Electronic Supplementary Material (ESI) for Physical Chemistry Chemical Physics.

SUPPORTING INFORMATION

Interaction of Imidazolium-based Lipids with Phospholipid Bilayer Membranes of Different Complexity

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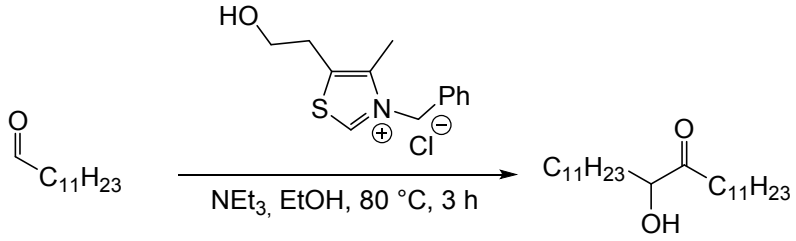
Content

1 General considerations

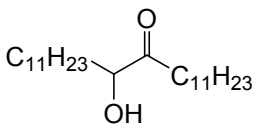
Reactions were performed in oven-dried glassware under an atmosphere of dry argon, unless otherwise noted. The solvents were either purified via distillation over standard drying agents or purchased dry and stored over molecular sieves. Solvents used for extraction, crystallisation or chromatography were technical grade and flash-distilled prior to use. All commercial chemicals and reagents were purchased from *ABCR, Acros Organics, Alfa Aesar, ChemPur, Combi-Blocks, Fluorochem, Merck, Sigma Aldrich* and *TCI Europe* and were used without further purification. Purification via flash column chromatography was performed with *Acros* silica gel (35–70 µm, 60 Å) with a head pressure of arcon (~ 0.2 atmospheres). NMR-spectra were recorded on a Bruker ARX-300, AV-300 or AV-400 MHz. Chemical shifts (δ) are quoted in parts per million (ppm) relative to tetramethylsilane. As references for ^{1}H and ^{13}C NMR-spectra $CDCl_3$ (δ_H = 7.26 ppm; δ_C = 77.16 ppm) was used. Coupling constants (*J*) are quoted in Hz. Multiplicities are reported as: s (singlet), d (doublet), t (triplet), q (quartet), p (quintet), hept (septet), m (multiplet) or a combination of these. In case of broad signals, b is added in front of the multiplicity.

2 Experimental

2.1 Synthesis of 13-hydroxytetracosan-12-one



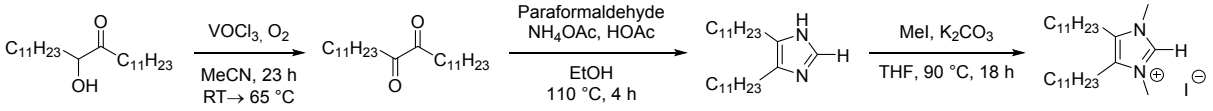
13-hydroxytetracosan-12-one



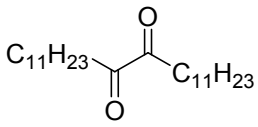
Following literature procedure[1,2] 3-benzyl-5-(2-hydroxyethyl)-4-methylthiazolium chloride (337 g, 1.25 mmol, 5 mol%) was suspended in dry EtOH (12.0 mL, 2.15 M). Dodecanal (5.55 mL, 25.0 mmol, 1.00 eq.) and NEt_3 (1.04 mL, 7.50 mmol, 0.30 eq.) was added and the mixture was heated to 80 °C for 3 h. Subsequently the mixture was poured on ice (35 mL) and stirred until all ice was molten. The white precipitate was filtered off and the crude product was recrystallized from EtOH. 13-hydroxytetracosan-12-one was obtained as white solid (4.15 g, 11.26 mmol, 90%).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) = 4.19 – 4.12 (m, 1H), 3.48 (bs, 1H), 2.54 – 2.33 (m, 2H), 1.87 – 1.75 (m, 1H), 1.68 – 1.38 (m, 5H), 1.38 – 1.16 (m, 32H), 0.88 (t, *J*=6.7 Hz, 6H).

