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

DOPC versus DOPE as helper lipids for gene-therapies: molecular dynamics simulations with DLin-MC3-DMA

Supplementary Information

Inna Ermilova, Jan Swenson

Department of Physics,
Chalmers University of Technology, SE 412 96, Gothenburg, Sweden

E-mail: ina.ermilova@gmail.com; inna.ermilova@chalmers.se;

jan.swenson@chalmers.se

Content

1 FF parameters

1.1 Partial atomic charges

The partial atomic charges are going to be used in the following equation for the Coulumbic component of the SLipids FF ($i \neq j$):

$$E_{Coulumb} = \sum_{i,j} \frac{q_i q_j}{4\pi\varepsilon_0 r_{i,j}}$$

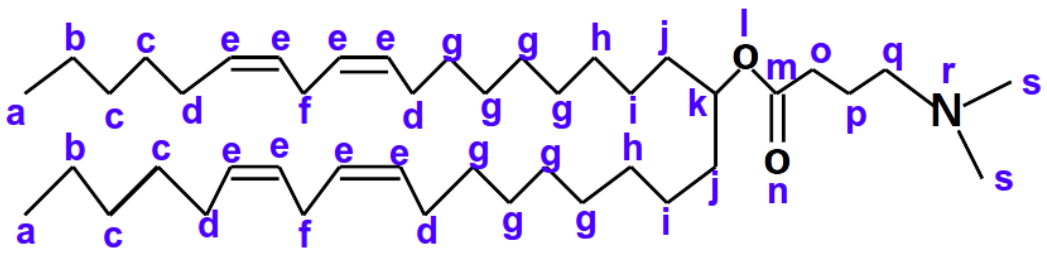

Figure S1: The partial atomic charges for DLin-MC3-DMA. Here a=-0.081 (0.016); b=0.047 (-0.007); c=0.000 (0.000); d=0.120 (0.000); e=-0.280 (0.000); f=0.280 (0.000); g=0.000 (0.000); h=-0.060 (0.030); i=0.120 (0.050); j=-0.180 (0.090); k=0.410 (0.050); l=-0.410; m=0.790; n=-0.570; o=-0.280 (0.125); p=0.140 (0.070); q=-0.060 (0.090); r=-0.220; s=-0.290 (0.150)

1.2 Dihedrals

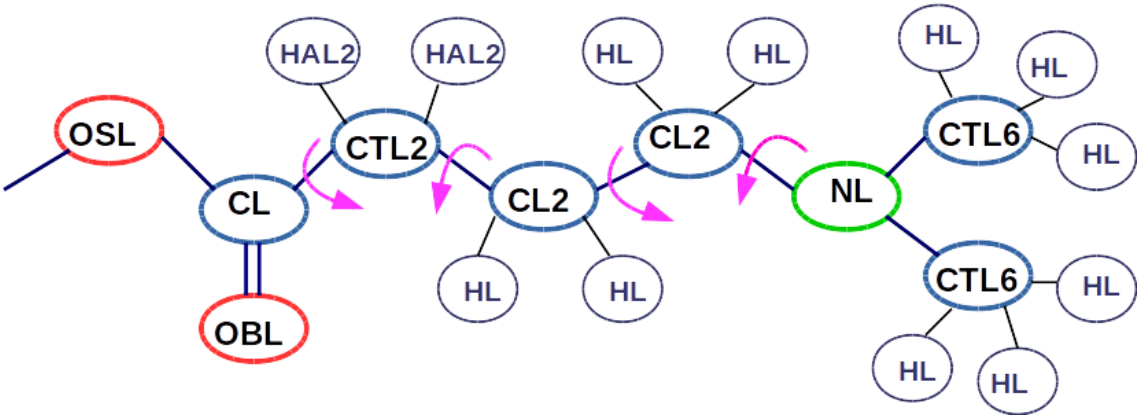

Figure S2: Illustration of derived dihedrals for the DLin-MC3-DMA head-group

The parameters for the dihedrals are going to be used in the following equation for the dihedral component of the SLipids FF:

