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Aggregation of charged rigid amphiphilic COSAN complexes: unexpected transition from monolayer vesicles to micelles^{**}

Pierre Bauduin*, Sylvain Prevost, Pau Farràs, Francesc Teixidor, Olivier Diat and Thomas Zemb

Self-assembly is ubiquitous in nature and in surfactant science.[1] Globular micelles or vesicles in water are usually obtained with surfactants[2] or amphiphilic block copolymers[3] composed of a hydrophilic part and a hydrophobic part. The aggregation mechanism is then controlled by the tendency of the nonpolar part to avoid contact with water, known as the hydrophobic effect,[4] while the polar part tends to be strongly hydrated. Consequently, the minimum free energy is reached during the aggregation process by minimal contact of the hydrocarbon chains with water and by maximal entropy that lead to the formation of the smallest possible aggregates, that is, spherical micelles for single-chain surfactants. As the concentration increases, the shape changes from spherical micelles to rods (hexagonal phase) to a lamellar phase, that is, from high to low curvature toward the apolar part.[5] Double-chained surfactants, or some block copolymers with a pronounced hydrophobic tendency, cannot pack into spheres because of steric reasons, and are forced immediately into closed bilayers (vesicles) of near-zero curvature at the surfactant/copolymer scale.[6] Recently, the formation of vesicles has been reported for more exotic, that is, non-amphiphilic chemical systems such as amino acid derivatives, oligopeptides, cyclodextrins, macrocycles, fluorofullerenes, and polyelectrolytes.[7]

Herein, we show here that cobaltabisdicarbollide (mono-)anion ($\text{H}^+ [3,3'\text{-Co}(1,2\text{-C}_2\text{B}_9\text{H}_{11})_2]^-$, H^+COSAN^- , Fig.1) forms monolayer vesicles at low concentrations in water. Increasing concentration leads to a Coulomb explosion of the vesicles into small micelles (Fig.1) resulting in the coexistence of both aggregation states at higher concentrations. The formation of monolayer vesicles and small micelles is so far unknown for water soluble carborane derivatives.

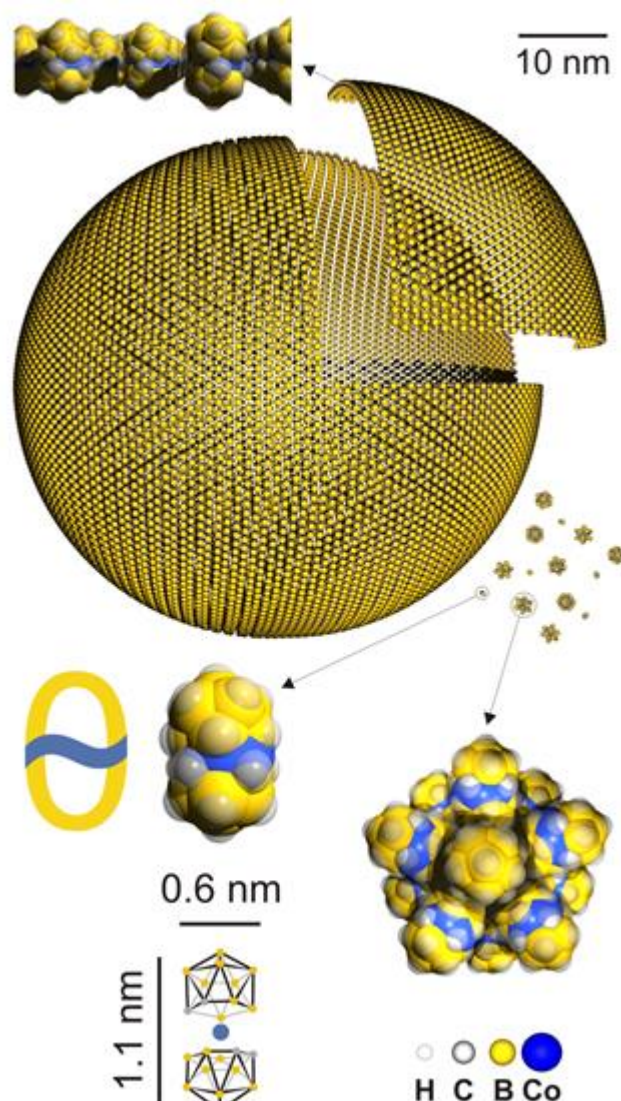


Figure 1. Cobaltabisdicarbollide anion (COSAN^- , $[(\text{C}_2\text{B}_9\text{H}_{11})_2\text{Co}]^-$) is composed of two bulky and hydrophobic dicarbollide semi-cages (yellow) that “sandwich” a cobalt (III) ion as a polar part (blue). For the sake of clarity hydrogen atoms are omitted in the crystallographic structure. A θ -shaped amphiphile is a good representation of this molecule. In water H^+COSAN^- self-aggregates by forming large monoshell vesicles ($R \sim 20$ nm) coexisting with small globular micelles ($R \sim 1$ nm) and monomers.