2.2 Synthesis of C_{11}IMe•HI



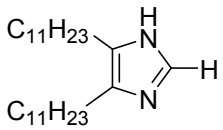
tetracosane-12,13-dione



Following literature procedure[2,3] 13-hydroxytetracosan-12-one (4.15 g, 11.26 mmol, 1.00 eq.) was suspended in acetonitrile (113 mL, 0.1 M) and $VOCl_3$ (11 µL, 0.113 mmol, 1mol%) was added dropwise. The flask was equipped with an oxygen balloon and was stirred for 20 h at room temperature. Subsequently the mixture was heated for 3 h at 65 °C. The reaction was quenched after completion by addition of sat. $NaHCO_3$ solution (250 mL) and extracted with *n*-pentane/EtOAc (1/1, 3 x 125 mL). The organic layers were combined and washed with sat. NH_4Cl solution and brine, dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was recrystallized from EtOH (100 mL). Tetracosane-12,13-dione was isolated as a yellow-white solid (2.95 g, 8.05 mmol, 72%).

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 2.72 (t, *J*=7.3 Hz, 4H), 1.64 – 1.48 (m, 4H), 1.37 – 1.15 (m, 32H), 0.87 (t, *J*=6.6 Hz, 6H).

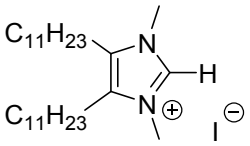
4,5-diundecylimidazole



Following literature procedure[2,4] tetracosane-12,13-dione (1.00g, 2.73 mmol, 1.00 eq.), paraformaldehyde (98.0 mg, 3.28 mmol, 1.20 eq.) and NH_4OAc (505 mg, 6.55 mmol, 2.40 eq.) were suspended in dry EtOH (6 mL, 0.5 M) and a catalytic amount of HOAc (~ 5 drops) was added. After heating the mixture for 4h at 110 °C, sat. $NaHCO_3$ solution was added to quench the reaction. Subsequently the mixture was extracted with DCM (3 x 80 mL) and the organic layers dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified via column chromatography (SiO_2, DCM/MeOH: 33/1 → 10/1). 4,5-Diundecylimidazole was isolated as yellow-white solid (159 mg, 0.421 mmol, 15%).

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) =7.47 – 7.44 (m, 1H), 2.51 (t, *J*=7.6 Hz, 4H), 1.71 – 1.51 (m, 4H), 1.36 – 1.19 (m, 32H), 0.92 – 0.83 (m, 6H). (NH not detected)

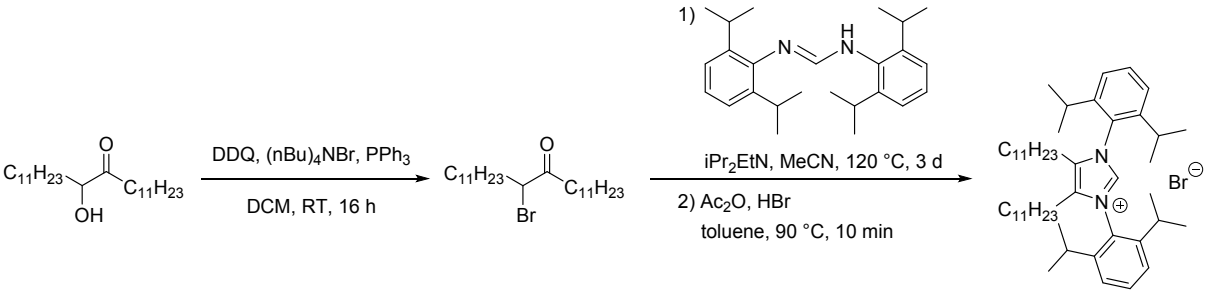
1,3-bismethyl-4,5-diundecylimidazolium iodide



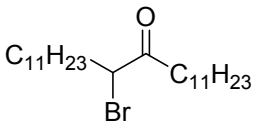
Following literature procedure[2,5] 4,5-diundecylimidazole (159 mg, 0.421 mmol, 1.00 eq.) was suspended in THF (2.0 mL, 0.2 M), followed by the addition of K_2CO_3 (70.0 mg, 0.506 mmol, 1.20 eq.) and MeI (132 µL, 2.11 mmol, 5.00 eq.). The mixture was heated for 18 90 °C and was subsequently quenched by addition of water. Followed by extraction with DCM (3 x 50 mL), the combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified via column chromatography (SiO_2, DCM/MeOH: 1/0 → 10/1). 1,3-Bismethyl-4,5-diundecylimidazolium iodide was isolated as pale yellow solid (107 mg, 0.202 mmol, 48%).

