Aggregation of Amphiphilic Molecules

- micelles, bilayers, hexagonal phases and vesicles

- surfactants and lipids can aggregate into a variety of structures and transform with changes in
  - temperature
  - ionic strength
  - pH

- must understand
  - thermodynamics (entropy effects)
  - interaction between amphiphiles in the aggregates

- goal is simple model based on molecular geometry
  \[\rightarrow\] molecular packing constraints
Aggregation of Amphiphilic Molecules

micelle

inverted micelles

bilayer

bilayer vesicle

Associative structures of amphiphilic molecules

Norde
Various Types of Phospholipid Organization

- Fluid liquid crystalline state: $L_\alpha$
- Ordered gel state: $L_\beta$
- Reversed hexagonal state: $H_{\Pi}$

From Dowhan
Lipid-Water Phase Diagram

Review of Some Thermodynamics

- Gibbs free energy (one component system)
  \[ G = U + PV - TS \]
  \[ dG = dU + PdV + VdP - TdS - SdT \]
  but \[ dU = TdS - PdV \] (1st + 2nd laws combined)
  \[ \Rightarrow dG = VdP - SdT \]

\[ : G = G(P, T) \] ← natural choice for experimental parameters

with \[ \left. \frac{\partial G}{\partial P} \right|_T = V \] and \[ \left. \frac{\partial G}{\partial T} \right|_V = -S \]
Multicomponent Systems

- Gibb's free energy of $\phi$th phase

\[ G^\phi = G^\phi (T, P, n_1, \ldots, n_N) \]

where $n_i$ is number of moles of $i$th component

\[ dG^\phi = \left. \frac{\partial G^\phi}{\partial T} \right|_{P, n_i} dT + \left. \frac{\partial G^\phi}{\partial P} \right|_{T, n_i} dP + \sum_{i=1}^{N} \left. \frac{\partial G^\phi}{\partial n_i} \right|_{T, P} dni \]

\[ = -S^\phi dT + V^\phi dP + \sum_i \mu_i^\phi dni \]

where $\mu_i^\phi$ is chemical potential of component $i$ in the phase $\phi$

\[ \mu_i^\phi = \left. \frac{\partial G^\phi}{\partial n_i} \right|_{T, P} \]

in general, depends on concentration of all components
Conditions for Equilibrium

\[ \rightarrow G \text{ is a minimum} \]
\[ \mu_i^1 = \mu_i^2 = \ldots = \mu_i^N \]

\[ \rightarrow \text{chemical potential of the } i^{\text{th}} \text{ component must be same in each phase} \]

**Ideal Gases**

\[ P = \frac{RT}{V} \sum_{i=1}^{N} n_i \]
\[ n_i \text{ is } \# \text{ of moles of } i^{\text{th}} \text{ component} \]

\[ P_i = n_i \frac{RT}{V} \text{ partial pressure } + P = \sum_{i} P_i \text{ (Dalton's law)} \]

- Gibb's free energy / mole (one component)

\[ \left. \frac{\partial G_m}{\partial P} \right|_T = V_m = \frac{RT}{P} \]
Ideal Gases

- integrate
\[ G_m(T, P) = G_{m0}(T) + RT \ln P \]

- for mixture
\[ G_{mi}(T, P_i) = G_{m0}(T) + RT \ln P_i \]

- define
\[ x_i = \frac{n_i}{\sum n_i} \text{ molar concentration of component } i \]

where
\[ \frac{P_i}{P} = \frac{n_i}{\sum n_i} = x_i \]

\[ G_{mi}(T, P, x_i) = G_{m0}(T) + RT \ln P + RT \ln x_i \]
\[ = G_{m0}(T, P) + RT \ln x_i \]

- for mixtures of ideal gases
\[ \Rightarrow \mu_i^\phi(T, P, x_i) = \mu_{i0}^\phi(T, P) + RT \ln x_i^\phi \]
Ideal Solutions

- Henry's Law
  - for a sufficiently dilute solution, the partial pressure of the solute in the vapor phase is proportional to its concentration in the solution

