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FULL PAPER

Detergent-Like Polymerizable Monomers: Synthesis, Physicochemical, and Biochemical Characterization

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Abstract: Three monomers with a maltose polar head, an alkyl hydrogenated chain, and an acrylamide-based polymerizable moiety were synthesized. The self-assembly properties in aqueous solutions of these monomers were studied by means of isothermal titration calorimetry (ITC), surface tension (SFT) measurements, and dynamic light scattering (DLS), which indicated the formation of small micellar aggregates of about 6 nm diameter. The critical micellar concentration (CMC) was found to depend on the length of the alkyl chain and on the nature of the polymerizable moiety, ranging from 0.35 mM to ~10 mM. The monomers were found to solubilize phospholipid vesicles and to extract a broad range of proteins from *Escherichia coli* membranes. Finally, the extraction of two membrane proteins, namely, the full-length, wild-type human G-protein-coupled receptor (GPCR) adenosine receptor ($A_{2A}R$) and the bacterial transporter AcrB was demonstrated.

Introduction

Membrane proteins (MPs) perform a wide range of essential cellular functions and are involved in a large number of pathologies, which makes them priority drug targets representing nearly 70 % of therapeutic targets.[1] Because MPs exhibit high insolubility in water and poor stability outside their native membrane environment, their extraction from the membrane is highly challenging and may result in denaturation and/or aggregation of the protein once removed from their native environment. The need of natively isolated, yet stable proteins has prompted the development of sophisticated chemically well-defined detergents over the recent years. Among these new, chemically homogenous systems, one can cite neo-pentyl glycols derivatives,[2] derivatives with branched[3] or fluorinated chains,[4] as well as steroid-based and facial derivatives.[5]
Other approaches for handling and studying MPs relate to the use of heterogeneous systems such as protein-lipid nanodiscs[6], A8-35 amphipol (APols),[7], and nanodiscs bounded by poly(styrene-*co*-maleic acid) (SMA)[8] and poly(diisobutylene-*alt*-maleic acid) (DIBMA)[9] copolymers. Amphipols adsorb onto the hydrophobic transmembrane surface of membrane proteins thanks to their alkyl chains and the complex thus formed remains water-soluble thanks to the hydrophilic groups. MP/amphipols complexes are indeed very stable even at high dilutions due to the slow dynamic of the polymer which remains tightly attached to the protein. Unlike the other heterogeneous systems, SMA and DIBMA can efficiently recruit MPs and associated lipids directly from natural or artificial membranes into nanoscale lipid-bilayer patches that closely mimic the lamellar organization of cellular membranes. However, one common limitation of A8-35, SMA, and DIBMA lies in the presence of carboxylic groups along the polymer chain that result in polymer aggregation at acidic pH or in the presence of multivalent cations.[10]

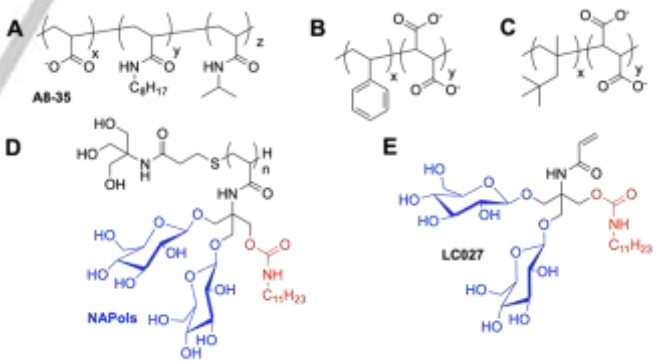
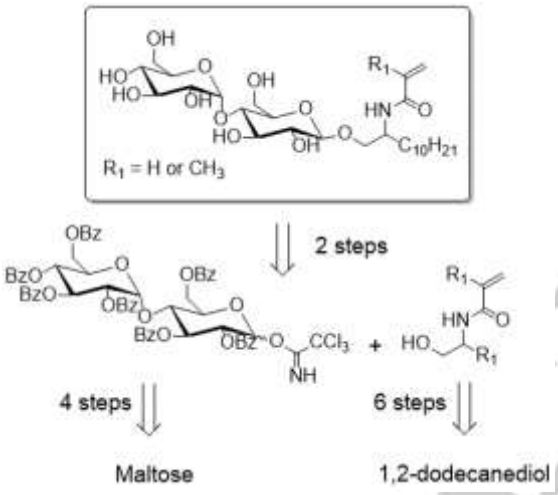


Figure 1. Structure of (**A**) A8-35 amphipol, (**B**) poly(styrene-*co*-maleic acid) (SMA) copolymer, (**C**) poly(diisobutylene-*alt*-maleic acid) (DIBMA) copolymer, (**D**) non-ionic amphipol (NAPol), and (**E**) its constituting detergent-like monomer (**LC027**).

This limitation has prompted the development of several amphipols derivatives including zwitterionic,[11] sulphonated,[12] or phosphocholine-based amphipols[13] as well as non-ionic APols called NAPols.[14] A first series of glucose-based NAPols was obtained either from co-telomerization of hydrophilic and hydrophobic monomers[14b] or by homo-telomerization of hydrophilic monomers, followed by hydrophobization of the polymer.[15] These glycosylated NAPols showed good potency at

keeping various MPs soluble in their native state in the absence of detergent.[14b, 15] We further designed homopolymeric NAPols (**Figure 1**) consisting of an amphiphilic repeating unit[16] (called **LC027** in the current study).[14a] This more convenient synthetic route offers the advantage of resorting to only one amphiphilic monomer and to allow better batch-to-batch reproducibility and higher yields. **LC027** due to its amphiphilic chemical structure and its surface activity belongs to the family of surfmers.[17] Surfmers combine the functionalities of surface active agents with the reactivity of monomers. The polymerization of surfmers has been successfully employed for several applications such as emulsion stabilization, nanomaterials synthesis, drug-delivery systems, and hydrogels. The promising results obtained with this most advanced series of NAPols further confirmed their advantages over the classical A8-35 for specific applications such as cell-free synthesis, nuclear magnetic resonance (NMR) spectroscopy, and mass spectrometry (MS), to name but a few.[18] More recently, the first cryo-EM structure of the translocase of the outer membrane (TOM) core complex in NAPol has been reported.[19]



Scheme 1. Retrosynthetic pathway for compounds **LC048** and **LC058**.

However, like others amphipols, NAPols are unable to solubilize membrane proteins. It is therefore necessary to proceed in two distinct steps by doing first the extraction of the protein with a detergent and then performing the exchange with the polymer. As part of our long-term project, the work presented herein deals with the evaluation of the solubilizing properties of detergent-like monomers that could be further used in the synthesis of new NAPols. We expected that, while polymeric NAPols are very efficient stabilizing agents, the constituting monomers could exhibit solubilizing properties.

We report the synthesis of three detergent-like monomers refer to as surfmers and called **LC048**, **LC049**, and **LC058** that present chemical similarity with conventional *n*-dodecyl-β-d-maltopyranoside (DDM), which so far is considered as the gold standard for membrane-protein extraction. These new compounds are characterized by the presence of a maltose polar head, a hydrogenated alkyl chain, and an acrylamide or methacrylamide moiety that enables polymerization for further work. We chose to use acrylamide group instead of acrylester due to higher stability of the amide bond compared to the ester one. For the sake of comparison, **LC027** was also included in the study.

The colloidal properties of the four surfmers were evaluated by means of isothermal titration calorimetry (ITC), surface tension (SFT) measurements, as well as dynamic light scattering (DLS). Their potency to act as solubilizing agents was further evaluated with model membranes as well as with different membrane proteins from two cell membranes.

Results and Discussion

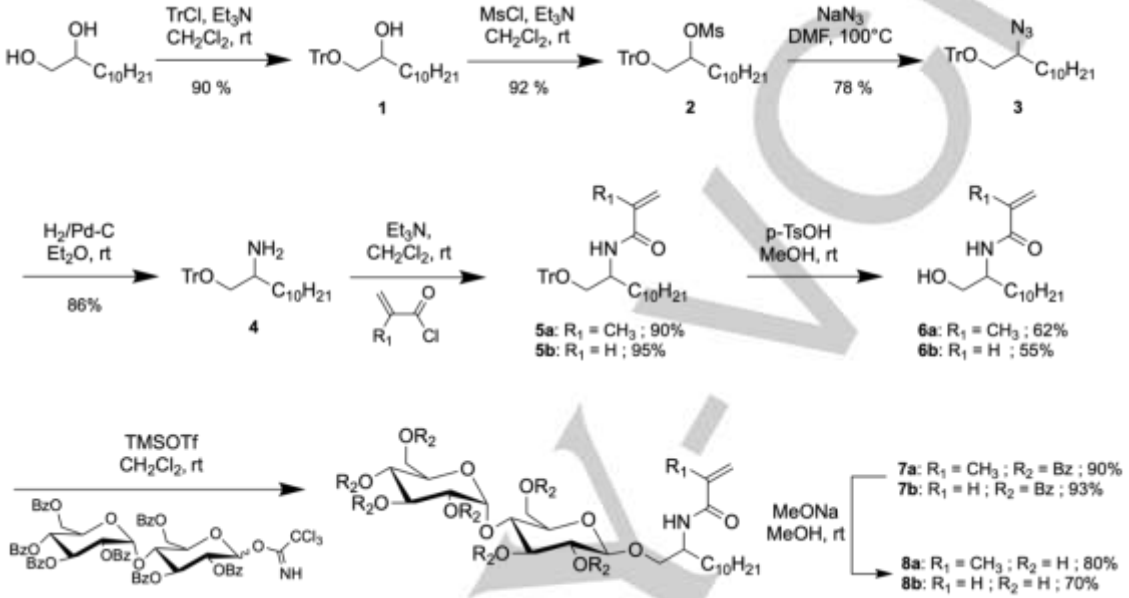
Synthesis. The synthesis followed a convergent synthetic pathway, based on three key steps: (i) synthesis of the hydrophobic parts; (ii) synthesis of the maltose polar head; (iii) coupling of the hydrophobic and hydrophilic parts (Scheme 1).