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 10.11 (s, 1H), 3.89 (s, 6H), 2.55 (t, *J*=7.8 Hz, 4H), 1.57 – 1.43 (m, 4H), 1.39 – 1.14 (m, 32H), 0.90 – 0.81 (m, 6H).

2.3 Synthesis of C_{11}IPr•HBr



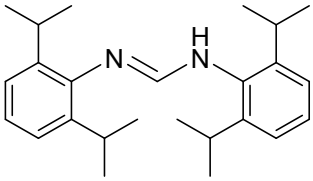
13-bromotetracosan-12-one



Following literature procedure[2,6] DDQ (4.09 g, 18.0 mmol, 1.20 eq.) and PPh_3 (4.68 g, 18.0 mmol, 1.20 eq.) were suspended in DCM (150 mL, 0.1 M) and *N*-butyl ammonium bromide (5.80 g, 18.0 mmol, 1.20 eq.) and 13-hydroxytetracosan-12-one (5.53 g, 15.0 mmol, 1.00 eq.) were added. The reaction mixture was stirred at room temperature for 16 h and was subsequently adsorbed on silica. After column chromatography (SiO_2, *n*-pentane/EtOAc: 99/1) 13-bromotetracosan-12-one was isolated as white solid (4.70 g, 10.9 mmol, 73%).

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 4.27 – 4.20 (m, 1H), 2.77 – 2.54 (m, 2H), 2.05 – 1.86 (m, 2H), 1.66 – 1.56 (m, 2H), 1.49 – 1.21 (m, 34H), 0.87 (t, *J*=6.6 Hz, 6H).

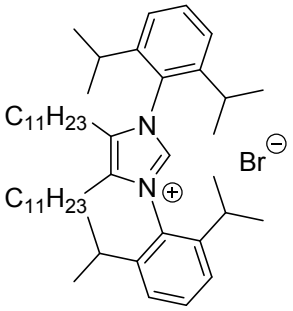
***N,N*-bis(2,6-diisopropylphenyl)formimidamide**



Following literature procedure[7,8] a mixture of acetic acid (43 µL, 0.750 mmol, 0.05 eq.), triethylorthoformate (2.5 mL, 15.0 mmol, 1.00 eq.) and 2,6-diisopropylamine (5.7 mL, 30.0 mmol, 2.00 eq.) was heated to 140 °C overnight. After addition of cold *n*-pentane the solid was filtered of and washed with *n*-pentane. *N,N*-bis(2,6-diisopropylphenyl)formimidamide was isolated without further purification as a white solid (1.09 g, 2.99 mmol, 20%).

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.48 – 7.22 (m, 7H), 3.55 – 3.28 (m, 4H), 1.52 – 1.21 (m, 24H).

1,3-bis(2,6-diisopropylphenyl)-4,5-diundecylimidazolium bromide



Following literature procedure[2,7] 13-bromotetracosan-12-one (8.61 g, 20.0 mmol, 2.00 eq.) and *N,N*-bis(2,6-diisopropylphenyl)formimidamide (3.65 g, 10 mmol, 1.00 eq.) were suspended in MeCN (20 mL, 1.0 M). Following *N,N*-diisopropylethylamine (5.95 mL, 35 mmol, 3.5 eq.) was added and the reaction mixture was heated at 120 °C for 3 days. After removing the solvent of the reaction under reduced pressure, toluene (25 mL) was added, followed by the addition of acetic anhydride (2.84 mL, 30.0 mmol, 3.00 eq.). The reaction mixture was heated to 90 °C for 10 min. Subsequently at room temperature aqueous HBr (1.83 mL, 15 mmol, 1.50 eq.) was added and the mixture was heated further at 90 °C for 20 h. After cooling the reaction to room temperature, the reaction mixture was transfered into a separatory funnel containing DCM (150 mL) and H_2O (150 mL). The aqueous phase was extracted with DCM (3 x 100 mL) and the combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified via column chromatography (SiO_2, DCM/MeOH: 1/0 → 10/1). 1,3-bis(2,6-diisopropylphenyl)-4,5-diundecylimidazolium bromide was isolated as a white solid (5.96 g, 7.68 mmol, 76%).