$$E_{dihedrals} = \sum_{n=1}^{6} k_n(1 + cos(n\phi - \delta_n))$$

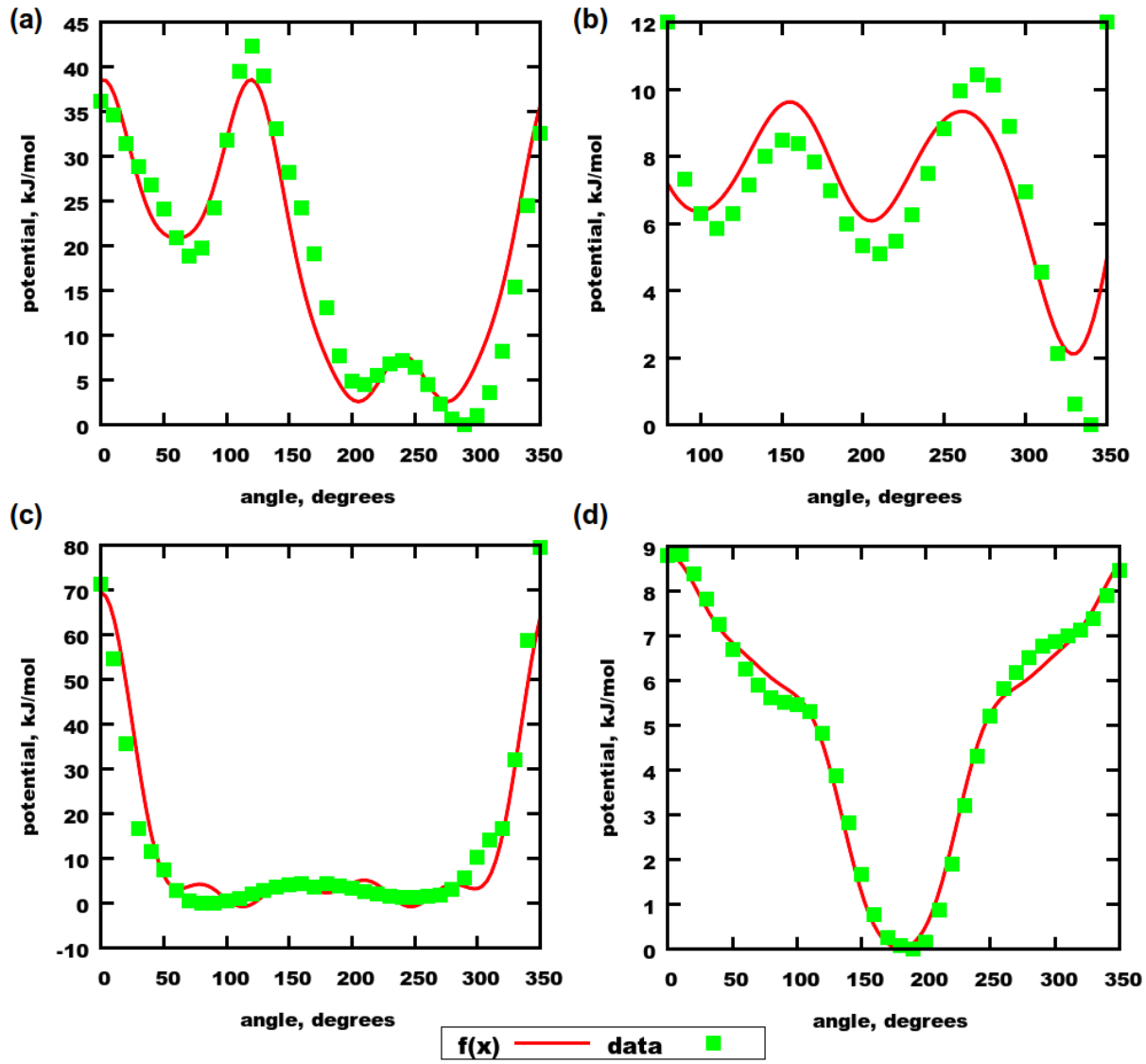

Figure S3: Illustration of the fitting of the dihedrals. (a) $CTL6-NL-CL2-CL2$ (b) $NL-CL2-CL2-CTL2$ (c) $CL2-CL2-CTL2-CL$ (d) $CL2-CTL2-CL-OSL$. Here: $f(x)$ represents the function which was obtained during the fitting procedure, *data* stands for the dihedral energy $E_{dihedral}$ which was achieved from the quantum chemical and MD calculations. Parameters for the fitting function can be found in a table for each dihedral (Tables S1-S4). On (b) non-physical values of the dihedrals (the ones which cause overlaps and non-physical distances) were taken away from the fitting procedure.