Compounds **8a-b** were synthesized following an eight-step synthetic route starting from 1,2-dodecanediol (**Scheme 2**). Selective protection of the primary alcohol group was achieved using Et_3N and 1.2 equivalent of trityl chloride as previously reported.[20] Mesylation of the secondary alcohol group followed by nucleophilic substitution in the presence of NaN_3 afforded compound **3** in good yield (65% in three steps). The azide group was next reduced under hydrogen atmosphere at room temperature, using catalytic amounts of Pd-C to lead to compound **4** in high yield. The insertion of the polymerizable moiety on the amine group was realized using either acryloyl chloride or methacryloyl chloride at room temperature in the presence of trimethylamine (TEA). Deprotection of **5a-b** in acidic condition led to compounds **6a-b**. In our hands, only moderate yields of deprotection were observed, that is, 55 and 63%, respectively.

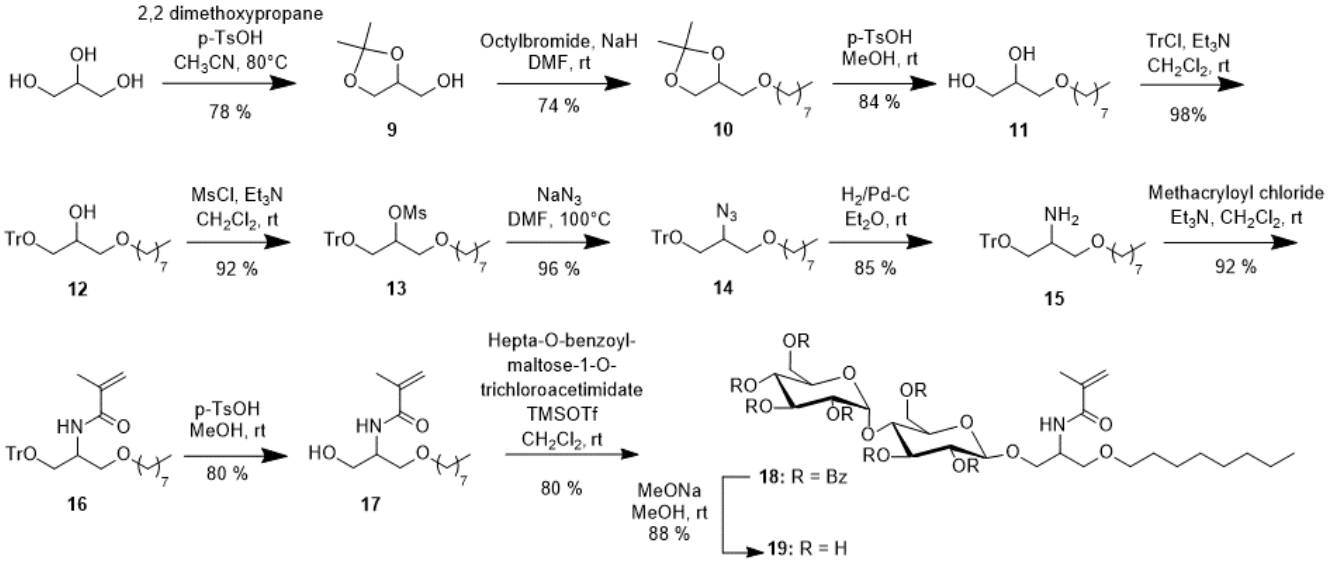
In order to obtain high-yield and stereoselective *O*-glycosylation leading to the β-anomer, activation of the anomeric position and protection of the other free hydroxy groups seemed preferable. We therefore activated maltose into its trichloroacetimidate form and used benzyl esters protecting groups.[21] Hepta-O-benzoyl-maltose-1-O-trichloroacetimidate was readily prepared from commercially available maltose following a four-step synthetic route[22] and was next condensed onto the hydrophobic parts **6a** and **6b** at room temperature following a Schmidt glycosylation[23] to give compounds **7a-b** in very good yields. Hydrolysis of benzoyl groups using catalytic amount of sodium methoxide in MeOH afforded compounds **8a-b** in good yields also called **LC048** and **LC058**, respectively. Analysis of the proton NMR spectra showed the formation β anomer witnessed by a doublet between 4.0 and 4.5 ppm with a coupling constant of ~8 Hz (J_{trans}) corresponding to the anomeric proton H_1. The second anomeric proton between the two glucose units appeared at 5.2 ppm with a coupling constant of ~4 Hz (J_{cis}).

LC049 was synthesized following an eleven-step synthetic route starting from glycerol (**Scheme 3**). The two hydroxyl groups were protected by reaction using 2,2-dimethoxypropane and catalytic amount of p-TsOH in CH_3CN to afford compound **9** also called solketal.[24] The addition of the hydrogenated chain was achieved by an S_N2 reaction in the presence of sodium hydride (NaH) and 1.2 equivalent of octyl bromide to give compound **10** in 74 % yield. Then, hydrolysis in acidic conditions gave compound **11** in good yield, which was next put in reaction with Et_3N and 1.2 equivalent of trityl chloride to yield compound **12**. Mesylation of the secondary alcohol group followed by nucleophilic substitution in the presence of NaN_3, afforded compound **13** in good yield. The azide group was reduced at room temperature using a catalytic

amount of Pd-C under hydrogen pressure to afford compound **15** in 64 % yield in three steps. Next, the insertion of the methacrylamide moiety on the amino group was achieved using triethylamine and methacryloyl chloride, followed by a deprotection in acidic conditions to lead to compound **17.** Hepta-O-benzoyl-maltose-1-O-trichloroacetimidate was condensed onto **17** at room temperature following a Schmidt glycosylation[23] to give compounds **18** in 80% yield. Finally, hydrolysis of benzoyl groups using catalytic amount of sodium methoxide (MeONa) in MeOH afforded compound **19**, also called **LC049**. The overall yield for the synthesis of **19** is ~18% while that of **8a** and **8b** is respectively, 22 and 19%. Since we started from racemic starting materials, we expected the formation of mixture of diastereomers although neither NMR nor HPLC analysis allowed us to distinguish the presence of such diastereomers. Therefore, the investigated properties reported below are considered as the result of a mixture of diastereomers.



Scheme 2. Synthesis of **LC048 (8a)** and **LC058 (8b)**.



Scheme 3. Synthesis of **LC049 (19)**

Micellization. The micellization processes of the monomers were characterized by means of high-sensitivity ITC and surface tension such as exemplified in Figure 2. CMC values derived from these two techniques (Table 1) were found to be in very good agreement between each other. **LC027**, **LC049**, and **LC058** were well soluble in aqueous solution; once the compounds were solubilized, the solutions remained transparent. By contrast, **LC048** tended to precipitate after solubilization. Several attempts at heating and using sonication failed to keep it soluble for long periods of time.

The surface activity of surfactants in solution at the air−water interface was determined by the Wilhelmy plate technique for the four monomers. The two derivatives **LC048** and **LC058** exhibited CMC values of 0.35 and 0.64 mM, respectively. Compared with that of DDM (0.17 mM, see Table 1), these values indicate a strong influence of the polymerizable moiety. Indeed, introducing the acrylamide group contributes to shortening the alkyl chain from C12 to C10. This effect is likely due to the polarity of the amide bond directly attached to alkyl chain that can favor hydration. The CMC of **LC048** and **LC058** lie in between that of DDM and of the undecyl derivative UDM (0.65 mM). This indicates that the double bond of the acrylamide group brings also hydrophobicity to the molecule, the contribution of the methacrylamide being obviously more pronounced than that of the acrylamide. **LC049** has a CMC close to 10 mM, which is ~25 times higher than that of **LC048**, indicating that the position of the oxygen atom within the chain contributes to shortening it to a C8 alkyl chain. The CMC of **LC049** lies in between that of the *n*-nonylmaltoside (6 mM) and that of the octyl derivative (19.5 mM) in agreement with the slight hydrophobic contribution of the double bond of the acrylamide group. Since ITC requires good solubility of the tested compounds for preparation of stock solution at ~10 times the CMC, only **LC049**, **LC058**, and **LC027** were tested, as the rather limited water solubility of **LC048** made the preparation of such stock solutions impossible.