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 11.02 (s, 1H), 7.56 (t, *J*=7.8 Hz, 2H), 7.34 (d, *J*=7.8 Hz, 4H), 2.44 – 2.34 (m, 4H), 2.30 – 2.17 (m, 4H), 1.43 – 1.08 (m, 60H), 0.90 – 0.81 (m, 6H).

3 Temperature dependent fluorescence microscopy images

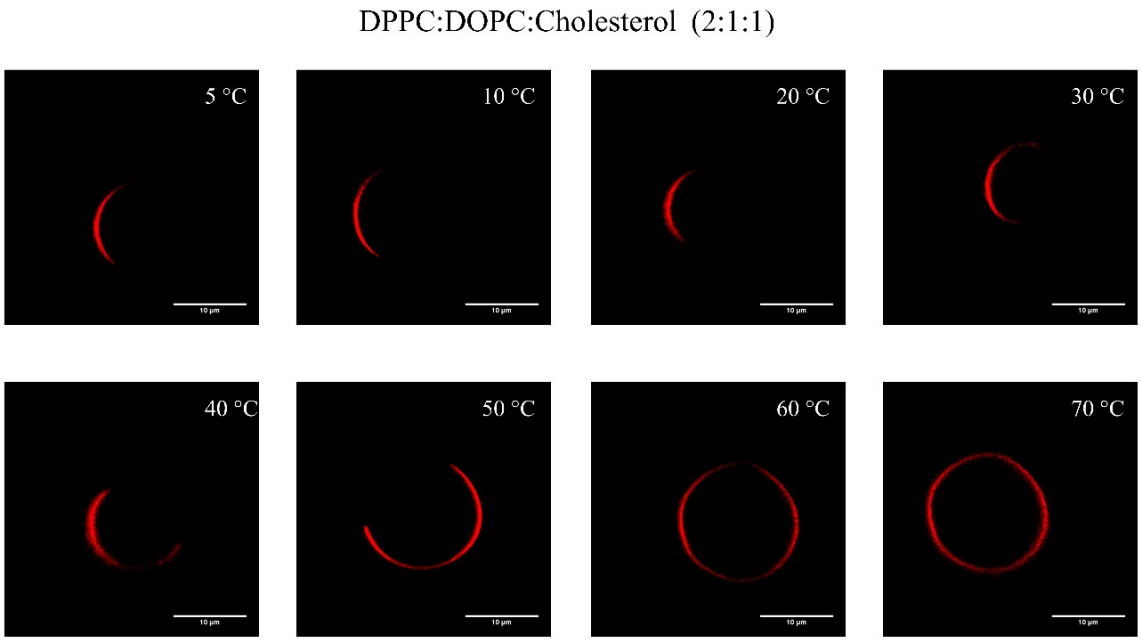


Figure SI 1 Representative confocal fluorescence microscopy cross-section images of the neat neutral three component membrane consisting of DPPC:DOPC:cholesterol (2:1:1) from 5 to 70 °C. The red fluorescence originates from the fluorescence marker *N*-Rh-DHPE.