Table S1: Parameters for the dihedral $CTL6-NL-CL2-CL2$

n	δ, *degrees*	k_n, kJ/mol
1	180	-14.5291
2	180	-5.14318
3	180	-4.1335
4	180	-0.4464413
5	180	-0.437291
6	180	-0.678073

Table S2: Parameters for the dihedral $NL-CL2-CL2-CTL2$

n	δ, *degrees*	k_n, kJ/mol
1	90	1.21123
2	90	1.9363
3	90	2.9167
4	90	0.397682
5	90	0.388571
6	90	-0.0007507

Table S3: Parameters for the dihedral $CL2-CL2-CTL2-CL$

n	δ, $degrees$	k_n, kJ/mol
1	0	-19.1095
2	0	-16.373
3	0	-9.99395
4	0	-6.50576
5	0	-4.3865

Table S4: Parameters for the dihedral $CL2-CTL2-CL-OSL$

n	δ, $degrees$	k_n, kJ/mol
1	180	-3.62862
2	180	0.859066
3	180	-0.796021
4	180	-0.0849933
5	180	0.0311658
6	180	-0.140195

2 Snapshots of starting configurations

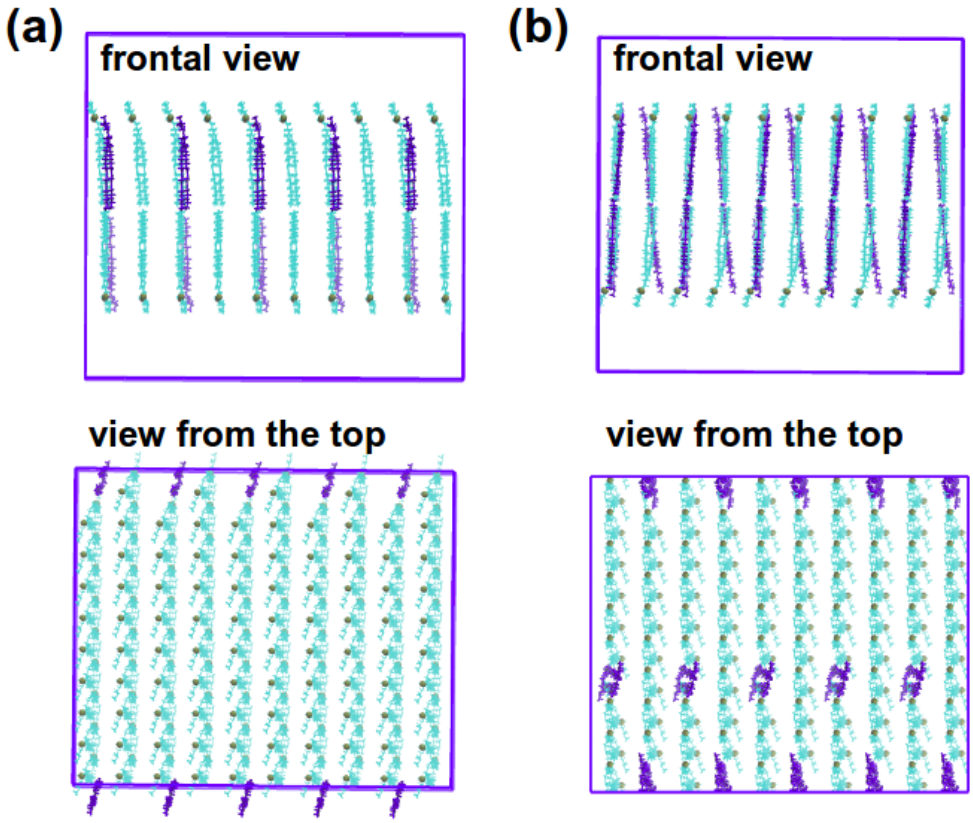

Figure S4: Snapshots of starting configurations (a) Systems with 5 % of DLin-MC3-DMA (b) Systems with 15 % of DLin-MC3-DMA. Phospholipids are visualized by cyan color with phosphorus shown as spheres of dark lime color. DLin-MC3-DMA is visualized by the dark blue color. The molecular graphics software is VMD [1].