Table 1. Self-Aggregation Properties of DDM, **LC027**, **LC048**, **LC058**, and **LC049**.

	Monomers	DDM[25]	LC027	LC048	LC058	LC049
Molar mass (g/mol)		510.6	696.8	593.7	595.7	579.7
ITC	CMC (mM)[a]	0.147	0.55 ± 0.02	nd	0.70 ± 0.04	10.6 ± 0.04
	$-T\Delta S°_{mic}$ (kJ/mol)[b]	-35.1	-28.3 ± 0.10	nd	-29.0 ± 0.2	-25.3 ± 0.1
	$\Delta H°_{mic}$ (kJ/mol)[c]	3.8	-0.22 ± 0.01	nd	0.97 ± 0.1	4.02 ± 0.03
	$\Delta G°_{mic}$ (kJ/mol)[d]	-31.30	-28.6 ± 0.1	nd	-28.0 ± 0.1	-21.2 ± 0.02
	Δc (mM)[e]		0.05 ± 0.02	nd	0.12 ± 0.03	0.86 ± 0.04
SFT	CMC (mM)[a]	0.17	0.51 ± 0.07	0.35 ± 0.02	0.64 ± 0.10	10.28[f]
	γ_{CMC} (mN/m)[g]	34.7	35.1 ± 2.8	34.4 ± 0.2	35.7 ± 2.2	32.9[f]
	$\Delta G°_{mic}$ (kJ/mol)[d]	-30.7	-28.8 ± 0.3	-29.7 ± 0.2	−28.8 ± 1.0	−21.1[f]
DLS	D_H (nm)[h]	7.2	5.9	6.0	5.9	5.7

[a] Data are averages of three experiments. ± indicates standard errors from the three experiments. [b] Entropic contribution to micelle formation. ± indicates 95 % confidence interval boundaries. [c] Enthalpic contribution to micelle formation. ± indicates 95 % confidence interval boundaries. [d] Gibbs free energy of micellization. ± indicates 95 % confidence interval boundaries. [e] Micellization concentration range. ± indicates 95 % confidence interval boundaries. [f] Only one experiment. [g] Surface tension attained at the CMC. [h] Hydrodynamic diameter at 2×(CMC + 5 mM) in buffer (50 mM Tris, 200 mM NaCl, pH 7.4).

The changes in Gibbs free energy $\Delta G^{m/aq,°}_{Det}$, enthalpy $\Delta H^{m/aq,°}_{Det}$, and entropy $-T\Delta S^{m/aq,°}_{Det}$ accompanying the transfer of monomers from the aqueous solution into micelles are summarized in Table 1 and show that micellization was almost exclusively driven by entropy, with enthalpy making only a minor contribution that decreased and changed sign with increasing chain length. The contribution of the oxygen atom to micellization accounted for about ~8.0 kJ/mol, as deduced by a comparison between **LC049** and **LC048**, which is in rather good accordance with a reduction of the chain length of two CH_2 (typically -3.0 kJ/mol par CH_2 unit).

We next conducted DLS experiments in Tris buffer to determine the hydrodynamic diameters of the aggregates formed. Whatever monomer tested, volume size distribution indicated the presence of one population of aggregates of about 6 nm in diameter as exemplified in Figure 2C. This is similar to what is observed for DDM (6.6 nm), indicating that the additional polymerizable moiety did not substantially affect the morphology of the aggregates.

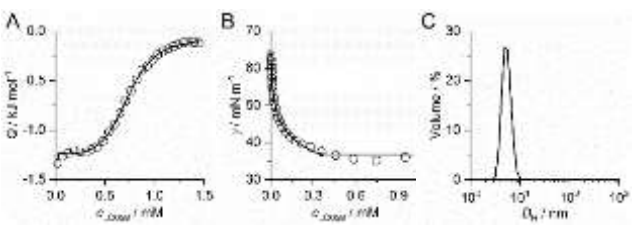


Figure 2. (A) ITC data for **LC058**. Shown are an experimental isotherm (open symbols) and a fit based on a generic sigmoidal function (solid line). (B) Surface tension versus **LC058** concentration. The solid line represents the nonlinear fit of the experimental points. (C) Normalized volume-weighted particle size distributions for **LC058**.

Complementary experiments were done in pure water and led to similar observation with only one population of aggregates of about 5 nm in diameter (Figure S40).

Number size distribution also showed unimodal distribution with aggregates of about 4 nm in diameter while intensity distribution showed a bimodal distribution with main aggregates of about 5 to 6 nm and a second minor population of bigger aggregates (Figure S40).

Detergency. Because of the rather limited water solubility of **LC048**, this compound was not further studied in the following biochemical validation. To investigate detergency, that is, the ability both to solubilize artificial lipid bilayers and to extract membrane proteins, we first investigated the solubilization of large unilamellar vesicles (LUVs) composed of monounsaturated zwitterionic phospholipid 1-plamitoyl-2-oleyl-*sn*-glycero-3-phosphocholine (POPC) into mixed micelles with the aid of light scattering measurements.[4a] The solubilization of 0.3 mM POPC in the form of LUVs was complete within a few hours for **LC027**, **LC049**, and **LC058** (Figure 3). While **LC058** enabled complete solubilization in less than an hour, **LC027** also allowed complete but slower solubilization over a time period of ~5 h. Finally, **LC049** achieved fast but only partial solubilization or formed larger mixed micelles than these obtained from **LC027** or **LC058**. POPC was chosen because—under the premise that a complex cellular membrane can be mimicked by one single phospholipid species—it is generally considered the most "typical" eukaryotic lipid.

Next, we investigated the extraction of integral membrane proteins from *E. coli* membranes in terms of sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS-PAGE) band patterns and overall amounts of extracted proteins. We compared the protein-extraction yields thus obtained with those afforded by DDM. As can be seen in Figure 4A, the three derivatives were able to extract MPs spanning a broad range of molar masses. Figure 4B shows the overall protein-extraction yields relative to the value obtained using 10 mM micellar DDM in dependence on the concentration of micellar detergent (*i.e.*, total detergent concentration minus CMC). As expected, all protein-extraction yields were concentration-dependent, but this dependence varied clearly among the derivatives tested. At a concentration of 1 and 2 mM above the respective CMC, the three surfmers performed better than DDM, with **LC027** and **LC049** being the most efficient protein solubilizers. Increasing the concentration further to 5 and 10 mM above the CMC did not enhance the yields for **LC027** and **LC058** and slightly reduced that of **LC049**, whereas the protein-extraction yield of DDM continued to increase steeply as previously observed.[26] However, it needs to be pointed out that the superior performance of DDM at high concentrations was largely due to its unusually efficient extraction of a single abundant membrane protein, namely, outer membrane protein A (OmpA, ~35 kDa), as previously observed in other cases.[27]

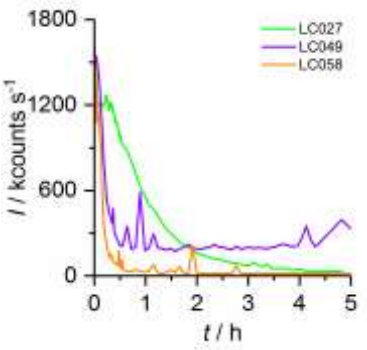


Figure 3. Vesicle solubilization by 5.55 mM **LC027**, 15.56 mM **LC049**, or 5.70 mM **LC058** (*i.e.*, 5 mM above the respective CMC determined by ITC) at 25 °C as monitored in terms of the light scattering intensity recorded at an angle of 90°. Initially, each sample contained 0.3 mM POPC present in the form of LUVs.

In order to evaluate if the solubilizing properties of these surfmers can be extended to other membranes and other membrane proteins, we applied them to membrane proteins recombinantly produced in *E. coli* and insect cells (*Sf*9), namely, the bacterial transporter AcrB and the adenosine receptor $A_{2A}R$. These targets represent two important but distinct classes of membrane proteins, that is, transporters and G-protein-coupled receptors (GPCRs), respectively. Solubilization efficiency was assessed using stain-free SDS-PAGE and Western blots for total and target proteins, respectively, for both pure surfmers at 10 times the CMC and for DDM/monomer mixtures at a molar ratio of [10:1]. As previously reported, for solubilizing $A_{2A}R$, a DDM/cholesterol hemi-succinate [DDM:CHS] mixture was used as a reference condition, while we used DDM as reference for solubilizing AcrB. Solubilization of $A_{2A}R$ showed that **LC058** exhibited rather good extraction yields (~79 %), while that of **LC049** remained moderate (~49 %). When used as solubilization additives, both [DDM:**LC049**] and [DDM:**LC058**] mixtures outperformed the reference conditions, with extraction yields of ~73 % and ~90 %, respectively, indicating additive effects (**Figure 5A**). For the sake of comparison, **LC027** was also tested and showed good solubilizing properties (~70%) similar to the reference. Solubilization of AcrB led to lower extraction yields for both **LC049** and **LC058** monomers than for the reference. However, when [DDM:**LC049**] and [DDM:**LC058**] mixtures were used, extraction yields were as high as that of the reference (**Figure 5B**), indicating that, even if the new compounds failed to extract significant amounts of AcrB on their own, they did not preclude extraction by the reference detergent DDM. As has been observed numerous times before, there appears to be no obvious correlation between membrane composition, protein structure, and detergent chemistry on the one hand and their potency of protein extraction on the other.