- for $i^{th}$ component
  \[ x_i^v = \frac{p_i}{p} \] in vapor phase
  but $x_i^v = x_i^s$

- for equilibrium, the chemical potential of the $i^{th}$ component must be the same in the solution and vapor phases
  \[ \therefore \mu_i = \mu_{i0}(T, P) + RT \ln x_i \]
  is valid for the solute in solution
Hydrophobic Effect

- hydrocarbon molecules have a much higher solubility in liquid hydrocarbons (organic solvents) than in water

\[ \mu_{HC_0} < \mu_{W_0} \]

- example

CH\(_2\) group \( \mu_{HC_0} - \mu_{W_0} = -850 \text{ cal/mol} \)

CH\(_3\) group \( \mu_{HC_0} - \mu_{W_0} = -2000 \text{ cal/mol} \)

- what interaction is responsible for the difference in \( \mu_{i_0} \)?

[Note: van der Waals forces between hydrocarbon chains is a minor effect]
Hydrophobic Effect

- due to disruption of the water "structure"
  - water molecules strongly attracted to each other

- Strength of hydrocarbon interaction is proportional to the surface area of the cavity created in the aqueous solvent by the addition of the hydrocarbon moiety

- hydrocarbon chains are "squeezed" out of aqueous region
Hydrophilic Interaction

- polar moieties in water
  - form strong polar bonds with the water molecules which have a large dipole moment
- compensates for disruption of the binding between water molecules
- attraction between polar solutes, and water lipid head groups
Thermodynamics of Micelle Formation

- want to relate chemical potential of an amphiphile in the micellar state to that of a free monomer

$$\mu_i^\phi = \mu_{i0}^\phi + RT \ln X_i^\phi$$

- both contributions change upon micellization
  inherent: due to changes in local environment
  cratic: due to aggregation

inherent part

$$\mu_{i0}^\phi$$ - consider micelles of different sizes as distinct components of the solution with distinct $$\mu_{N0}^{\text{mic}}$$, where $$N$$ is # monomers per micelle

- depends on geometry, surface to volume ratio
Thermodynamics of Micelle Formation

cratic part

\[ \frac{RT \ln ( \text{mole fraction of micelles of size } N )}{N} \]

- neglect micelle-micelle interactions
- express in terms of mole fraction of monomeric amphiphile incorporated in micelle of size \( N \): \( X_N \)

\[ \frac{RT}{N} \ln \left( \frac{X_N}{N} \right) \]

[factor of \( \frac{1}{N} \) because it is expressed as per mole of amphiphile]
Form of $\mu_{N0}$ (Inherent Part)

- the form of $\mu_{N0}^0 = \mu_{N0}$ (inherent part)

\[
\mu_{N0}^0 = \mu_{N0}^B + \mu_{N0}^S + \mu_{N0}^C + \text{"packing term"}
\]

- bulk - constant - same for all aggregates
  - measures the hydrophobic free energy of removing the hydrocarbon tails from water into the interior of the aggregate

- surface - \(a \frac{\gamma A}{\text{area per molecule}}\)
  - allows for the fact that the hydrophobic tails still have some contact with water

- \(b\frac{c}{a}\)
  - repulsive head group interaction due to steric repulsion, hydration, electrostatics
Form of $\mu_{N0}$ (Inherent Part)

- **curvature** - when the surface is curved, the head groups may have more or less area in which to move

- **packing** (repulsive part) - assume hydrocarbon region is fluid-like, incompressible and there are no holes

  - for spheres and cylinders, the radius $R < l_c$

  where $l_c$ is the length of the hydrocarbon tail
Law of Mass Action

- rate of association: $K_1 X_1^N$
- "" "" dissociation: $K_N \left( \frac{X_N}{N} \right)$

$X_N$: mole fraction

\[
\frac{(\text{mole})}{(\text{litre})}/55.5 \quad \text{for aqueous solutions}
\]
Law of Mass Action

\[
\frac{k_1}{k_N} = \frac{X_N/N}{X_1^N} = \exp \left[ -N \left( \frac{\mu_{N^0} - \mu_{1^0}}{kT} \right) \right]
\]

\[
X_N = N \left\{ X_1 \exp \left( \frac{\mu_{1^0} - \mu_{N^0}}{kT} \right) \right\}^N
\]

or from thermodynamics

\[
\mu_1 = \mu_N
\]

\[
\mu_{10} + kT \ln X_1 = \mu_{N0} + \frac{kT}{N} \ln \frac{X_N}{N}
\]