3 Areas per lipids during the simulation time

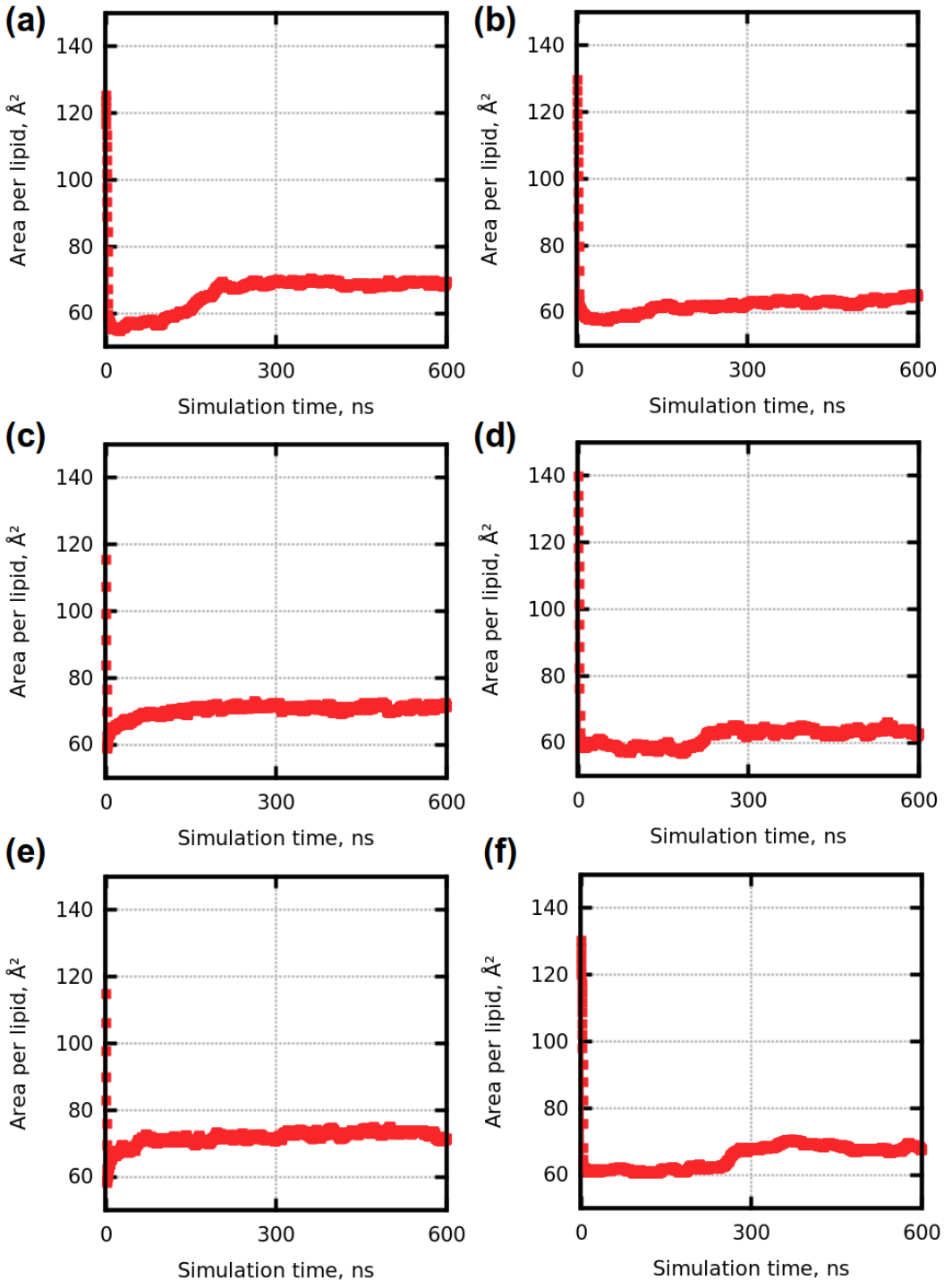

Figure S5: The area per lipid during the simulation time (a) DOPC (pure) (b) DOPE (pure) (c) DOPC with 5% of DLin-MC3-DMA (d) DOPE with 5% of DLin-MC3-DMA (e) DOPC with 15% of DLin-MC3-DMA (f) DOPE with 15% of DLin-MC3-DMA