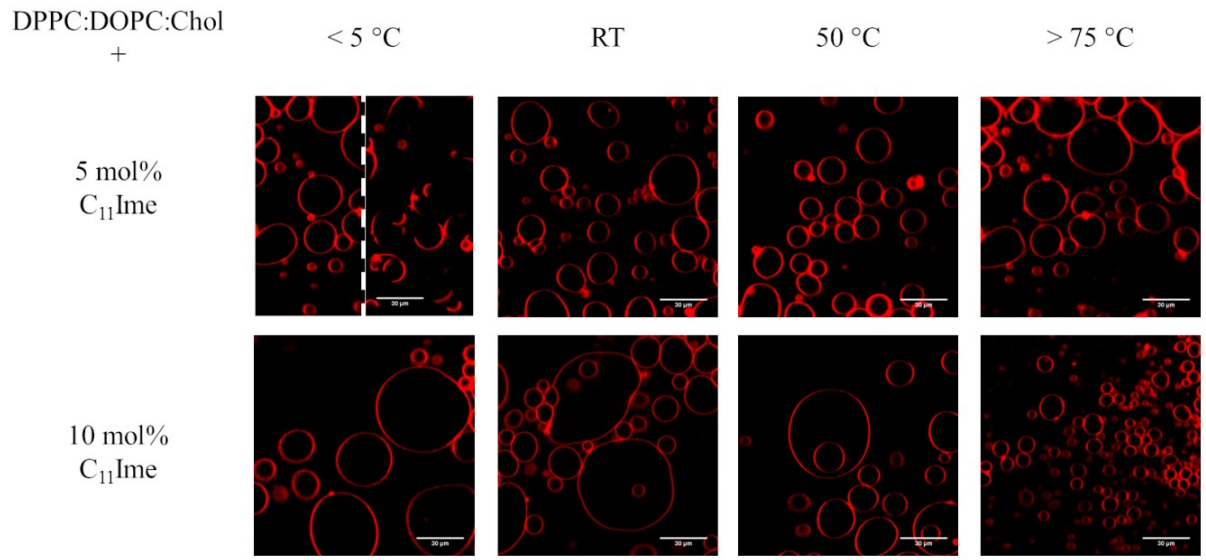


Figure SI 2 Representative confocal fluorescence microscopy cross-section images of the impact of various concentrations of the C_{11}IMe salt on the structure of the neutral three component membrane consisting of DPPC:DOPC:cholesterol (2:1:1) from < 5 to 75 °C. The red fluorescence originates from the fluorescence marker *N*-Rh-DHPE.

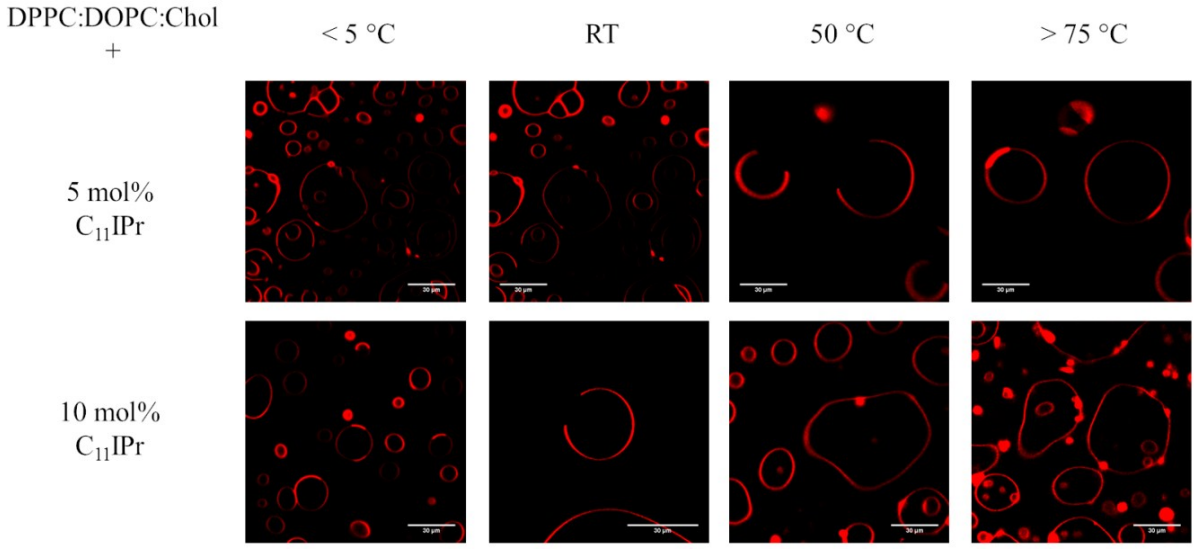


Figure SI 3 Representative confocal fluorescence microscopy cross-section images of the impact of various concentrations of the C_{11}IPr salt on the structure of the neutral three component membrane consisting of DPPC:DOPC:cholesterol (2:1:1) from < 5 to 75 °C. The red fluorescence originates from the fluorescence marker *N*-Rh-DHPE.