--- there may be micelles of different sizes

--- total solution concentration

\[
C = X_1 + X_2 + X_3 + \ldots + X_N = \sum_{i=1}^{2} X_i
\]
Formation of Aggregates

- aggregates only form when there is a difference in the cohesive or bonding energies for molecules in the aggregated as opposed to the monomer state

Example - all molecules in different size aggregates experience the same interaction

\[ \mu_{N_0} \text{ is independent of size} \]

\[ \mu_{10} = \mu_{20} = \ldots = \mu_{N_0} \]

- in general,

\[ X_N = N \left\{ X_1 \exp \left( \frac{\mu_{10} - \mu_{N_0}}{kT} \right) \right\}^N \]

then \[ X_N = N X_1^N \]

- since \( X_1 < 1 \), \( X_N \ll X_1 \) \( \rightarrow \) most of molecules will be in monomer state
Formation of Aggregates

Example - if $\mu_{N0}$ increases with $N$, the occurrence of large aggregates becomes even less probable.

Example - $\mu_{N0} < \mu_{0}$ for some value of $N$

   possibly 1) $\mu_{N0}$ decreases with $N$

   2) $\mu_{N0}$ has a minimum for some finite value of $N$

   - the form of $\mu_{N0}(N)$ determines the size of the aggregate

   - polydispersity can exist

   - can have a distribution of aggregate sizes

- consider consequences of 1) and 2) above

$\mu_{N0}$ decreases with $N$ tending to a finite value as $N \to \infty$

- this form can arise from end effects, e.g. hemispherical end caps on rods
Formation of Aggregates

- Second case to consider is the one for which $\mu_{N_0}$ has a minimum for a particular $N$
- occurs because of competing effects
  e.g. (a) increased hydrophobic free energy of the hydrocarbon tails for $N \leq M$
  (b) increased head group interaction due to electrostatic or geometric constraints for $N \geq M$

- consider a spherical micelle

- above a certain value of $N = M$
  there is a high energy cost to add another lipid
Formation of Aggregates

Fig. 16.4. One-, two- and three-dimensional structures formed by the association of identical monomer units in solution.
Simple Variations of $\mu_{N0}$ with N

Rods - one dimensional aggregates

- say that free energy of binding of a monomer to the aggregate is $\propto kT$

- total interaction free energy

$$N\mu_{N0} = -(N-1)\propto kT$$

$$\mu_{N0} = -(1-\frac{1}{N})\propto kT = \mu_{\infty} + \frac{\propto kT}{N}$$

:. as N increases, the mean free energy $\mu_{N0}$ decreases toward $\mu_{\infty}$

- also follows for cylindrical rods
Simple Variations of $\mu_{N_0}$ with $N$

Discs

radius of disk: $R$

radius of monomer: $L$

$\#$ monomers in disc $\approx \frac{\pi R^2}{\pi L^2} = N$

$\#$ monomers on circumference

$N_c = \frac{2\pi R}{2L} = \pi \sqrt{N}$

$\mu_{N_0}^0 = - \left(1 - \frac{N_c}{2N}\right) \alpha kT = - \left(1 - \frac{\pi \sqrt{N}}{2N}\right) \alpha kT$

half-fraction at circumference/total

$\therefore \mu_{N_0}^0 = \mu_{N_0} + \frac{\alpha kT}{N^{1/2}}$
Simple Variations of $\mu_{N0}$ with $N$