4 Contribution to mass density profiles from water molecules

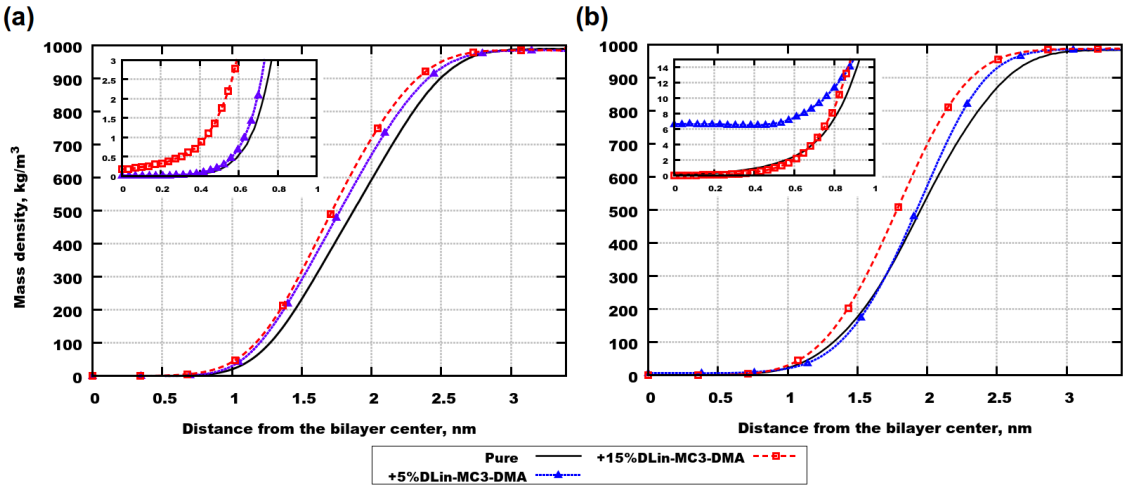

Figure S6: Mass density profiles for water molecules in the following systems: (a) DOPC (b) DOPE. Labels: "Pure" stands for lipid bilayers containing only phospholipids, +5% DLin-MC3-DMA means that it was 5% of the ionizable lipid and +15% DLin-MC3-DMA means that it was 15% of the ionizable lipid.