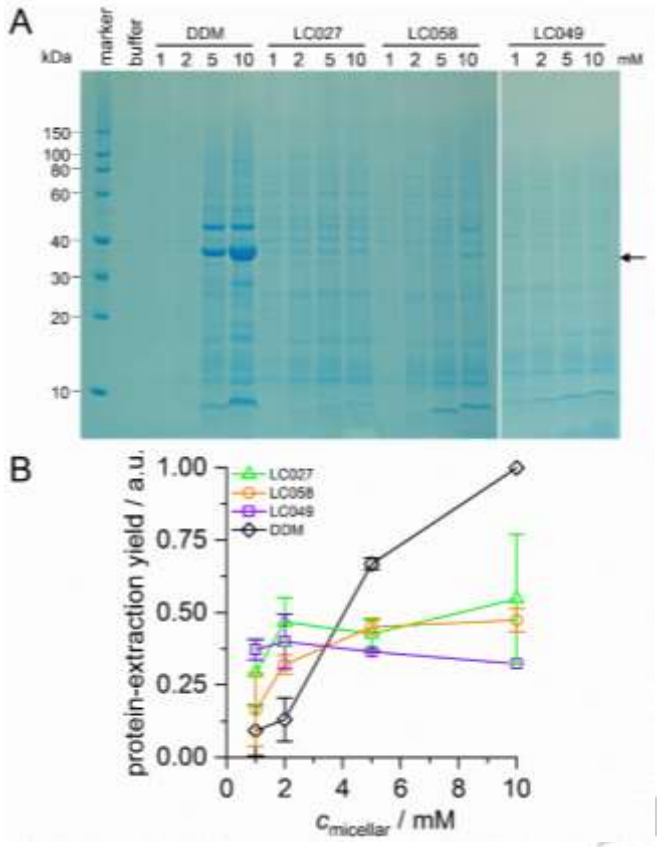


Figure 4. (A) SDS-PAGE of *E. coli* extracts upon exposure to different monomers at increasing micellar concentration (*i.e.*, total detergent concentration minus CMC). The arrow indicates the position of the abundant outer-membrane porin OmpA, which was extracted extraordinarily well by DDM. (B) Relative protein-extraction yields as functions of the micellar concentration of **LC027**, **LC058**, **LC049**, or DDM. Extraction yields are reported relative to the yield obtained when DDM was used at 10 mM. Error bars indicate standard deviations of 2 experiments except for 10 mM micellar **LC049**.

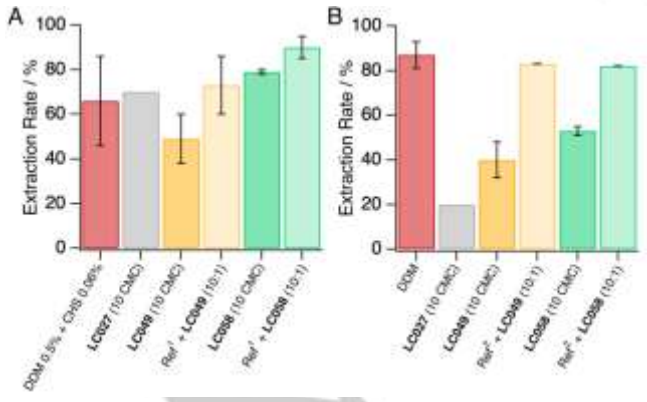


Figure 5. (A) Solubilization of $A_{2A}R$ (Ref^1 = DDM 0.5 % + CHS 0.06 %). (B) Solubilization of AcrB (Ref^2 = DDM 0.5 %).

Conclusion

We have synthesized a series of three amphiphilic monomers that are chemically similar to the conventional detergent DDM. **LC048** and **LC058** can be viewed as DDM molecules onto which were grafted, respectively, a methacrylamide and an acrylamide unit, while **LC049** differs from **LC048** by substitution of one oxygen atom for a CH_2 in the chain. The effect of attaching an amide bond within the chain contributes to shortening the length of the alkyl chain to 10 carbon atoms for **LC048** and **LC058**, and to 8 carbon atoms for **LC049**. All three monomers formed micellar aggregates of similar size (~6 nm in diameter), indicating that the attached polymerizable moiety did not significantly affect the self-association properties. However, we noticed that the nature of the polymerizable moiety had a much stronger effect on the water solubility, the methacrylamide derivative **LC048** being poorly soluble above its CMC, which precluded its use in biochemical evaluation. **LC049**, **LC058**, and **LC027** a previously designed monomer that is used for the synthesis of non-ionic amphipols (NAPols) showed potency in solubilizing a model membrane system which is POPC preformed liposomes, and in extracting integral membrane proteins from *E. coli* membranes. Further, the potency of these surfmers to extract the full-length, wild-type human GPCR adenosine receptor (A2AR) was demonstrated, while lower solubilization yields were observed for the bacterial transporter AcrB. Taken together, these findings demonstrate that the new amphiphilic monomers behave similarly to classical detergents. This warrants further development of poly-detergent based polymers that could be used for handling membrane proteins.

Experimental Section

Materials & Methods. All starting materials were commercially available and were used without further purification. Racemic 1,2-dodecanediol and racemic glycerol acetonide were used as starting materials. All solvents were of reagent grade and used as received unless otherwise indicated. MeOH was dried over Na under argon atmosphere. The progress of the reactions was monitored by thin layer chromatography. The compounds were detected either by exposure to ultraviolet light (254 nm) or by spraying with sulfuric acid (5% ethanol) and/or ninhydrin (5% ethanol), followed by heating at ~150 °C. ^1H and ^{13}C NMR analysis were performed at 400 and 100 MHz, respectively. Chemical shifts are given in ppm relative to the solvent residual peak as a heteronuclear reference for ^1H and ^{13}C. Abbreviations used for signal patterns are: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; dd, doublet of doublet; dt, doublet of triplet. High-resolution mass spectra were determined on a Synapt G2-S (Waters) mass spectrometer with a TOF mass analyzer in a positive ionization mode. Milli-Q water (resistivity of 18.2 MΩ cm, surface tension of 71.45 mN/m at 25 °C) was employed for all physicochemical experiments.

(((2-azidododecyl)oxy)methanetriyl)tribenzene (3). To a solution of **1** (24 g, 54.0 mmol, 1 eq) in anhydrous CH_2Cl_2, was added Et_3N (15.1 mL, 108.0 mmol, 2 eq). The solution was stirred for 20 minutes then methanesulfonyl chloride (5.0 mL, 64.8 mmol, 1.2 eq) was added dropwise. The reaction mixture was stirred for 16 h and the solution was filtered and concentrated *in vacuo*. The crude compound was purified by flash chromatography (cyclohexane/AcOEt 95:5 v/v) to yield compound **2** as a white solid (26.0 g, 92 %) which was directly used in the next step. To a solution of **2** (22 g, 42.1 mmol, 1 eq) in anhydrous DMF was added NaN_3 (6.8 g, 84.2 mmol, 2 eq). The reaction mixture was stirred for 16 h at 100°C. Then, the solution was diluted with water and extracted twice with AcOEt. The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The crude compound was purified by flash chromatography (cyclohexane/AcOEt 100:0 to 95:5 v/v) to yield compound **3** as a colorless oil (15.2 g, 78 %). **Rf** = 0.7 (cyclohexane/AcOEt 95:5 v/v). **^1H NMR** ($CDCl_3$, 400 MHz): δ 7.48-7.24 (15H, m); 3.38 (1H, m); 3.29 (1H,

dd, *J* = 4 Hz, *J* = 10 Hz); 3.16 (1H, dd, *J* = 8 Hz, *J* = 10 Hz); 1.40 (2H, m); 1.23 (16H, bs); 0.88 (3H, t, *J* = 8 Hz). **^{13}C [12] NMR** ($CDCl_3$, 100 MHz): *δ* 143.7; 128.6-127.0; 87.0; 66.3; 62.6; 31.8; 30.8; 29.6; 29.5; 29.4; 29.3; 29.2; 25.9; 22.6; 14.1. **HRMS** (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{31}H_{39}N_3ONa$ 492.2991; found 492.2989.

