Nanoparticle self-assembly in mixtures of phospholipids with styrene/maleic acid copolymers or fluorinated surfactants

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Theoretical Background

Pseudophases in lipid/surfactant mixtures

The pseudophase concept considers lipid (L) and surfactant (S) molecules in bilayer (b) and micellar (m) phases as well as surfactant monomers in the aqueous (aq) phase.[1] The concentrations of lipid and surfactant, c_L and c_S, respectively, together determine the presence and abundance of each of these phases. At given c_L, increasing c_S drives a transition from the bilayer range, which contains lipid and surfactant molecules in bilayers as well as surfactant monomers in the aqueous phase, to the coexistence range, where mixed micelles are found in addition to mixed bilayers and surfactant monomers. The first micelles appear at a threshold designated as the saturation (SAT) boundary. A further increase in c_S results in another transition from the coexistence range to the micellar range containing only micelles and surfactant monomers but no bilayer structures. This transition occurs at the so-called solubilisation (SOL) boundary, where bilayer solubilisation is complete.

Plotting the surfactant concentrations at the SAT and SOL boundaries, $c_\mathrm{S}^\mathrm{SAT}$ and $c_\mathrm{S}^\mathrm{SOL}$, respectively, against c_L gives rise to two straight lines described by:[1,2]

$$c_\mathrm{S}^\mathrm{SAT} = c_\mathrm{S}^\mathrm{aq,o} + R_\mathrm{S}^\mathrm{b,SAT} c_\mathrm{L} \tag{1}$$

$$c_\mathrm{S}^\mathrm{SOL} = c_\mathrm{S}^\mathrm{aq,o} + R_\mathrm{S}^\mathrm{m,SOL} c_\mathrm{L} \tag{2}$$

The slopes $R_\mathrm{S}^\mathrm{b,SAT}$ and $R_\mathrm{S}^\mathrm{m,SOL}$ denote the surfactant/lipid molar ratios in bilayers and micelles at which the membrane becomes saturated with surfactant and at which solubilisation is complete, respectively. Ideally, both lines meet at a common ordinate intercept, $c_\mathrm{s}^\mathrm{aq,o} = \mathrm{CMC}\, R_\mathrm{S}^\mathrm{m,SOL}/(1 + R_\mathrm{S}^\mathrm{m,SOL})$, which corresponds to the concentration of free surfactant monomers in the aqueous phase in equilibrium with surfactant-saturated bilayers and lipid-saturated micelles within the coexistence range. Note that $c_\mathrm{S}^\mathrm{aq,o} < \mathrm{CMC}$, because the latter refers to surfactant monomers in equilibrium with pure surfactant micelles in the absence of lipid.[3,4] The saturating and solubilising mole fractions of surfactant in bilayer and micellar phases, $X_\mathrm{S}^\mathrm{b,SAT}$ and $X_\mathrm{S}^\mathrm{m,SOL}$, respectively, thus amount to:

$$X_\mathrm{S}^\mathrm{b,SAT} = \frac{R_\mathrm{S}^\mathrm{b,SAT}}{1 + R_\mathrm{S}^\mathrm{b,SAT}} \tag{3}$$

$$X_\mathrm{S}^\mathrm{m,SOL} = \frac{R_\mathrm{S}^\mathrm{m,SOL}}{1 + R_\mathrm{S}^\mathrm{m,SOL}} \tag{4}$$

The partition coefficients characterising the transfer of lipid and surfactant from the bilayer phase into the micellar phase, $K_\mathrm{L}^\mathrm{b\to m}$ and $K_\mathrm{S}^\mathrm{b\to m}$, then are given by:

$$K_\mathrm{L}^\mathrm{b\to m} \equiv \frac{X_\mathrm{L}^\mathrm{m,SOL}}{X_\mathrm{L}^\mathrm{b,SAT}} = \frac{1 - X_\mathrm{S}^\mathrm{m,SOL}}{1 - X_\mathrm{S}^\mathrm{b,SAT}} = \frac{1 + R_\mathrm{S}^\mathrm{b,SAT}}{1 + R_\mathrm{S}^\mathrm{m,SOL}} < 1 \tag{5}$$