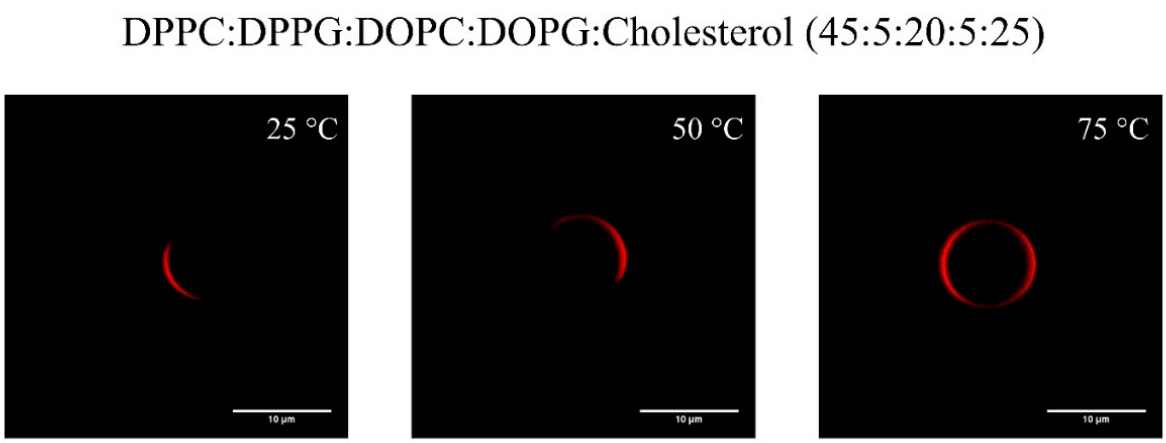


Figure SI 4 Representative confocal fluorescence microscopy cross-section images of the neat anionic five component raft mixture membrane consisting of DPPC:DPPG:DOPC:DOPG:cholesterol (45:5:20:5:25) from 25 to 75 °C. The red fluorescence originates from the fluorescence marker *N*-Rh-DHPE.

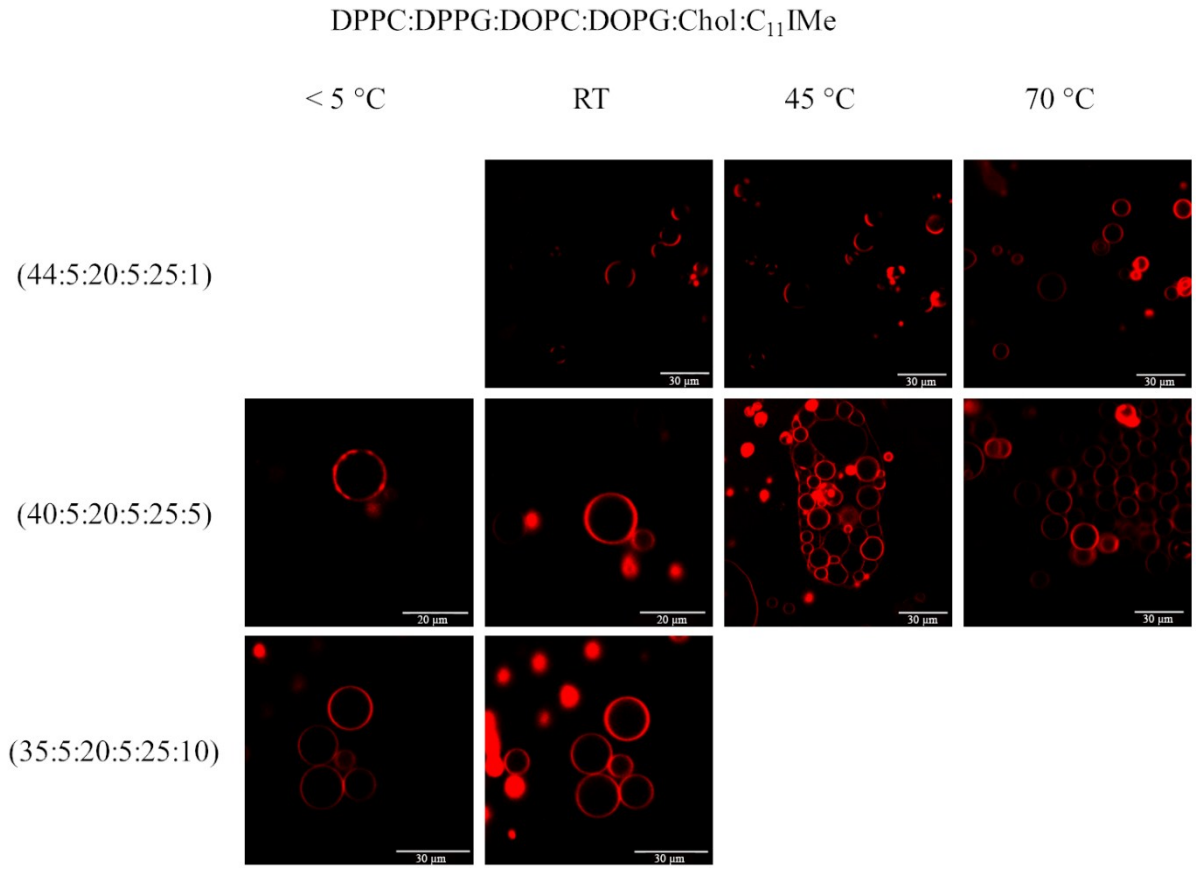


Figure SI 5 Representative confocal fluorescence microscopy cross-section images of the impact of various concentrations of the C_{11}IMe salt on the structure of the anionic five