1-(trityloxy)dodecan-2-amine (4). To a solution of **3** (6 g, 12.8 mmol, 1 eq) in Et_2O was added to a suspension of Pd-C (640 mg) in Et_2O. The reaction mixture was stirred overnight under a pressure of H_2. Then, the solution was filtered through a pad of Celite and concentrated *in vacuo*. The crude compound was purified by flash chromatography (cyclohexane/AcOEt 40:60 v/v) to yield compound **4** as a colorless oil (4.9 g, 86 %). **Rf** = 0.38 (cyclohexane/AcOEt 40:60 v/v). **^{1}H NMR** ($CDCl_3$, 400 MHz): *δ* 7.50-7.21 (15H, m); 3.11 (1H, dd, *J* = 4 Hz, *J* = 8 Hz); 2.98 (1H, m); 2.90 (1H, m); 1.55 (2H, bs); 1.24 (18H, bs); 0.89 (3H, t, *J* = 8 Hz). **^{13}C {^{1}H} NMR** ($CDCl_3$, 100 MHz): *δ* 144.1; 128.7-126.9; 86.3; 68.6; 51.5; 34.2; 31.8; 29.7; 29.6; 29.5; 29.3; 26.0; 22.6; 14.0. **HRMS** (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{31}H_{41}NONa$ 466.3086; found 466.3088.

N-(1-(trityloxy)dodecan-2-yl)methacrylamide (5a). To a solution of **4** (4.0 g, 9.0 mmol, 1 eq) in anhydrous CH_2Cl_2 was added Et_3N (2.5 mL, 18.0 mmol, 2 eq). The solution was stirred for 20 minutes then methacryloyl chloride (1.0 mL, 10.8 mmol, 1.2 eq) was added dropwise. The reaction mixture was stirred for 2 h and the solution was filtered and concentrated *in vacuo*. The crude compound was purified by flash chromatography (cyclohexane/AcOEt 95:5 v/v) to yield compound **5a** as a colorless oil (4.1 g, 90 %). **Rf** = 0.40 (cyclohexane/AcOEt 90:10 v/v). **^{1}H NMR** ($CDCl_3$, 400 MHz): *δ* 7.45-7.20 (15H, m); 5.99 (1H, d, *J* = 8 Hz); 5.64 (1H, s); 5.30 (1H, s); 4.10 (1H, m); 3.18 (2H, m); 1.95 (3H, s); 1.65 (2H, m); 1.24 (16H, bs); 0.88 (3H, t, *J* = 8 Hz). **^{13}C {^{1}H} NMR** ($CDCl_3$, 100 MHz): *δ* 167.7; 143.8; 140.4; 128.6-127.1; 118.9; 86.31; 64.4; 49.4; 32.2; 31.9; 29.6; 29.5; 29.3; 26.0; 22.7; 18.7; 14.1. **HRMS** (ESI+) m/z: $[M + Na]^+$ Calcd for $C_{35}H_{45}NO_2Na$ 534.3348; Found 534.3353.

N-(1-(trityloxy)dodecan-2-yl)acrylamide (5b). To a solution of **4** (4.1 g, 9.2 mmol, 1 eq) in anhydrous CH_2Cl_2 was added Et_3N (2.6 mL, 18.5 mmol, 2 eq). The solution was stirred for 20 minutes then acryloyl chloride (0.9 mL, 11.1 mmol, 1.2 eq) was added dropwise. The reaction mixture was stirred for 2 h and the solution was filtered and concentrated *in vacuo*. The crude compound was purified by flash chromatography (cyclohexane/AcOEt 90:10 v/v) to yield compound **5b** as a colorless oil (4.3 g, 95 %). **Rf** = 0.40 (cyclohexane/AcOEt 80:20 v/v). **^{1}H NMR** ($CDCl_3$, 400 MHz): *δ* 7.41-7.20 (15H, m); 6.22 (1H, d); 6.02 (1H, dd); 5.60 (1H, dd); 4.11 (1H, m); 3.18 (2H, m); 1.60 (2H, m); 1.24 (16H, bs); 0.86 (3H, t, *J* = 8 Hz). **^{13}C {^{1}H} NMR** ($CDCl_3$, 100 MHz): *δ* 164.9; 143.8; 131.2; 128.6-126.1; 86.4, 64.5; 49.4; 32.2; 31.9; 29.6; 29.5; 29.4; 29.3; 26.0; 22.7; 14.1. **HRMS** (ESI+) m/z: $[M + Na]^+$ Calcd for $C_{34}H_{43}NO_2Na$ 520.3186; Found 520.3193.

N-(1-hydroxydodecan-2-yl)methacrylamide (6a). To a solution of **5a** (3.6 g, 7.0 mmol, 1 eq) in MeOH was added p-TsOH (121 mg, 0.7 mmol, 0.1 eq) and the reaction mixture was stirred for 6 h. Then the solution was neutralized by addition of Et_3N and concentrated *in vacuo*. The crude compound was purified by flash chromatography (cyclohexane/AcOEt 60:40 v/v) to yield compound **6a** as a colorless oil (1.17 g, 62 %). **Rf** = 0.17 (cyclohexane/AcOEt 60:40 v/v). **^{1}H NMR** ($CDCl_3$, 400 MHz): *δ* 6.15 (1H, d, *J* = 8 Hz); 5.68 (1H, s); 5.30 (1H, s); 3.95 (1H, m); 3.66 (1H, dd, *J* = 4 Hz, *J* = 12 Hz, CH_2O); 3.56 (1H, dd, *J* = 8 Hz, *J* = 12 Hz, CH_2O); 1.93 (3H, s, CH_3); 1.55 (1H, m, CH_2); 1.45 (1H, m, CH_2); 1.22 (16H, bs, CH_2); 0.85 (3H, t, *J* = 8 Hz, CH_3). **^{13}C {^{1}H} NMR** ($CDCl_3$, 100 MHz): *δ* 169.1; 139.8; 119.7; 65.2; 51.8; 31.8; 31.2; 29.5; 29.4; 29.2; 26.1; 22.6; 18.6; 14.0. **HRMS** (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{16}H_{32}NO_2$ 270.2433; Found 270.2438.

N-(1-hydroxydodecan-2-yl)acrylamide (6b). To a solution of **5b** (3.0 g, 6.0 mmol, 1 eq) in MeOH was added p-TsOH (0.1 g, 0.6 mmol, 0.1 eq) and the reaction mixture was stirred for 6 h. The solution was neutralized by addition of Et_3N and the solution was concentrated *in vacuo*. The crude compound was purified by flash chromatography (cyclohexane/AcOEt 40:60 v/v) to yield compound **6b** as a white solid (0.8 g, 55 %). **Rf** = 0.2 (cyclohexane/AcOEt 40:60 v/v). **^{1}H NMR** ($CDCl_3$, 400 MHz): *δ* 6.27 (1H, d, *J* = 16 Hz); 6.15 (1H, dd, *J* = 10 Hz, *J* = 16Hz); 5.63 (1H, d, *J* = 12 Hz); 3.98 (1H, m); 3.68 (1H, dd, *J* = 4H z, *J* = 12 Hz); 3.57 (1H, dd, *J* = 8 Hz, *J* = 12 Hz) 3.30 (1H, bs) ; 1.51 (2H, m); 1.24 (16H, bs) ; 0.86 (3H, t, *J* = 8 Hz). **^{13}C {^{1}H} NMR** ($CDCl_3$, 100 MHz): *δ* 166.3; 130.8; 126.7; 65.33; 52.0; 31.9; 31.2; 29.6; 29.5; 29.3; 26.1; 22.7; 14.0. **HRMS** (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{15}H_{30}NO_2$ 256.2277; Found 256.2282.

(2R,3R,4S,5R,6R)-2-((benzoyloxy)methyl)-6-(((2R,3R,4S,5R,6R)-4,5-bis(benzoyloxy)-2-((benzoyloxy)methyl)-6-((2-methacrylamidododecyl)oxy)tetrahydro-2H-pyran-3-yl)oxy)tetrahydro-2H-pyran-3,4,5-triyl tribenzoate (7a). To a solution of **6a** (0.8 g, 3.0 mmol, 1 eq) and hepta-O-benzoyl-maltose-1-O-trichloroacetimidate[22] (3.6 g, 3.0 mmol, 1 eq) in anhydrous CH_2Cl_2 was added dropwise TMSOTf (0.54 mL, 3.0 mmol, 1 eq). The reaction mixture was stirred for 24 h. Then the solution was neutralized by addition of Et_3N and concentrated *in vacuo*. The crude compound was purified by flash chromatography (cyclohexane/AcOEt 80:20 v/v) to yield compound **7a** as a white solid (3.6 g, 90 %). **Rf** = 0.54 (cyclohexane/AcOEt 60:40 v/v). **^{1}H NMR** ($CDCl_3$, 400 MHz): *δ* 8.07-7.24 (35H, m); 6.18 (1H, t, *J* = 10 Hz); 5.92 (1H, m); 5.73 (1H, t, *J* = 10 Hz); 5.61 (1H, s); 5.41 (1H, dd, *J* = 4 Hz, *J* = 10 Hz); 5.35 (1H, s); 4.95 (1H, t, *J* = 10 Hz); 4.85 (1H, m); 4.65-4.40 (5H, m); 4.10-3.80 (5H, m); 3.50 (1H, m); 1.87 (3H, s); 1.40 (2H, m); 1.25 (16H, bs); 0.90 (3H, t, *J* = 8 Hz). **^{13}C {^{1}H} NMR** ($CDCl_3$, 100 MHz): *δ* 167.9-165.1; 140.1; 133.5-128.3; 119.1; 100.2; 97.0; 78.5; 78.2; 75.4; 75.3; 74.7; 72.6; 71.5; 71.4; 70.5; 69.9; 68.9; 63.4; 62.7; 48.7; 31.9. 31.5; 31.3; 29.5; 29.3; 26.0; 22.6; 18.5; 14.0. **HRMS** (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{77}H_{80}NO_{19}$ 1322.5319; Found 1322.5350.