$$K_\mathrm{S}^\mathrm{b\to m} \equiv \frac{X_\mathrm{S}^\mathrm{m,SOL}}{X_\mathrm{S}^\mathrm{b,SAT}} = \frac{R_\mathrm{S}^\mathrm{m,SOL}\left(1 + R_\mathrm{S}^\mathrm{b,SAT}\right)}{R_\mathrm{S}^\mathrm{b,SAT}\left(1 + R_\mathrm{S}^\mathrm{m,SOL}\right)} = \frac{R_\mathrm{S}^\mathrm{m,SOL}}{R_\mathrm{S}^\mathrm{b,SAT}} K_\mathrm{L}^\mathrm{b\to m} > 1 \tag{6}$$

Note that the above inequalities follow from $R_\mathrm{S}^\mathrm{m,SOL} > R_\mathrm{S}^\mathrm{b,SAT}$. With the partition coefficients at hand, the corresponding standard molar Gibbs free energies of transfer from bilayers into micelles are obtained as $\Delta G_\mathrm{L}^\mathrm{b\to m,o} = -RT \ln K_\mathrm{L}^\mathrm{b\to m} > 0$ and $\Delta G_\mathrm{S}^\mathrm{b\to m,o} = -RT \ln K_\mathrm{S}^\mathrm{b\to m} < 0$ for lipid and surfactant, respectively.

Conversely, solving the system of eqn (5) and (6) for the saturating and solubilising molar ratios yields:

$$R_{\mathrm{S}}^{\mathrm{b,SAT}} = \frac{1 - K_{\mathrm{L}}^{\mathrm{b\to m}}}{K_{\mathrm{S}}^{\mathrm{b\to m}} - 1} \tag{7}$$

$$R_{\mathrm{S}}^{\mathrm{m,SOL}} = \frac{K_{\mathrm{S}}^{\mathrm{b\to m}}\left(1 - K_{\mathrm{L}}^{\mathrm{b\to m}}\right)}{K_{\mathrm{L}}^{\mathrm{b\to m}}(K_{\mathrm{S}}^{\mathrm{b\to m}} - 1)} = \frac{K_{\mathrm{S}}^{\mathrm{b\to m}}}{K_{\mathrm{L}}^{\mathrm{b\to m}}} R_{\mathrm{S}}^{\mathrm{b,SAT}} \tag{8}$$

Comparison of eqn (7) and (8) shows that the relative width of the coexistence range is given as:

$$\frac{R_{\mathrm{S}}^{\mathrm{m,SOL}}}{R_{\mathrm{S}}^{\mathrm{b,SAT}}} = \frac{K_{\mathrm{S}}^{\mathrm{b\to m}}}{K_{\mathrm{L}}^{\mathrm{b\to m}}} = \exp\left(\frac{\Delta G_{\mathrm{L}}^{\mathrm{b\to m,o}} - \Delta G_{\mathrm{S}}^{\mathrm{b\to m,o}}}{RT}\right) \tag{9}$$

In the coexistence range, the concentration of surfactant monomers in the aqueous phase is:

$$c_{\mathrm{S}}^{\mathrm{aq,o}} = \mathrm{CMC}\,\frac{R_{\mathrm{S}}^{\mathrm{m,SOL}}}{1 + R_{\mathrm{S}}^{\mathrm{m,SOL}}} = \mathrm{CMC}\frac{K_{\mathrm{S}}^{\mathrm{b\to m}}(1 - K_{\mathrm{L}}^{\mathrm{b\to m}})}{K_{\mathrm{S}}^{\mathrm{b\to m}} - K_{\mathrm{L}}^{\mathrm{b\to m}}} \tag{10}$$