Spheres
radius of sphere: $R$
radius of monomer: $L$

$$N\mu_{N0} = - (N - \frac{N_S}{2}) \alpha kT$$

$$N = \frac{4}{3}\pi R^3 / \frac{4}{3}\pi L^3 \quad N_S = \frac{4\pi R^2}{\pi L^2}$$

$$N_S \propto N^{2/3}$$

$$\therefore \mu_{N0} = \mu_{\infty} + \frac{\alpha kT}{N^{1/3}}$$

$$\therefore \text{the form of } \mu_{N0} \text{ is}$$

$$\mu_{N0} = \mu_{\infty} + \frac{\alpha kT}{N^p}$$

$\alpha$: constant of proportionality
$p$: power
$1$: rods
$\frac{1}{2}$: discs
$\frac{1}{3}$: spheres
Critical Micelle Concentration

- at what concentration do aggregates form?

\[ X_N = N \left\{ X_1 \exp \left[ \frac{\mu_0 - \mu_{\text{NO}}}{kT} \right] \right\}^N \]

\[ \mu_{10} - \mu_{\text{NO}} = \mu_{\text{oo}} + \alpha kT - \mu_{\text{oo}} - \frac{\alpha kT}{N_P} \]

\[ = \alpha kT \left[ 1 - \frac{1}{N_P} \right] \]

\[ \therefore X_N = N \left\{ X_1 \exp \left[ \alpha \left( 1 - \frac{1}{N_P} \right) \right] \right\}^N \]

\[ \approx N \left\{ X_1 \exp \alpha \right\}^N \]

- at low \( X_1 \), \( X_1 \exp \alpha \ll 1 \)

\( X_1 > X_2 > X_3 \ldots \) for all \( \alpha \)

\( \rightarrow \) at very low concentrations, there are only isolated monomers
Critical Micelle Concentration

- since $X_N < 1$, once $X_1 \sim \exp(-\alpha)$
  
  $X_1$ cannot increase any further

  $\Rightarrow X_1 \sim \exp(-\alpha)$ defines the CMC

- what about the aggregates?

  $X_N = N \left[ X_1 \exp(\alpha) \right]^N \exp \left[ -\alpha N^{1-p} \right]$ 

- for concentrations greater than the CMC

  $X_1 \exp(\alpha) \approx 1$

  $\Rightarrow X_N \approx N \exp \left[ -\alpha N^{1-p} \right]$
Fig. 16.5. Monomer and aggregate concentrations as a function of total concentration (schematic). Most single-chained surfactants containing 12–16 carbons per chain have their CMC in the range $10^{-2}$–$10^{-5}$ M, while the corresponding double-chained surfactants have much lower CMC values due to their greater hydrophobicity. Some important CMC values are listed in Table 16.2.
Different Values of $p$

$\underline{p<1}$:

- since $\alpha > 0$ and greater than 1,

$$X_N \text{ is very small for } N > 5$$

$\Rightarrow$ there are very few aggregates of any appreciable size

- *Question*: where do the molecules go for concentrations greater than the CMC?

$\Rightarrow$ aggregates of infinite size $N \rightarrow \infty$

- for $p<1$, there is a transition to large macroscopic aggregates

  e.g. mixture of oil and water $\Rightarrow$ phase separation
Different Values of $p$

$p=1$ :  
$$X_N = N \left[ X_1 \exp(\alpha) \right]^N \frac{\exp(-\alpha)}{\text{constant}}$$

- above CMC, $X_1 \exp(\alpha) \leq 1$
  
  $\Rightarrow X_N \propto N$ for small $N$

- aggregates grow in proportion to their size

- only for very large $N$ does $\left[ X_1 \exp(\alpha) \right]^N$ begin to dominate, bringing $X_N$ back to zero as $N \to \infty$
  
  $\Rightarrow$ distribution is poly disperse

$p > 1$ : no finite or infinite sized aggregates are formed

$\Rightarrow p=1$ is a special case
Complex Amphiphilic Structures

- p is constant only for aggregates composed of fairly simple molecules that self assemble into simple geometrical shapes such as spheres, rods, discs

- there are cases in which \( \mu_{N0} \) no longer decays gradually with increasing N
  - instead it reaches a minimum value at some finite value of N, e.g. \( N = M \)
  - depending on the sharpness of the minimum, there is the possibility of monodisperse aggregates

\[ \rightarrow \text{form micelles or vesicles} \]
Lipid Aggregates

- major interactions
  - hydrophobic effect
    - induces association
  - hydrophilic nature of the headgroup
    - cannot get lipids too close
    - water must surround the headgroups