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COSAN is composed of two bulky and highly hydrophobic dicarbollide semi-cages, each of them bearing two negative charges, that “sandwich” a cobalt(III) ion as a polar part. The remaining negative charge is delocalized over the whole COSAN structure that can be represented by a theta, θ (see Figure 1). COSAN is used in its acidic form, with a hydronium ion (H^+) as counterion. Titration by a strong base shows that HCOSAN acts as a strong acid

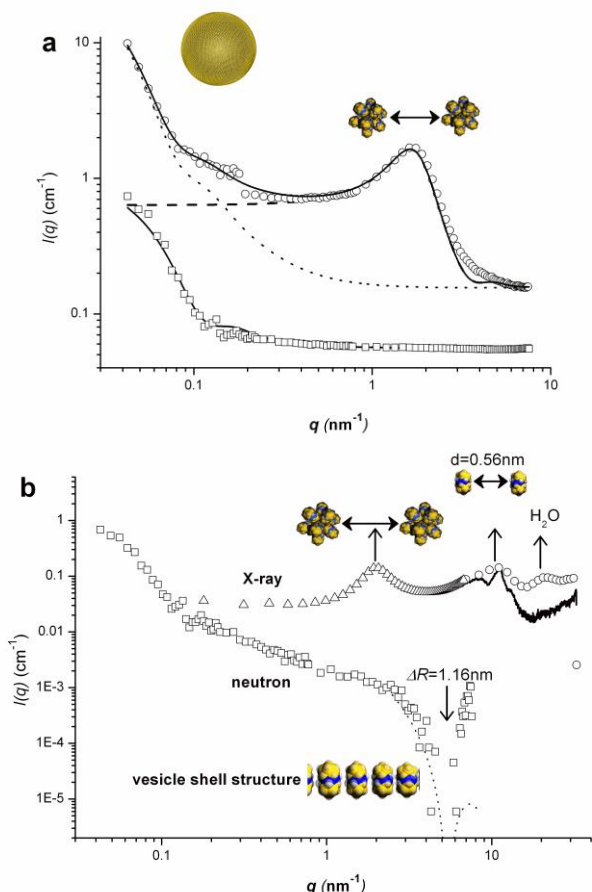


Figure 2. (a) SANS spectra of HCOSAN in D₂O at 0.19 (squares) and 33.3%v/v (circles). Solid lines represent the best fit obtained by combining two populations of spherical objects: (i) vesicles with polydisperse radius (25 nm) and constant wall thickness (1.16 nm), and (ii) spherical micelles of 1.16 nm radius interacting through a hard sphere potential. The contributions of the micelles and the vesicles to the total scattered intensity are given separately as dashed and dotted lines respectively. (b) Squares represent the SANS spectrum of HCOSAN in D₂O at 0.19%v/v when background is subtracted. The dotted curve is a simulation in absolute scale of infinite lamella with a wall thickness of 1.16 nm. The top curves are the SAXS (triangles) and WAXS (circles) spectra of HCOSAN at 33%v/v. At high q range the spectrum in black line correspond to the WAXS spectrum, in arbitrary units, of pure HCOSAN powder.

(Supplementary), hence it is charged and fully dissociated in water. This speciation provides high solubility in water and a monotonic surfactant-like reduction of water surface tension.^[8] As can be seen in Figure 1, counterions cannot condense closely to reduce the Born energy due to the charge and “theta” shape of the COSAN anion. Nor can the hydrophobic rigid ends deform to partition on one side of the head group as in double-tailed surfactants. These two peculiarities are at the origin of the unique microstructures formed.