Membranophobicity

If the surfactant has a pronounced preference for the micellar over the bilayer phase, as expressed by $K_{\mathrm{S}}^{\mathrm{b\to m}} \gg 1$, eqn (7) and (8) reduce to:

$$R_{\mathrm{S}}^{\mathrm{b,SAT}} \to \frac{1 - K_{\mathrm{L}}^{\mathrm{b\to m}}}{K_{\mathrm{S}}^{\mathrm{b\to m}}} \ll 1 \tag{11}$$

$$R_{\mathrm{S}}^{\mathrm{m,SOL}} \to \frac{1 - K_{\mathrm{L}}^{\mathrm{b\to m}}}{K_{\mathrm{L}}^{\mathrm{b\to m}}} \tag{12}$$

Thus, even if reliable determination of very low $R_{\mathrm{S}}^{\mathrm{b,SAT}}$ values may be difficult for experimental reasons (Fig. 1b), $K_{\mathrm{L}}^{\mathrm{b\to m}}$ can still be obtained from $R_{\mathrm{S}}^{\mathrm{m,SOL}}$ alone:

$$K_{\mathrm{L}}^{\mathrm{b\to m}} \approx \frac{1}{1 + R_{\mathrm{S}}^{\mathrm{m,SOL}}} \tag{13}$$

Poor detergency

If the lipid is very reluctant to partition from the bilayer into the micellar phase, as reflected in $K_{\mathrm{L}}^{\mathrm{b\to m}} \ll 1$, eqn (7) and (8) simplify to:

$$R_{\mathrm{S}}^{\mathrm{b,SAT}} \to \frac{1}{K_{\mathrm{S}}^{\mathrm{b\to m}} - 1} \tag{14}$$

$$R_{\mathrm{S}}^{\mathrm{m,SOL}} \to \frac{K_{\mathrm{S}}^{\mathrm{b\to m}}}{K_{\mathrm{L}}^{\mathrm{b\to m}}(K_{\mathrm{S}}^{\mathrm{b\to m}} - 1)} \gg 1 \tag{15}$$

Now, it is $R_{\mathrm{S}}^{\mathrm{m,SOL}}$ that is difficult to quantify (Fig. 1c), but $R_{\mathrm{S}}^{\mathrm{b,SAT}}$ still furnishes $K_{\mathrm{S}}^{\mathrm{b\to m}}$ as:

$$K_{\mathrm{S}}^{\mathrm{b\to m}} \approx \frac{1 + R_{\mathrm{S}}^{\mathrm{b,SAT}}}{R_{\mathrm{S}}^{\mathrm{b,SAT}}} \tag{16}$$

Data Analysis

Best-fit parameter values and 95% confidence intervals were derived by nonlinear least-squares fitting in Excel spreadsheets, as detailed elsewhere.[5]

^{31}P NMR spectroscopy

According to the pseudophase model, all lipid molecules reside in bilayer membranes as long as the surfactant concentration is lower than c_S^{SAT} (eqn (1)). In solution-state NMR experiments employing relatively narrow sweep widths, the NMR signal from ^{31}P nuclei residing in vesicular bilayers is broadened beyond detection.[6–9] Thus, the area under the ^{31}P NMR peak, A, vanishes in the absence of solubilised lipid:

$$A\left(c_S \leq c_S^{SAT}\right) = 0 \tag{17}$$

Once the surfactant concentration exceeds c_S^{SOL} (eqn (2)), all lipid molecules are solubilised and produce a sharp, isotropic NMR signal. Hence, the peak area amounts to:

$$A\left(c_S^{SOL} \leq c_S\right) = f c_L \tag{18}$$

where the proportionality factor, f, depends on experimental conditions but is constant for a given NMR spectrometer operated using identical instrument settings and acquisition parameters. Within the coexistence range, the peak area is proportional to the extent of solubilisation:

$$A\left(c_S^{SAT} \leq c_S \leq c_S^{SOL}\right) = f c_L \frac{c_S - c_S^{SAT}}{c_S^{SOL} - c_S^{SAT}} \tag{19}$$

Here, the last term on the right-hand side reflects the fraction of solubilised lipid as given by the lever rule.[1,10] Together, eqn (17)–(19) provide best-fit values of c_S^{SAT} and c_S^{SOL} at given c_L.

