely to represent the previous organization of these species in solution; this notwithstanding a protective effect of the native protein

structure is obtained. Indeed, the protein surfaces intolerant to water are sheltered by the alkyl chains of the surfactant. In addition, during MD simulation, a surfactant migration is observed that localizes head groups nearby the most polar protein surfaces that are prone to gas-phase unfolding, giving support to the protein structure through hydrogen bonding.

8 Conclusions

One of the most striking information that emerges from results obtained from all the computational approaches to surfactant aggregation studies is the prominent role of the charges and of the polar head to the self-assembling process. In addition, the overall stability of direct and reverse micelles, both in condensed phase and in vacuum, largely depends on the strength of polar interactions.

At this point is not surprising to observe crystal-like structure mostly when anhydrous direct and reverse micelles are formed. In these cases, the polar interaction does not suffer of the weakening effect of the water dipole on the attractive forces established between positive and negative charges. Neither is surprising that in gas phase, a crystal-like aggregation and fragmentation is observed, with strong interaction that requires hard collisions to obtain an often sudden fragmentation into very small nuclei.

Another non-trivial information given by the most complex simulations concerns the protective effect of surfactant on native structure of integral membrane proteins. While one can imagine the surfactant action similar to that of membrane phospholipids (where the protein fluctuates *in vivo*), the real stabilization here it comes again from the polar interactions. Indeed, the number of hydrogen bond increases, while surfactant polar head simply interacts with the most susceptible protein sites, prone to unfolding. The alkyl chains retracted on the macromolecule still have a shielding role, but cannot solvate the macromolecule at all.

This notwithstanding the protection effect has been evidenced and native structure is simply preserved, this in perspective, and should allow stoichiometric approaches to binding studies in gas phase.

Looking at the perspectives of computational approaches to supramolecular structures such as micelle vesicles and liposomes, they appears very appealing and promising. The increase of computational power and the increased accuracy of the force fields applied, allowed to simulate very complex systems on simple workstations or small clusters. Results proved to be at least in agreement with experimental results, and shown a wealth of information

enabling to better understand the dynamic features of the aggregates under investigation.

On the other hand, the self-assembly pathways and its driving forces have been ascertained and this information comes handy in the design of delivery systems. In addition, these could be useful as well to forecast some rheological aspects of surfactant made aggregates.

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