5 RDFs

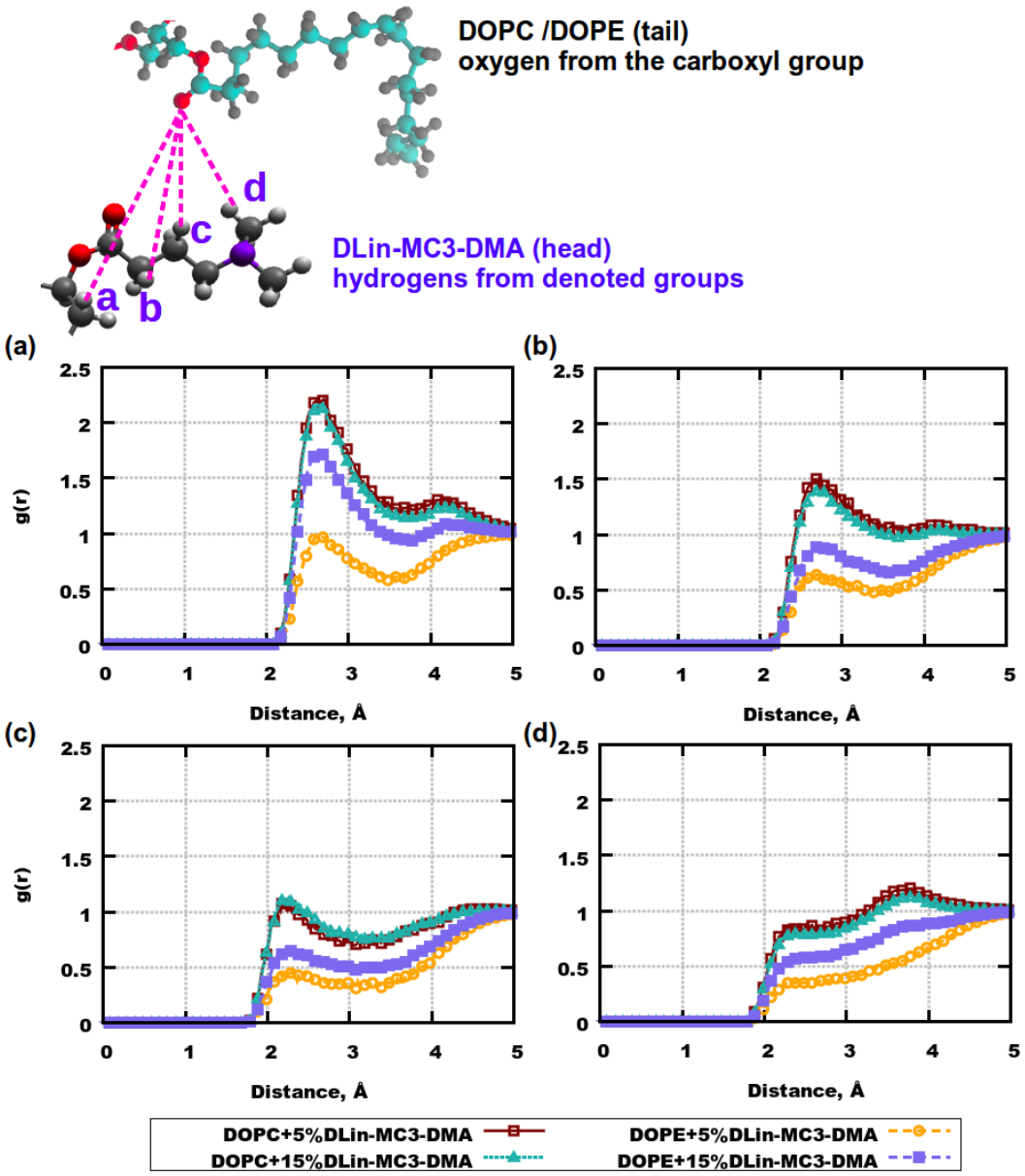

Figure S7: RDFs between pairs of atoms in a phospholipid head-group and in the tail of DLin-MC3-DMA. (a) RDFs between carbons labeled as "a" in DLin-MC3-DMA and hydrogens from the CH-group of DOPC/hydrogens from the amine group of DOPE. (b) RDFs between carbons labeled as "b" in DLin-MC3-DMA and hydrogens from the CH_2-group of DOPC/hydrogens from the amine group of DOPE. (c) RDFs between carbons labeled as "c" in DLin-MC3-DMA and hydrogens from the CH_2-group of DOPC/hydrogens from the amine group of DOPE. (d) RDFs between carbons labeled as "d" in DLin-MC3-DMA and hydrogens from the CH_3-group of DOPC/hydrogens from the amine group of DOPE. Parts of phospholipids were colored in a following way: cyan color - carbon, blue color - nitrogen, yellow color - phosphorus, red color - oxygen, gray color - hydrogen. Parts of DLin-MC3-DMA were colored in a different way: light gray - hydrogen, dark gray - carbon, blue - nitrogen, red - oxygen.