Isothermal titration calorimetry

By analogy to calorimetric demicellisation titrations without lipid,[11,12] isotherms obtained by titration of surfactant micelles into buffer in the presence of lipid vesicles can be fitted using a sigmoidal function of the form:[12]

$$Q(c_S) = \frac{(m_1 - m_2)(c_S - c_S^{SAT}) - \Delta H_S \dfrac{c_{S,syr} - c_S^{SAT}}{c_{S,syr}}}{1 + \exp\left(\dfrac{c_S - c_S^{SAT}}{\Delta c}\right)} + b_2 + m_2 c_S \tag{20}$$

with c_S denoting the surfactant concentration in the calorimeter cell, $c_{S,syr}$ the surfactant concentration in the syringe, and c_S^{SAT} the surfactant concentration at which the bilayer is saturated. Here, ΔH_S denotes the net change in enthalpy per mole of micellar surfactant in the syringe, which accounts for both demicellisation and membrane partitioning, and Δc is a generic parameter modulating the width of the transition region. The coefficients m_1 and m_2 are the slopes of straight pre- and post-transition baselines, respectively, and b_2 is the ordinate intercept of the post-transition baseline.

In the absence of micelles, the water-to-bilayer partition coefficient of the surfactant, $K_S^{aq\to b}$, is given as:

$$K_S^{aq\to b} \equiv \frac{X_S^b}{X_S^{aq}} = \frac{c_S^b/(c_S^b + \gamma c_L)}{c_S^{aq}/(c_S^{aq} + c_W)} \approx \frac{c_S^b c_W}{c_S^{aq} \gamma c_L} \tag{21}$$

with $c_W = 55.5$ M denoting the molar concentration of water and γ the fraction of lipid that is accessible to the surfactant; $\gamma = 0.5$ if the surfactant cannot translocate across the bilayer, while $\gamma = 1.0$ if it has access to both bilayer leaflets on the experimental timescale.[13,14] Thus, the fraction of surfactant in the bilayer phase is:

$$\frac{c_S^b}{c_S^b + c_S^{aq}} = \frac{K_S^{aq\to b}\gamma c_L}{K_S^{aq\to b}\gamma c_L + c_W} \tag{22}$$

With this expression, the net enthalpy change retrieved from a nonlinear least-squares fit according to eqn (20) can be parsed into contributions from (de)micellisation and bilayer partitioning as:

$$\Delta H_S = \Delta H_S^{aq\to m} - \frac{K_S^{aq\to b}\gamma c_L}{K_S^{aq\to b}\gamma c_L + c_W}\Delta H_S^{aq\to b} \tag{23}$$

where $\Delta H_S^{aq\to m}$ and $\Delta H_S^{aq\to b}$ are the molar enthalpy changes accompanying micelle formation and bilayer partitioning, respectively. According to eqn (23), a series of demicellisation isotherms recorded at various lipid concentrations provides these two enthalpies as the ordinate intercept and the negative slope, respectively, of a plot of ΔH_S versus the fraction of membrane-bound surfactant as given by eqn (22).

^{19}F NMR spectroscopy

In the presence of micelles, the peak chemical shift, δ_p, observed by ^{19}F NMR spectroscopy is a linear combination of the chemical shift of the free monomer in the aqueous phase as measured in the absence of micelles, δ_{mon}, and the chemical shift in the micellar state, δ_{mic}. The saturating surfactant concentration, c_S^{SAT}, and δ_{mic} were treated as fitting parameters in the equation:[9,15]

$$\delta_p(c_S) = \frac{c_S^{SAT}}{c_S}\delta_{mon} + \left(1 - \frac{c_S^{SAT}}{c_S}\right)\delta_{mic} \tag{24}$$

In the absence of lipid, c_S^{SAT} is replaced by the CMC in eqn (24).

Literature Data

Table S1. Changes in standard molar Gibbs free energy, $\Delta G^{\mathrm{b\rightarrow m,o}}$, accompanying the transfer of synthetic head-and-tail surfactants (S) and lipids (L) from bilayers (b) into micelles (m). $\Delta G^{\mathrm{b\rightarrow m,o}}$ values were calculated from $R_{\mathrm{S}}^{\mathrm{b,SAT}}$ and $R_{\mathrm{S}}^{\mathrm{m,SOL}}$ with the aid of eqn (5) and (6).