COSAN aggregation was characterized by combining small- and wide-angle X ray and neutron scattering (SAXS, SANS and WAXS) in D₂O at concentrations ranging from 0.0065 to 1.127 M, i.e. 0.19 to 33.3%v/v. Figure 2 shows the SANS spectra for 0.0065 to 1.127 M (Fig.2a). The neutron scattered intensity (SANS) is plotted as a function of the wave vector q , defined as $q \text{ (nm}^{-1}\text{)} = 2\pi/\lambda \sin(\theta/2)$ where θ is the scattering angle. For the very dilute sample a strong intensity upturn at low scattering vectors (q -values), characteristic of large heterogeneities ($2\pi/q > 10$ nm), is observed. For concentrations above 20 mM (0.5%v/v) a correlation peak appears at larger q -

values, typical of small interacting colloids (\sim nm), in addition to the low q -signal. Two types of COSAN aggregates, large and small, are thus formed successively as the concentration increases. Similar conclusions can be drawn from SAXS measurements.

By using a spherical shell model for the large (vesicle-like) aggregates and a dense sphere model for the small ones (globular micelles) the SANS spectra in a logarithmic scale can be described over the whole concentration range (Fig. 2a and Supplementary). The contributions of the micelles and the vesicles to the total scattered intensity are given separately for information as dashed and dotted lines respectively. For 0.0065 M (squares) only the vesicles contribute to the scattered intensity as no micelles are present in the solution.

For vesicles, the radius R_{vesicle} obtained by fitting the SANS spectra on the available q -range is around 20 nm. Information on the vesicles size is also obtained by static light scattering in the very low concentration range from 0.02 to 0.69 mM (i.e. 5.9×10^{-4} to 2.0×10^{-2} %v/v), where only vesicles are present in solution. Calculating the aggregation number of the vesicle, $N_{\text{agg}}^{\text{vesicle}} = 12\,500 \pm 100$, the vesicle radius is determined ($R_{\text{vesicle}} = 19 \pm 1$ nm). Moreover plotting the scattered light intensity vs. COSAN concentration gives access to the critical aggregation concentration, $cac_{\text{vesicle}} \sim 0.01$ mM, corresponding to the monomer-to-vesicle transition. Such low aggregation concentrations are usual for vesicles forming surfactants or polymers e.g. doubled chained surfactants such as phospholipids.

For the micelles, a radius R_{mic} of 1.16 nm (approximately the length of a COSAN molecule) is obtained, indicating that small globular micelles with an aggregation number of about 14 are formed (Fig. 1). A subtle increase in the micelle concentration, n_{mic} , resulting from the fit, is observed at a COSAN concentration of 18.6 mM, i.e. $\phi_{\text{cac}}^{\text{mic}} = 0.54\%$ (Supplementary), which corresponds to the critical aggregation concentration of the micelles (cac_{mic}). Above cac_{mic} micelles begin to form resulting in the coexistence with the vesicles.

The thickness of the vesicle shell, ΔR , was determined from the scattering curve at 0.19%v/v, when only the vesicles are present, using an expression for the scattered intensity in absolute scale of infinite lamella (Supplementary).^[9] The first oscillation in the scattered intensity, observed in the q -range $2.4\text{--}7 \text{ nm}^{-1}$ when the background contribution is subtracted (see Fig. 2b), is well reproduced by this model for a wall thickness of 1.16 nm corresponding to the length of a COSAN ion (dotted line in Fig. 2b). The shell is then formed by a COSAN monolayer with the COSANs oriented orthogonally to the shell surface as sketched in Fig. 1 and 2b. This is an outstanding feature of COSAN vesicles compared to “conventional” vesicles, i.e. made from surfactants of comparable sizes. For those systems the shell is formed by a bilayer that prevents the contact of the hydrophobic tails with water.

As HCOSAN is fully dissociated in water, electrostatic repulsions between COSAN anions must be substantial. In order to study the influence of the electrostatic interactions on the aggregation, salt (NaCl) was added to a solution containing vesicles ([HCOSAN] = 3.7mM). The size of the vesicles was followed by using dynamic light scattering (Supplementary) as a function of salt concentration. A large increase in the hydrodynamic diameter from 80 to 890nm is observed when salt is added. This confirms that electrostatics plays an important role in the aggregation process. Consequently the aggregation of COSAN in water results then from a subtle combination of electrostatic, hydrophobic and dispersion forces.