(2R,3R,4S,5R,6R)-2-(((2R,3R,4S,5R,6R)-6-((2-acrylamidododecyl)oxy)-4,5-bis(benzoyloxy)-2-((benzoyloxy)methyl)tetrahydro-2H-pyran-3-yl)oxy)-6-((benzoyloxy)methyl)tetrahydro-2H-pyran-3,4,5-triyl tribenzoate (7b). To a solution of **6b** (0.75 g, 2.94 mmol, 1 eq) and hepta-O-benzoyl-maltose-1-O-trichloroacetimidate[22] (3.57 g, 2.94 mmol, 1 eq) in anhydrous CH_2Cl_2 was added dropwise TMSOTf (0.54 mL, 2.97 mmol, 1 eq). The reaction mixture was stirred for 24 h. Then the solution was neutralized by addition of Et_3N and concentrated *in vacuo*. The crude compound was purified by flash chromatography (cyclohexane/AcOEt 80:20 v/v) to yield compound **7b** as a white solid (3.57 g, 93 %). **Rf** = 0.7 (cyclohexane/AcOEt 60:40 v/v). **^{1}H NMR** ($CDCl_3$, 400 MHz): *δ* 8.16-7.19 (35H, m); 6.08 (2H, m, CH); 5.78 (2H, m); 5.69 (1H, t, *J* = 10 Hz); 5.55 (1H, m); 5.32 (3H, m); 4.97 (1H, m); 4.75 (2H, m, CH); 4.86 (3H, m); 4.31 (1H, m); 4.10 (2H, m); 3.92 (1H, m); 3.62 (1H, m); 1.25 (18H, bs); 0.89 (3H, t, *J* = 8 Hz). **^{13}C {^{1}H} NMR** ($CDCl_3$, 100 MHz): *δ* 169.7-164.9; 133.6-126.0; 101.4; 96.5; 74.5; 73.4; 73.0; 72.7; 72.4; 71.9; 70.9; 69.9; 63.4; 62.5; 48.9; 31.9; 31.6; 31.2; 29.4; 26.9; 26.0; 22.7; 14.1. **HRMS** (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{76}H_{78}NO_{19}$ 1308.5181; Found 1308.5189.

N-(1-(((2R,3R,4R,5S,6R)-3,4-dihydroxy-6-(hydroxymethyl)-5-(((2R,3R,4S,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2H-pyran-2-yl)oxy)tetrahydro-2H-pyran-2-yl)oxy)dodecan-2-yl)methacrylamide (8a). To a solution of **7a** (3.6 g, 2.72 mmol, 1 eq) in MeOH was added catalytic amount of MeONa (58 mg, 1.1 mmol, 0.4 eq) and the reaction mixture was stirred for 16 h. Then IRC-50 was added, and the solution was filtered and concentrated *in vacuo*. The crude compound was purified by flash chromatography ($CHCl_3$/MeOH 80:20 v/v) to yield compound **8a** as a white solid (1.3 g, 80 %). **Rf** = 0.71 ($CHCl_3$/MeOH 70:30 v/v). **^{1}H NMR** (CD_3OD, 400 MHz): *δ* 5.67 (1H, d, *J* = 4 Hz); 5.36 (1H, d, *J* = 4 Hz); 5.16 (1H, d, *J* = 4 Hz); 4.28 (1H, d, *J* = 8 Hz); 4.12 (1H, m); 3.95-3.20 (14H, m); 1.92 (3H, s); 1.60 (2H, m); 1.29 (16H, bs); 0.90 (3H, t, *J* = 8 Hz). **^{13}C {^{1}H} NMR** (CD_3OD, 100 MHz): *δ* 169.5; 139.6; 119.1; 103.1; 101.2; 79.7; 75.7; 74.7; 73.2; 72.7; 72.6; 72.1; 71.7; 71.3; 69.7; 61.2; 60.4; 49.4; 49.1; 31.3; 30.7; 29.0; 28.9; 28.8; 25.6; 25.5; 22.1; 17.8; 13.3. **HRMS** (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{28}H_{52}NO_{12}$ 594.3490; Found 594.3493.

N-(1-(((2R,3R,4R,5S,6R)-3,4-dihydroxy-6-(hydroxymethyl)-5-(((2R,3R,4S,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2H-pyran-2-yl)oxy)tetrahydro-2H-pyran-2-yl)oxy)dodecan-2-yl)acrylamide (8b). To a solution of **7b** (3 g, 2.29 mmol, 1 eq) in MeOH was added catalytic amount of MeONa (49 mg, 0.92 mmol, 0.4 eq) and the reaction mixture was stirred for 16 h. Then IRC-50 was added, and the solution was filtered and concentrated *in vacuo*. The crude compound was purified by flash chromatography ($CHCl_3$/MeOH 80:20 v/v) to yield compound **8b** as a white solid (0.93 g, 70 %). **Rf** = 0.55 ($CHCl_3$/MeOH 70:30 v/v). **^{1}H NMR** (CD_3OD, 400 MHz): δ 6.22 (2H, m); 5.62 (1H); 5.13 (1H, dd); 4.25 (1H, d, J = 8 Hz); 4.07 (1H, m); 3.90-3.20 (14H, m); 1.55 (2H, m); 1.25 (16H, bs); 0.86 (3H, t, J = 8 Hz). **^{13}C {^{1}H} NMR** (CD_3OD, 100 MHz): δ 167.9; 132.2; 126.7; 104.8; 102.8; 81.2; 77.6; 76.6; 74.9; 74.7; 74.6; 74.5; 74.0; 72.9; 71.5; 62.7; 62.1; 50.9; 50.6; 32.9; 32.3; 30.6; 30.5; 30.4; 27.0; 23.7. **HRMS** (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{27}H_{49}NO_{12}Na$ 602.3152; Found 602.3153.

2,2-dimethyl-4-((octyloxy)methyl)-1,3-dioxolane (10) To a suspension of NaH (3.0 g, 127.2 mol, 2.4 eq) in anhydrous DMF, was added a solution of **9**[24] (7 g, 53.0 mmol, 1 eq) in anhydrous DMF. The solution was stirred for 20 minutes and 1-bromooctane (11 mL, 63.6 mmol, 1.2 eq) was added dropwise. The reaction mixture was stirred for 24 h. Then water is added and the solution was extracted twice with AcOEt. The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The crude compound was purified by flash chromatography (cyclohexane/AcOEt 95:5 v/v) to yield compound **10** as a colorless oil (9.5 g, 74 %). **Rf** = 0.6 (cyclohexane/AcOEt 90:10 v/v). **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 4.24 (1H, qt, J = 8 Hz); 4.03 (1H, dd, J = 6 Hz, J = 8 Hz); 3.71 (1H, dd, J = 6 Hz, J = 8 Hz); 3.45 (4H, m); 1.55 (2H, m); 1.40 (3H, s); 1.34 (3H, s); 1.25 (10H, bs); 0.86 (3H, t, J = 8 Hz). **^{13}C {^{1}H} NMR** ($CDCl_3$, 100 MHz): δ 109.3; 74.8; 71.9; 71.8; 66.9; 31.8; 29.5; 29.4; 29.2; 26.7; 26.0; 25.4; 22.6; 14.0. **HRMS** (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{14}H_{20}O_3$ 245.2112; Found 245.2118.

3-(octyloxy)propane-1,2-diol (11) To a solution of **10** (9.3 g, 38.0 mmol, 1 eq) in MeOH was added p-TsOH (0.65 g, 3.8 mmol, 0.1 eq), and the reaction mixture was stirred for 6 h at 80 °C. Then the solution was neutralized by addition of Et_3N and concentrated *in vacuo*. The crude compound was purified by flash chromatography (cyclohexane/AcOEt 60:40 v/v) to yield compound **11** as a colorless oil (6.5 g, 84 %). **Rf** = 0.35 (cyclohexane/AcOEt 40:60 v/v). **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 3.88 (1H, m); 3.71 (1H, dd, J = 4 Hz, J = 12 Hz); 3.64 (1H, dd, J = 8 Hz, J = 12 Hz); 3.55-3.45 (4H, m); 2.50 (2H, bs); 1.56 (2H, qt, J = 8 Hz); 1.26 (10H, bs); 0.87 (3H, t, J = 8 Hz). **^{13}C {^{1}H} NMR** ($CDCl_3$, 400 MHz): δ 72.4; 71.8; 70.5; 64.2; 31.8; 29.5; 29.4; 29.2; 26.0; 22.6; 14.0. **HRMS** (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{11}H_{25}O_3$ 205.1804; Found 205.1804.