Surfactant	Lipid	Comment	T (°C)	$R_{\mathrm{S}}^{\mathrm{b,SAT}}$	$R_{\mathrm{S}}^{\mathrm{m,SOL}}$	$\frac{R_{\mathrm{S}}^{\mathrm{m,SOL}}}{R_{\mathrm{S}}^{\mathrm{b,SAT}}}$	$\Delta G_{\mathrm{S}}^{\mathrm{b\rightarrow m,o}}$ (kJ mol^{-1})	$\Delta G_{\mathrm{L}}^{\mathrm{b\rightarrow m,o}}$ (kJ mol^{-1})	$\frac{\Delta G_{\mathrm{L}}^{\mathrm{b\rightarrow m,o}}}{\Delta G_{\mathrm{S}}^{\mathrm{b\rightarrow m,o}}}$	Ref.
OG	*E. coli* lipid		8	0.947	3.11	3.28	–1.03	1.75	–1.69	16
OG	POPC		8	1.22	2.38	1.95	–0.58	0.98	–1.70	16
OG	POPC		25	1.28	2.2	1.72	–0.50	0.84	–1.67	17
OG	EPC		25	1.3	3.6	2.77	–0.81	1.72	–2.13	18
OG	EPC/EPA		25	1.66	2.74	1.65	–0.40	0.84	–2.12	19
OG	SPC		27	1.55	3.06	1.97	–0.54	1.16	–2.16	20
OG	SPC		70	1.72	2.55	1.48	–0.36	0.76	–2.09	20
OG	DMPC		27	1.56	1.79	1.15	–0.13	0.21	–1.67	20
OG	DMPC		70	1.66	2.03	1.22	–0.20	0.37	–1.83	20
OG	DPPC		70	1.5	1.94	1.29	–0.27	0.46	–1.70	20
OG	DSPC		70	1.33	2.47	1.86	–0.63	1.14	–1.80	20
OG	EPC		25	1.3	3.6	2.77	–0.81	1.72	–2.13	21
OG	EPC		28	1.6	3.1	1.94	–0.52	1.14	–2.21	22
OG	POPC		28	1.31	2.8	2.14	–0.66	1.25	–1.90	23
OG	EPC		24	1.5	3	2.00	–0.55	1.16	–2.11	6
OG	EPC	0 M NaCl	25	1.41	2.36	1.67	–0.45	0.82	–1.82	24
OG	EPC	0.02 M NaCl	25	1.75	2.96	1.69	–0.40	0.90	–2.27	24
OG	EPC	0.1 M NaCl	25	1.69	3.12	1.85	–0.46	1.06	–2.28	24
OG	EPC	0.5 M NaCl	25	1.82	3.19	1.75	–0.41	0.98	–2.40	24
OG	EPC	1 M NaCl	25	1.75	3.29	1.88	–0.46	1.10	–2.38	24
OG	EPC	1.5 M NaCl	25	1.77	3.35	1.89	–0.46	1.12	–2.42	24
OG	EPC	0 M sucrose	25	1.66	2.79	1.68	–0.41	0.88	–2.14	24
OG	EPC	0.01 M sucrose	25	1.78	2.97	1.67	–0.39	0.88	–2.29	24
OG	EPC	0.5 M sucrose	25	1.53	2.7	1.76	–0.47	0.94	–2.02	24