Crude model

- hydrophobic effect $\gamma a$ : attractive, where $a$ is interfacial area per lipid
- hydration "forces" $c/a$ : electrostatic repulsion between headgroups
  $(a^{1/2})$ : steric interaction between chains and headgroups
Crude Model of $\mu_{N0}^{\text{mic}}$

$$\mu_{N0}^{\text{mic}} = \delta a + c/a$$

Minimum inherent chemical potential

$$\frac{\partial \mu_{N0}^{\text{mic}}}{\partial a} = 0 = \delta - c/a^2$$

This gives optimal surface area $a_0 = \sqrt{c/\delta}$

Which gives $\mu_{N0}^{\text{mic}}$ (at minimum) = $2\delta a_0$

$$\therefore \mu_{N0}^{\text{mic}} = \frac{\delta}{a} (a^2 + a_0^2) = \frac{2\delta}{a} a_0^2 + \frac{\delta}{a} (a^2 - a_0^2)$$

Elastic energy
Crude Model of $\mu_{N0}^{\text{mic}}$
Zeroth Order Theory

- use geometrical considerations to determine which structure will actually result for a given lipid

- packing of lipids depends on
  \( a_o \) : area per polar headgroup
  \( V \) : volume of the hydrocarbon chain
  \( l_c \) : maximum length of the chain

- construct dimensionless parameter \( \frac{V}{a_o \cdot l_c} \)

- possible to find which structures allow the lipids to pack for a given set of \( a_o, V, l_c \)
Zeroth Order Theory

Example: spherical micelle

- radius of spherical micelle cannot exceed a certain critical length \( l_c \) (extended length of hydrocarbon chain)
- mean aggregation number determined by

\[
\frac{4\pi R^2}{a_0} = \frac{4\pi R^3}{3V}
\]

\[\Rightarrow \text{radius } R = \frac{3V}{a_0}\]

\[\therefore \frac{3V}{a_0} \leq l_c, \text{ can have spherical micelle}\]

\[\therefore \frac{V}{a_0 l_c} < \frac{1}{3}\]

- can also show that for cylindrical micelles, \( \frac{V}{a_0 l_c} < \frac{1}{2} \)

  - bilayer (or vesicles), \( \frac{V}{a_0 l_c} < 1 \)
  - inverted structures, \( \frac{V}{a_0 l_c} \geq 1 \)
Zeroth Order Theory

- more than one structure can satisfy the geometrical constraint

- find that $\mu_{\text{NO}}^{\text{mic}}$ is roughly the same for each

- entropy favours structure with smallest aggregation number

- large structure $\rightarrow$ entropically unfavoured

- small structure $\rightarrow$ it becomes larger than $a_0$
  (trying to force too many molecules into structure)

- best method - minimum size aggregate for which $a = a_0$
  (minimum inherent chemical potential)

- result

\[ \frac{V}{a_0 l_c} < \frac{1}{3} \]
\[ \frac{1}{3} < \frac{V}{a_0 l_c} < \frac{1}{2} \]
\[ \frac{1}{2} < \frac{V}{a_0 l_c} < 1 \]
\[ 1 < \frac{V}{a_0 l_c} \]

- spherical micelles
- nonspherical micelles
- bilayer
- inverted structures
## Zeroth Order Theory

<table>
<thead>
<tr>
<th>Effective Shape of the Surfactant Molecule</th>
<th>Packing Parameter ( \frac{a_{m,0} l}{\nu} )</th>
<th>Aggregate Morphology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cone</td>
<td>( &gt;3 )</td>
<td>Spherical Micelles</td>
</tr>
<tr>
<td>Truncated Cone</td>
<td>( 2 - 3 )</td>
<td>Wormlike Micelles</td>
</tr>
<tr>
<td>Cylinder</td>
<td>( 1 - 2 )</td>
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<td>Inverted (Truncated) Cone</td>
<td>( &lt;1 )</td>
<td>Inverted Micelles</td>
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Contribution of Different Types of Lipids to Bilayer Curvature

From Kung