1-(octyloxy)-3-(trityloxy)propan-2-ol (12). To a solution of **11** (5.2 g, 21.3 mmol, 1 eq) in anhydrous CH_2Cl_2, was added Et_3N (6.0 mL, 42.6 mmol, 2 eq). The solution was stirred at rt for 20 min, and trityl chloride (7.2 g, 25.6 mmol, 1.2 eq) was added portion-wise. The reaction mixture was stirred for 24 h and the solution was filtered and concentrated *in vacuo*. The crude compound was purified by flash chromatography (cyclohexane/AcOEt 90:10 v/v) to yield compound **12** as a colorless oil (9.3 g, 98 %). **Rf** = 0.32 (cyclohexane/AcOEt 90:10 v/v). **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.47-7.20 (15H, m); 3.96 (1H, m); 3.54 (1H, dd, J = 4 Hz, J = 12 Hz); 3.48 (1H, dd, J = 8 Hz, J = 12 Hz); 3.44 (2H, m); 3.20 (2H, m); 2.45 (1H, m); 1.55 (2H, m); 1.28 (10H, bs); 0.89 (3H, t, J = 8 Hz). **^{13}C {^{1}H} NMR** ($CDCl_3$, 100 MHz): δ 143.8; 128.6-127.0; 86.6; 72.0; 71.6; 69.8; 64.6; 31.8; 29.6; 29.4; 29.2; 26.0; 22.6; 14.0. **HRMS** (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{30}H_{38}O_3Na$ 469.2713; Found 469.2709.

((2-azido-3-(octyloxy)propoxy)methanetriyl)tribenzene (14). To a solution of **12** (9.3 g, 20.8 mmol, 1 eq) in anhydrous CH_2Cl_2, was added Et_3N (5.8 mL, 41.6 mmol, 2 eq). The solution stirred for 20 minutes then methanesulfonyl chloride (1.9 mL, 25.0 mmol, 1.2 eq) was added dropwise. The reaction mixture was stirred for 16 h and the solution was filtered and concentrated *in vacuo*. The crude compound was purified by flash chromatography (cyclohexane/AcOEt 95:5 v/v) to yield compound **13** as a colorless oil (10.0 g, 92 %) which was directly used without further characterization. To a solution of **13** (10.0 g, 19.0 mmol, 1 eq) in anhydrous DMF was added portion wise NaN_3 (2.47 g, 38.0 mmol, 2 eq). The reaction mixture was stirred for 16 h at 80 °C. Then the solution was diluted with water and extracted twice with AcOEt. The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The crude compound was purified by flash chromatography (cyclohexane/AcOEt 100:0 to 95:5 v/v) to yield compound **14** as a colorless oil (8.3 g, 96 %). **Rf** = 0.7 (cyclohexane/AcOEt 95:5 v/v). **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.46-7.24 (15H, m); 3.65 (1H, m); 3.55 (2H, m); 3.41 (2H, m); 3.26 (1H, dd, J = 4 Hz, J = 12 Hz); 3.21 (1H, dd, J = 8 Hz, J = 12 Hz); 1.55 (2H, m); 1.27 (10H, bs); 0.89 (3H, t, J = 8 Hz). **^{13}C {^{1}H} NMR** ($CDCl_3$, 100 MHz): δ 143.6; 128.6-127.1; 87.0; 71.6; 70.4; 63.3; 61.2; 31.8; 29.6; 29.4; 29.2; 25.9; 22.6; 14.1. **HRMS** (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{30}H_{38}N_3O_2$ 472.2959; Found 472.2957.

1-(octyloxy)-3-(trityloxy)propan-2-amine (15). To a solution of **14** (8.3 g, 18.2 mmol, 1 eq) in Et_2O was added Pd-C (910 mg). The reaction mixture was stirred overnight under a pressure of H_2. Then the solution was filtered through a pad of Celite and concentrated *in vacuo.* The crude compound was purified by flash chromatography (cyclohexane/AcOEt 40:60 v/v) to yield compound **15** as a colorless oil (6.9 g, 85 %). **Rf** = 0.51 (cyclohexane/AcOEt 40: 60 v/v). **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.47-7.20 (15H, m); 3.49 (1H, dd, J = 4 Hz, J = 12 Hz); 3.44-3.31 (3H, m); 3.15 (2H, m); 3.05 (1H, m); 1.50 (4H, m); 1.28 (10H, bs); 0.89 (3H, t, J = 8 Hz). **^{13}C {^{1}H} NMR** ($CDCl_3$, 100 MHz): δ 144.1; 128.7-126.9; 86.5; 73.3; 71.5; 65.7; 51.4; 31.8; 29.7; 29.4; 26.9; 26.2; 22.6; 14.1. **HRMS** (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{30}H_{39}NO_2Na$ 468.2878; Found 468.2869.

N-(1-(octyloxy)-3-(trityloxy)propan-2-yl)methacrylamide (16). To a solution of **15** (6.9 g, 15.5 mmol, 1 eq) in anhydrous CH_2Cl_2 was added Et_3N (4.3 mL, 31.0 mmol, 2.0 eq). The solution was stirred for 20 minutes then methacryloyl chloride (1.8 mL, 18.6 mmol, 1.2 eq) was added dropwise. The reaction mixture was stirred for 2h and the solution was filtered and concentrated *in vacuo*. The crude compound was purified by flash chromatography (cyclohexane/AcOEt 90:10 v/v) to yield compound **16** as a yellow oil (7.32 g, 92 %). **Rf** = 0.51 (cyclohexane/AcOEt 80:20 v/v). **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.50-7.20 (15H, m); 6.15 (1H, d, J = 8 Hz); 5.65 (1H, s); 5.30 (1H, s); 4.30 (1H, m); 3.71 (1H, dd, J = 4 Hz, J = 8 Hz); 3.58 (1H, dd, J = 6 Hz, J = 10 Hz); 3.42 (2H, t, J = 8 Hz); 3.39 (1H, dd, J = 4 Hz, J = 12 Hz); 3.14 (1H, dd, J = 8 Hz, J = 12 Hz); 1.93 (3H, s); 1.55 (2H, m); 1.27 (10H, bs); 0.89 (3H, t, J = 8 Hz). **^{13}C {^{1}H} NMR** ($CDCl_3$, 100 MHz): δ 167.7; 143.9; 140.0; 128.6-127.0; 119.5; 86.5; 71.3; 69.1; 61.8; 60.3; 48.8; 31.8; 29.7; 29.4; 29.2; 26.1; 22.6; 18.6; 14.1. **HRMS** (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{34}H_{43}NO_3Na$ 536.3141; Found 536.3136.

N-(1-hydroxy-3-(octyloxy)propan-2-yl)methacrylamide (17). To a solution of **16** (0.92 g, 1.8 mmol, 1 eq) in MeOH was added p-TsOH (0.03 g, 0.18 mmol, 0.1 eq) and the reaction mixture was stirred for 2 h. Then the solution was neutralized by addition of Et_3N and concentrated *in vacuo*. The crude compound was purified by flash chromatography (cyclohexane/AcOEt 50:50 v/v) to yield compound **17** as a colorless oil (0.35 g, 80 %). **Rf** = 0.24 (cyclohexane/AcOEt 50:50 v/v). **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 6.54 (1H, d, J = 8 Hz); 5.71 (1H, s); 5.32 (1H, s); 4.08 (1H, m); 3.80-3.50 (5H, m); 3.41 (2H, m); 1.94 (3H, s); 1.52 (2H, m); 1.23 (8H, bs); 0.84 (3H, t, J = 8 Hz). **^{13}C {^{1}H} NMR** ($CDCl_3$, 100 MHz): δ 168.5; 139.6; 120.0; 71.6; 70.7; 64.0; 50.7; 31.7; 29.4; 29.3; 29.1; 26.0; 22.5; 18.5; 14.0. **HRMS** (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{15}H_{30}NO_3$ 272.2226; Found 272.2234.

(2R,3R,4S,5R,6R)-2-((benzoyloxy)methyl)-6-(((2R,3R,4S,5R,6R)-4,5-bis(benzoyloxy)-2-((benzoyloxy)methyl)-6-(2-methacrylamido-3-(octyloxy)propoxy)tetrahydro-2H-pyran-3-yl)oxy)tetrahydro-2H-pyran-3,4,5-triyl tribenzoate (18). To a solution of **17** (0.35 g, 1.29 mmol, 1 eq) and hepta-O-benzoyl-maltose-1-O-trichloroacetimidate[22] (1.57 g, 1.29 mmol, 1 eq) in anhydrous CH_2Cl_2 was added dropwise TMSOTf (0.23 mL, 1.29 mmol, 1 eq). The reaction mixture was stirred for 24 h.