Focusing on a larger q -range, wide-angle X-ray scattering experiments (empty circles in Fig. 2b) reveal the presence of two

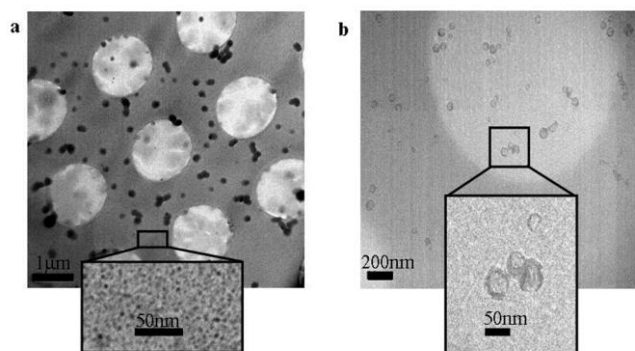


Figure 3. Cryo-TEM images of HCOSAN in H₂O at 33%v/v show: (a) the presence of small globular micelles of about 2 nm coexisting with larger vesicle-like aggregates, and (b) the hollow structure of the vesicle-like aggregates about 50 nm in diameter. In both images the large bright circles are the holes in the TEM grid.

other broad interaction peaks. The peak at higher q -range corresponds to the liquid order of water and is of no interest here. Another peak is observed at 10.8 nm^{-1} , characteristic of the closest accessible Co-Co distance ($d = 2\pi/q = 0.58 \text{ nm}$) between two COSANs in aggregates. From molecular modeling, see Figure 1, the shape of the COSAN molecule can be approximated by a biaxial ellipsoid with the Co atom at the centre and characterized by a main axis of about 1.1 nm and a semi axis of about 0.6 nm. For comparison, this liquid-order correlation peak is at the same q -value as the main Bragg peak observed in the WAXS spectrum of pure HCOSAN powder. Consequently it can be concluded that COSAN ions are at close contact and in liquid-like state in the aggregates.

To validate this unusual sequence of shapes observed via combined X-ray, neutron and light scattering, cryo-transmission electron microscopy (cryo-TEM) was performed on a sample at a concentration above c_{acmic} (Fig. 3). It confirms the sizes of the micelles and vesicles as well as their coexistence, see Fig. 3(a). The hollow structure of the vesicles inferred from the fit of the SANS spectra could also be evidenced, see Fig. 3(b).

The unconventional aggregation behaviour of COSAN originates from the combination of its θ -shape amphiphilic structure and its high charge/rigidity. From these peculiarities emerge unexpected applicative properties of COSAN derivatives such as selective ion pairing used in the reprocessing of spent nuclear fuel,^[10] as main component in ion-selective electrodes^[11] or as HIV-protease inhibition.^[12] Indeed COSAN and its derivatives have been proposed lately as novel nonpeptide enzyme inhibitors for rational drug design. The multi scale self-assembly of COSAN is also of potential interest in material science. In most of these applications COSAN derivatives are dissolved in water where aggregation

properties may play a crucial role. A better understanding of the aggregation process would then be helpful for the design and optimization of these applications.

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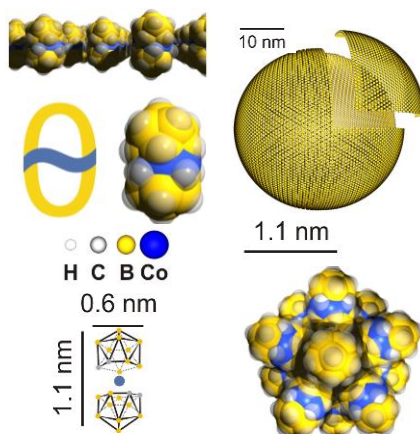
Keywords: COSAN • vesicles • micelles • SANS • cryo-TEM • carborane

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Boron cluster vesicles

Pierre Bauduin*, Sylvain Prevost, Pau Farràs, Francesc Teixidor, Olivier Diat and Thomas Zemb

Aggregation of charged rigid amphiphilic complexes: Coulomb explosion of monolayer vesicles



Cobaltabisdicarbollide (mono-)anion ($[3,3'\text{-Co}(1,2\text{-C}_2\text{B}_9\text{H}_{11})_2]^-$, COSAN⁻, is proved to form monolayer vesicles about 50 nm in diameter at low concentration in water. Increasing concentration leads to a Coulomb explosion of the closely packed vesicles into small micelles. This results in the coexistence of both aggregation states at higher concentrations. The formation of monolayer vesicles and small micelles was so far unknown for water soluble carborane derivatives.