OG	EPC	2 M sucrose	25	2.31	4.29	1.86	–0.37	1.16	–3.12	24
OG	EPC	0.01 M urea	25	1.53	2.7	1.76	–0.47	0.94	–2.02	24
OG	EPC	0.5 M urea	25	1.46	2.8	1.92	–0.54	1.08	–2.01	24
OG	EPC	2 M urea	25	1.29	2.5	1.94	–0.59	1.05	–1.79	24
OG	EPC	4 M urea	25	1.63	1.8	1.10	–0.09	0.16	–1.71	24
OG	EPC		25	1.3	3.6	2.77	–0.81	1.72	–2.13	25
NG	EPC		25	1.4	3.9	2.79	–0.77	1.77	–2.30	25
DG	EPC		25	1.6	4.5	2.81	–0.71	1.86	–2.63	25
UG	EPC		25	2	5.0	2.50	–0.55	1.72	–3.11	25
DDG	EPC		25	2.8	6.0	2.14	–0.37	1.51	–4.04	25
NM	POPC		25	0.48	1.45	3.02	–1.49	1.25	–0.84	17
DDM	POPC		25	0.9	2.23	2.48	–0.93	1.32	–1.41	26
DDM	POPC		25	0.7	1.44	2.06	–0.89	0.90	–1.00	17
$C_{12}EO_5$	POPC		25	3.1	7.3	2.35	–0.37	1.75	–4.66	27
$C_{12}EO_6$	POPC		25	1.2	4.9	4.08	–1.04	2.45	–2.35	27
$C_{12}EO_7$	POPC		25	0.7	2.6	3.71	–1.39	1.86	–1.34	27
$C_{12}EO_8$	POPC		25	0.57	1.9	3.33	–1.46	1.52	–1.04	27
$C_{12}EO_8$	POPC		11	0.32	1.33	4.20	–2.05	1.35	–0.66	27
$C_{12}EO_8$	POPC		25	0.54	1.86	3.45	–1.54	1.54	–1.00	27
$C_{12}EO_8$	POPC		40	0.79	2.33	2.97	–1.21	1.63	–1.34	27
$C_{12}EO_8$	POPC		50	1.08	2.85	2.63	–0.95	1.65	–1.74	27
$C_{12}EO_8$	POPC		75	2.13	3.17	1.49	–0.32	0.83	–2.59	27
$C_{12}EO_8$	EPC		20	0.66	2.2	3.33	–1.33	1.60	–1.20	8
$C_{12}EO_8$	EPC		25	0.62	2.3	3.71	–1.49	1.76	–1.19	28
LDAO	POPC		25	1.39	2.62	1.88	–0.54	1.03	–1.90	3
SDS	DMPC	0.1 M NaCl	60	1.05	1.52	1.45	–0.45	0.57	–1.26	29
SDS	POPC		65	1.5	2.7	1.80	–0.55	1.10	–2.00	30
Triton	EPC		25	0.64	2.5	3.91	–1.50	1.88	–1.25	18
Triton	EPC		25	0.64	2.6	4.06	–1.53	1.95	–1.28	31
Average				**1.38**	**2.91**	**2.31**	**–0.72**	**1.23**	**–1.96**	
SD				**0.55**	**1.11**	**0.83**	**0.44**	**0.48**	**0.71**	