Then the solution was neutralized by addition of Et_3N and concentrated *in vacuo*. The crude compound was purified by flash chromatography (cyclohexane/AcOEt 80:20 v/v) to yield compound **18** as a white solid (1.37 g, 80 %). **Rf** = 0.49 (cyclohexane/AcOEt 60:40 v/v). **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 8.10-7.20 (35H, m); 6.20 (1H, t, J = 10 Hz); 5.95 (1H, m); 5.75 (1H, t, J = 10 Hz); 5.50 (1H, s); 5.44 (1H, dd, J = 4 Hz, J = 12 Hz); 5.13 (1H, s); 4.95 (1H, t, J = 10 Hz); 4.86 (1H, d, J = 12 Hz); 4.70-4.40 (5H, m); 4.25 (1H, m); 4.10-3.90 (4H, m); 3.65 (1H, dd, J = 6 Hz, J = 10 Hz); 3.45 (1H, dd, J = 4 Hz, J = 10 Hz); 3.35-3.20 (3H, m); 2.90 (1H, d, J = 4 Hz); 1.88 (3H, s); 1.46 (2H, m); 1.25 (10H, bs); 0.90 (3H, t, J = 8 Hz). **^{13}C {^{1}H} NMR** ($CDCl_3$, 100 MHz): δ 167.8-165.1; 139.6; 133.4-128.2; 119.5; 100.6; 96.9; 78.2; 75.4; 74.7; 72.6; 71.4; 71.2; 69.9; 69.1; 68.9; 68.4; 68.1; 67.7; 63.4; 62.7; 48.2; 31.7; 29.4; 29.3; 29.2; 25.9; 22.6; 18.3; 18.4; 14.0. **HRMS** (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{76}H_{78}NO_{20}$ 1324.5117; Found 1324.5132.

N-(1-(((2R,3R,4R,5S,6R)-3,4-dihydroxy-6-(hydroxymethyl)-5-(((2R,3R,4S,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2H-pyran-2-yl)oxy)tetrahydro-2H-pyran-2-yl)oxy)-3-(octyloxy)propan-2-yl)methacrylamide (19). To a solution of **18** (1.3 g, 0.98 mmol, 1 eq) in MeOH was added catalytic amount of MeONa (21 mg, 0.39 mmol, 0.4 eq) and the reaction mixture was stirred for 16 h. Then IRC-50 was added, and the solution was filtered and concentrated *in vacuo*. The crude compound was purified by flash chromatography ($CHCl_3$/MeOH 80:20 v/v) to yield compound **19** as a white solid (0.51 g, 88 %). **Rf** = 0.28 ($CHCl_3$/MeOH 80:20 v/v). **^{1}H NMR** (CD_3OD, 400 MHz): δ 5.70 (1H, d, J = 4 Hz); 5.37 (1H, d, J = 4 Hz); 5.15 (1H, d, J = 4 Hz); 4.28 (2H, m); 4.10-3.20 (18H, m); 1.94 (3H, s, CH_3); 1.54 (2H, qt, J = 8 Hz); 1.28 (10H, bs); 0.89 (3H, t, J = 8 Hz). **^{13}C {^{1}H} NMR** (CD_3OD, 100 MHz): δ 171.3; 141.4; 120.5; 104.7; 102.9; 81.2; 77.7; 76.7; 75.0; 74.7; 74.6; 74.1; 72.3; 71.5; 70.4; 70.2; 69.8; 62.7; 62.2; 50.8; 33.0; 30.7; 30.5; 27.3; 23.7; 18.8; 14.4. **HRMS** (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{27}H_{50}NO_{13}$ 596.3282; Found 596.3283.

Isothermal titration calorimetry. High-sensitivity microcalorimetry was performed at 25 °C on a VP-ITC (Malvern Instruments, Malvern, UK) for **LC027** and on an iTC200 (Malvern Instruments) for **LC049** and **LC058**. All solutions were prepared in Phosphate buffer (10 mM NaH_2PO_4/Na_2HPO_4 and 150 mM NaCl at pH 7.4). For Demicellization experiments 10-µL aliquots of 7 mM **LC027** and 1.5-µL aliquots 8 mM **LC058** were titrated into buffer, whereas 1-µL aliquots of 70 mM **LC049** were titrated into a cell preloaded with 3 mM monomer. Time spacings between consecutive injections were chosen long enough to allow for complete re-equilibration. Baseline subtraction and peak integration were performed using NITPIC.[28] All reactions heats were normalized with respect to the molar amount of detergent. Non-linear least-squares fitting was performed using D/STAIN.[29]

Surface tension measurements. The surface activity of detergents in solution at the air/water interface was determined using a K100 tensiometer (Kruss, Hamburg, Germany). Surface tensions were determined by dilution of stock solutions (~5×CMC) using the Wilhelmy plate technique. In a typical experiment, 20–30 concentration steps were used with ~5–10 min between each concentration step. All measurements were performed at (25.0 ± 0.5) °C.

Dynamic light scattering. Hydrodynamic particle size distributions were determined on a Nano Zetasizer ZS90 (Malvern Instruments, UK) equipped with a He−Ne laser (λ = 633 nm). Except for **LC048** all measurements were performed at (25 ± 0.5) °C. Measurements for **LC048** were performed at 35 °C to keep the compound in solution. The concentration for each measurement was 2×(CMC + 5 mM) in buffer (50 mM Tris, 200 mM NaCl, pH 7.4). The time dependent correlation function of the scattered light intensity was measured at an angle of 90°.The hydrodynamic diameter (D_H) of the particles was estimated from their diffusion coefficient (D) using the Stokes−Einstein equation, $D = k_BT/3\pi\eta D_H$, where k_B is Boltzmann's constant, T absolute temperature, and η the viscosity of the solvent.

Vesicle solubilization. POPC in powder form was suspended in phosphate buffer (10 mM NaH_2PO_4/Na_2HPO_4 and 150 mM NaCl at pH 7.4). To obtain large unilamellar vesicles (LUVs), the suspension was extruded 35 times through two stacked polycarbonate membranes with a nominal pore diameter of 100 nm using a LiposoFast extruder (Avestin, Ottawa, Canada). Unimodal size distribution was confirmed by DLS. A 0.6 mM stock solution of POPC LUVs and detergent were mixed in a 3 mm × 3 mm quartz glass cuvette (Hellma, Müllheim, Germany) before the light scattering intensity was monitored at 25 °C using a Nano Zetasizer ZS90 (Malvern) equipped with a 633-nm He–Ne laser and a detection angle of 90°. To ensure quantitative comparability of scattering intensities, the attenuator was fixed to the maximum open position.

Extraction of MPs from *E. coli* membranes. *E. coli* BL21(DE3) cells were transformed with an empty pET-24 vector and thus selected by kanamycin resistance. After incubation in lysogeny broth overnight at 37 °C under permanent agitation, cells were harvested by centrifugation and washed twice with saline (154 mM NaCl). Cell pellets were resuspended in ice-cold buffer (100 mM Na_2CO_3, pH 11.5) to a concentration below ~0.1 g mL^{-1} and ultrasonicated twice for 10 min in an S-250A sonifier (Branson Ultrasonics, Danbury, USA). To remove cell debris, the lysate was centrifuged at 4 °C for 30 min at 1000 *g*. The supernatant was centrifuged at 4 °C for 1 h at 100,000 *g* to separate membrane fragments from soluble and peripheral proteins. Membrane fragments were resuspended in buffer (50 mM Tris, 200 mM NaCl, pH 7.4) to a final concentration of 100 mg wet-weight pellet per 1 mL of buffer and mixed in a 1:1 volume ratio with stock solutions of DDM or monomers in buffer. Surfactant concentrations were chosen based on the CMC values determined in this study to ensure comparable extraction conditions. All samples were incubated for 16 h at 20 °C under gentle agitation. After ultracentrifugation at 4 °C for 1 h at 100,000 *g*, the supernatant containing micelles was analyzed using SDS-PAGE. Extraction yields were then determined densitometrically using ImageJ gel analysis.[30]

Solubilization of A_{2A}R and AcrB. Adenosine receptor (A_{2A}R) was expressed in insect cells as described.[31] AcrB was expressed in *E.coli* as previously reported.[32] Membrane fractions were incubated for 2h at 4°C at a final concentration of 5mg/mL in 50mM Hepes buffer pH 7.4, 200 mM NaCl, 1X protease inhibitor cocktail, and with 10-fold the CMC of DDM in combination with CHS or LC compounds. After solubilization samples were centrifuged at 100000g for 45min at 4°C and an aliquot of the total extract, the pellet and the supernatant from each solubilization condition was analyzed by SDS-PAGE and western-blot using an antibody A_{2A}R (7F6-G5-A2) and against the his-tag for AcrB, respectively. Solubilization efficiency was evaluated by comparing the band intensity (in western blot) of the Soluble (S) to the insoluble (P for Pellet) fractions.

Supporting Information available. ^{1}H and ^{13}C NMR spectra of compounds; HPLC chromatograms of **LC027**, **LC048**, **LC049**, and **LC058**. Contin distribution plots in pure water for **LC027**, **LC048**, and **LC058**.

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Surfmers for Membrane Proteins extraction

Surfmers were synthesized and were found to self-assemble in water into micelles of ~ 6 nm in diameter at a critical micellar concentration that depends on the length of the alkyl chain. They were found to solubilize phospholipid vesicles and to extract a broad range of proteins from Escherichia coli membranes as well as the human adenosine receptor A2AR and the bacterial transporter AcrB.