component raft mixture membrane consisting of DPPC:DPPG:DOPC:DOPG:cholesterol (45:5:20:5:25) from <5 to 70 °C.

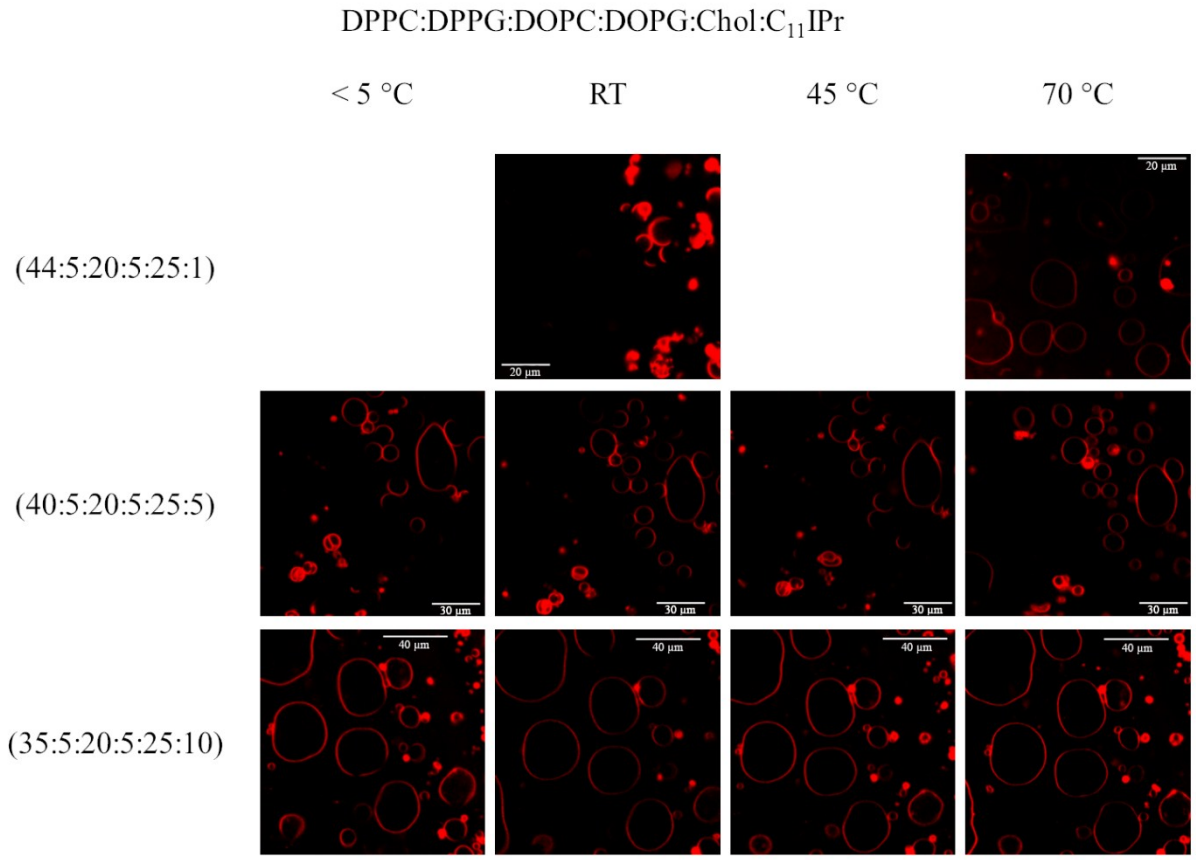


Figure SI 6 Representative confocal fluorescence microscopy cross-section images of the impact of various concentrations of the C_{11}IPr salt on the structure of the anionic five component raft mixture membrane consisting of DPPC:DPPG:DOPC:DOPG:cholesterol (45:5:20:5:25) from < 5 to 70 °C.

4 References

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