Surfactants: OG, NG, DG, UG, DDG, *n*-octyl-, *n*-nonyl-, *n*-decyl-, *n*-undecyl-, *n*-dodecyl-β-D-glucopyranoside; NM, DDM, *n*-nonyl-, *n*-dodecyl-β-D-maltopyranoside; $C_{12}EO_n$, with n = 5, 6, 7, 8, penta-, hexa-, hepta-, octa(ethylene oxide) dodecyl ether; LDAO, lauryldimethylamine *N*-oxide; SDS, sodium dodecyl sulphate; Triton, Triton X-100. *Lipids:* DMPC, 1,2-dimyristoyl-*sn*-glycero-3-phosphocholine; DPPC, 1,2-dipalmitoyl-*sn*-glycero-3-phosphocholine; DSPC, 1,2-distearoyl-*sn*-glycero-3-phosphocholine; *E. coli* lipid, *E. coli* polar lipid extract (67.0% phosphatidylethanolamine, 23.2% phosphatidylglycerol, 9.8% diphosphatidylglycerol); EPA, egg phosphatidic acid; EPC, egg phosphatidylcholine; POPC, 1-palmitoyl-2-oleoyl-*sn*-glycero-3-phosphocholine; SPC, soybean phosphatidylcholine.

Table S2. Changes in standard molar Gibbs free energy, $\Delta G^{\mathrm{b\rightarrow m,o}}$, accompanying the transfer of sterol-based surfactants (S) and lipids (L) from bilayers (b) into micelles (m). $\Delta G^{\mathrm{b\rightarrow m,o}}$ values were calculated from $R_{\mathrm{S}}^{\mathrm{b,SAT}}$ and $R_{\mathrm{S}}^{\mathrm{m,SOL}}$ with the aid of eqn (5) and (6).

Surfactant	Lipid	Comment	T (°C)	$R_{\mathrm{S}}^{\mathrm{b,SAT}}$	$R_{\mathrm{S}}^{\mathrm{m,SOL}}$	$\frac{R_{\mathrm{S}}^{\mathrm{m,SOL}}}{R_{\mathrm{S}}^{\mathrm{b,SAT}}}$	$\Delta G_{\mathrm{S}}^{\mathrm{b\rightarrow m,o}}$ (kJ mol^{-1})	$\Delta G_{\mathrm{L}}^{\mathrm{b\rightarrow m,o}}$ (kJ mol^{-1})	$\frac{\Delta G_{\mathrm{L}}^{\mathrm{b\rightarrow m,o}}}{\Delta G_{\mathrm{S}}^{\mathrm{b\rightarrow m,o}}}$	Ref.
CHAPS	POPC		25	0.11	0.5	4.55	–3.01	0.75	–0.25	17
CHAPS	POPC		25	0.09	0.4	4.44	–3.08	0.62	–0.20	1
CHAPS	EPC		25	0.1*	0.52	5.20	–3.29	0.80	–0.24	32
CHAPS	EPC		20	0.4	1.04	2.60	–1.41	0.92	–0.65	33
CHAPSO	EPC		20	0.21	0.74	3.52	–2.18	0.89	–0.41	33
NaC	EPC		25	0.3	0.4	1.33	–0.53	0.18	–0.35	34
NaC	EPC		25	0.3	0.9	3.00	–1.78	0.94	–0.53	18
NaC	POPC		25	0.3	0.45	1.50	–0.73	0.27	–0.37	35
NaC	POPC		60	0.37	0.54	1.46	–0.72	0.32	–0.45	35
NaC	SPC		30	0.33	0.82	2.48	–1.50	0.79	–0.53	35
NaC	SPC		60	0.45	0.91	2.02	–1.19	0.76	–0.64	35
NaC	DPPC		60	0.19	0.29	1.53	–0.95	0.22	–0.24	36
NaC	DPPC	0.1 M NaCl	60	0.21	0.32	1.52	–0.93	0.24	–0.26	37
NaC	DPPG	0.1 M NaCl	60	0.28	0.4	1.43	–0.74	0.25	–0.34	37
NaC	DPPC/PG 3:1	0.1 M NaCl	60	0.15	0.38	2.53	–2.07	0.50	–0.24	37
NaC	DPPC/PG 1:1	0.1 M NaCl	60	0.19	0.37	1.95	–1.46	0.39	–0.27	37
NaDC	DPPC	0.1 M NaCl	60	0.19	0.38	2.00	–1.51	0.41	–0.27	37
NaDC	DPPG	0.1 M NaCl	60	0.17	0.33	1.94	–1.48	0.36	–0.24	37
NaDC	DPPC/PG 3:1	0.1 M NaCl	60	0.17	0.58	3.41	–2.57	0.83	–0.32	37
NaDC	DPPC/PG 1:1	0.1 M NaCl	60	0.15	0.44	2.93	–2.36	0.62	–0.26	37
NaDC	POPC		25	0.25	0.52	2.08	–1.33	0.48	–0.36	35
NaDC	POPC		60	0.32	0.66	2.06	–1.37	0.63	–0.46	35
NaDC	SPC		30	0.35	0.81	2.31	–1.38	0.74	–0.54	35
NaDC	SPC		60	0.29	0.82	2.83	–1.93	0.95	–0.50	35
NaDC	DPPC		60	0.2	0.39	1.95	–1.44	0.41	–0.28	36
Average				**0.24**	**0.56**	**2.50**	**–1.64**	**0.57**	**–0.37**	
SD				**0.10**	**0.22**	**1.04**	**0.76**	**0.25**	**0.13**	

Surfactants: CHAPS, 3-[(3-cholamidopropyl)dimethylammonio]-1-propanesulphonate; CHAPSO, 3-[(3-cholamidopropyl)dimethylammonio]-2-hydroxy-1-propanesulphonate; NaC, sodium cholate; NaDC, sodium deoxycholate. *Lipids:* DPPC, 1,2-dipalmitoyl-*sn*-glycero-3-phosphocholine; DPPG, 1,2-dipalmitoyl-*sn*-glycero-3-[phospho-*rac*-(1-glycerol)]; EPC, egg phosphatidylcholine; POPC, 1-palmitoyl-2-oleoyl-*sn*-glycero-3-phosphocholine; SPC, soybean phosphatidylcholine. Included in the table are only datasets for which the saturation and solubilisation boundaries (eqn (1) and (2), respectively) have identical or, at least, similar ordinate intercepts, $c_{\mathrm{S}}^{\mathrm{aq,o}}$. This is usually not the case for many of the above lipid/surfactant systems at low ionic strength,[35–37] necessitating more sophisticated thermodynamic analysis.[38] *See ref. 17 for a discussion of this value.

Table S3. Changes in standard molar Gibbs free energy, $\Delta G^{\mathrm{b\rightarrow m,o}}$, accompanying the transfer of unconventional surfactants (S) and lipids (L) from bilayers (b) into micelles (m). $\Delta G^{\mathrm{b\rightarrow m,o}}$ values were calculated from $R_{\mathrm{S}}^{\mathrm{b,SAT}}$ and $R_{\mathrm{S}}^{\mathrm{m,SOL}}$ with the aid of eqn (5) and (6).

Surfactant	Lipid	Comment	T (°C)	$R_{\mathrm{S}}^{\mathrm{b,SAT}}$	$R_{\mathrm{S}}^{\mathrm{m,SOL}}$	$\frac{R_{\mathrm{S}}^{\mathrm{m,SOL}}}{R_{\mathrm{S}}^{\mathrm{b,SAT}}}$	$\Delta G_{\mathrm{S}}^{\mathrm{b\rightarrow m,o}}$ (kJ mol^{-1})	$\Delta G_{\mathrm{L}}^{\mathrm{b\rightarrow m,o}}$ (kJ mol^{-1})	$\frac{\Delta G_{\mathrm{L}}^{\mathrm{b\rightarrow m,o}}}{\Delta G_{\mathrm{S}}^{\mathrm{b\rightarrow m,o}}}$	Ref.
Surfactin	POPC	lipopeptide	25	**0.22**	**0.46**	**2.09**	**–1.38**	**0.45**	**–0.32**	39
P2A2	POPC	lipopeptide	25	**0.012**	**0.13**	**10.8**	**–5.63**	**0.27**	**–0.05**	40
SMA(3:1)	POPC	copolymer	25	**0.099**	**0.147**	**1.49**	**–0.87**	**0.11**	**–0.05**	*
F_6OM	POPC	fluorinated	25	**1.0**	**3.0**	**3.00**	**–1.01**	**1.72**	**–1.71**	9
F_6OPC	POPC	fluorinated	25	**0.031**	**>1000**	**>30000**	**–8.68**	**>17**	**<–1.96**	*

Surfactants: P2A2, dipalmitoylated tandem peptide derived from apolipoprotein E; SMA(3:1), styrene/maleic acid copolymer with styrene/maleic acid molar ratio of 3:1; F_6OM, 3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluoro-*n*-octyl-β-D-maltopyranoside; F_6OPC, 3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluoro-*n*-octylphosphocholine. *Lipid:* POPC, 1-palmitoyl-2-oleoyl-*sn*-glycero-3-phosphocholine. Colour code is matched to Fig. 6 in main text. *This work.

Supplementary References

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