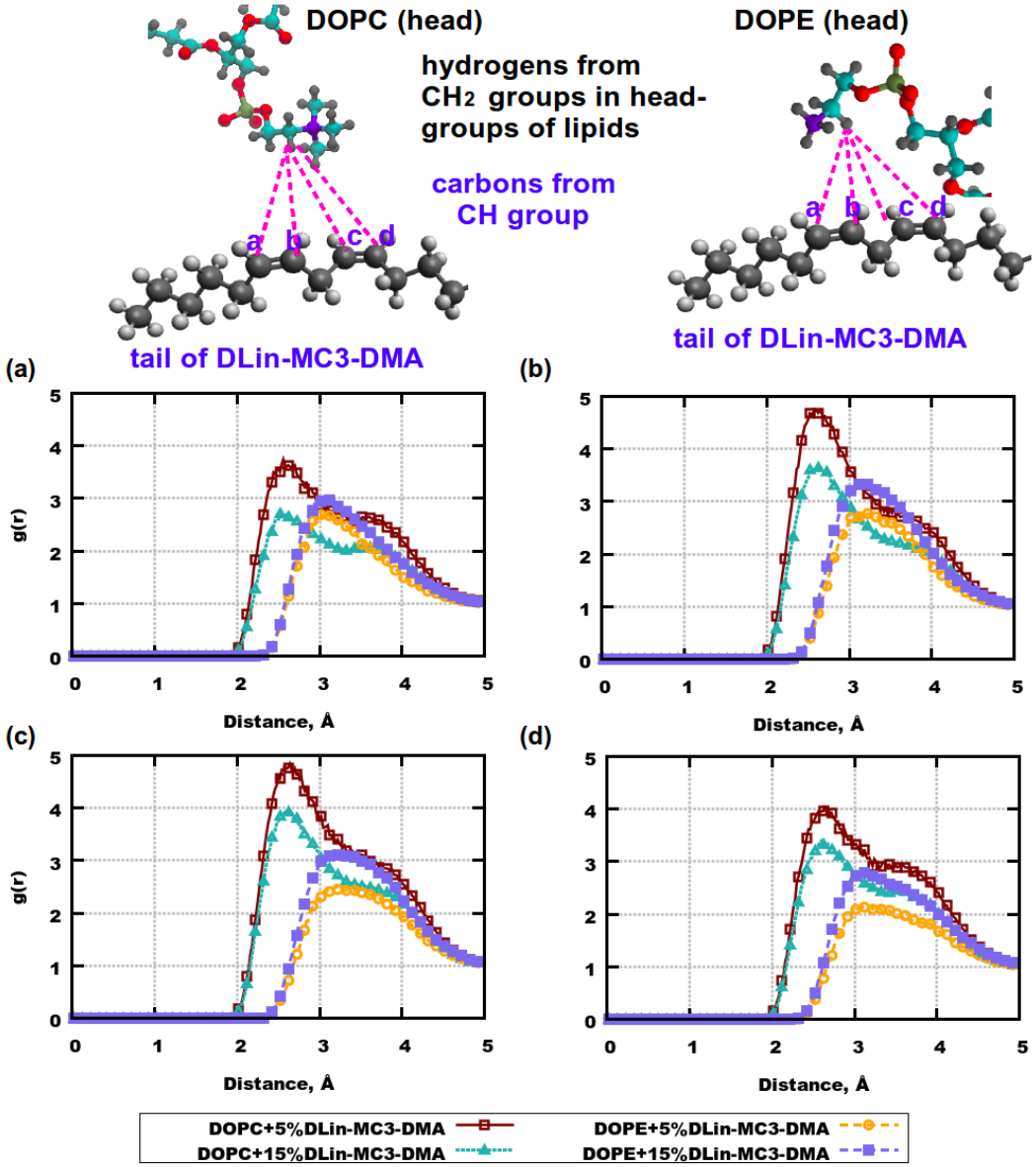

Figure S8: RDFs between pairs of atoms in a phospholipid head-group and in the tail of DLin-MC3-DMA. (a) RDFs between carbons labeled as "a" in DLin-MC3-DMA and hydrogens from the CH_2-group of DOPC/hydrogens from the amine group of DOPE. (b) RDFs between carbons labeled as "b" in DLin-MC3-DMA and hydrogens from the CH_2-group of DOPC/hydrogens from the amine group of DOPE. (c) RDFs between carbons labeled as "c" in DLin-MC3-DMA and hydrogens from the CH_2-group of DOPC/hydrogens from the amine group of DOPE. (d) RDFs between carbons labeled as "d" in DLin-MC3-DMA and hydrogens from the CH_2-group of DOPC/hydrogens from the amine group of DOPE. Parts of phospholipids were colored in a following way: cyan color - carbon, blue color - nitrogen, yellow color - phosphorus, red color - oxygen, gray color - hydrogen. Parts of DLin-MC3-DMA were colored in a different way: light gray - hydrogen, dark gray - carbon, blue - nitrogen, red - oxygen.

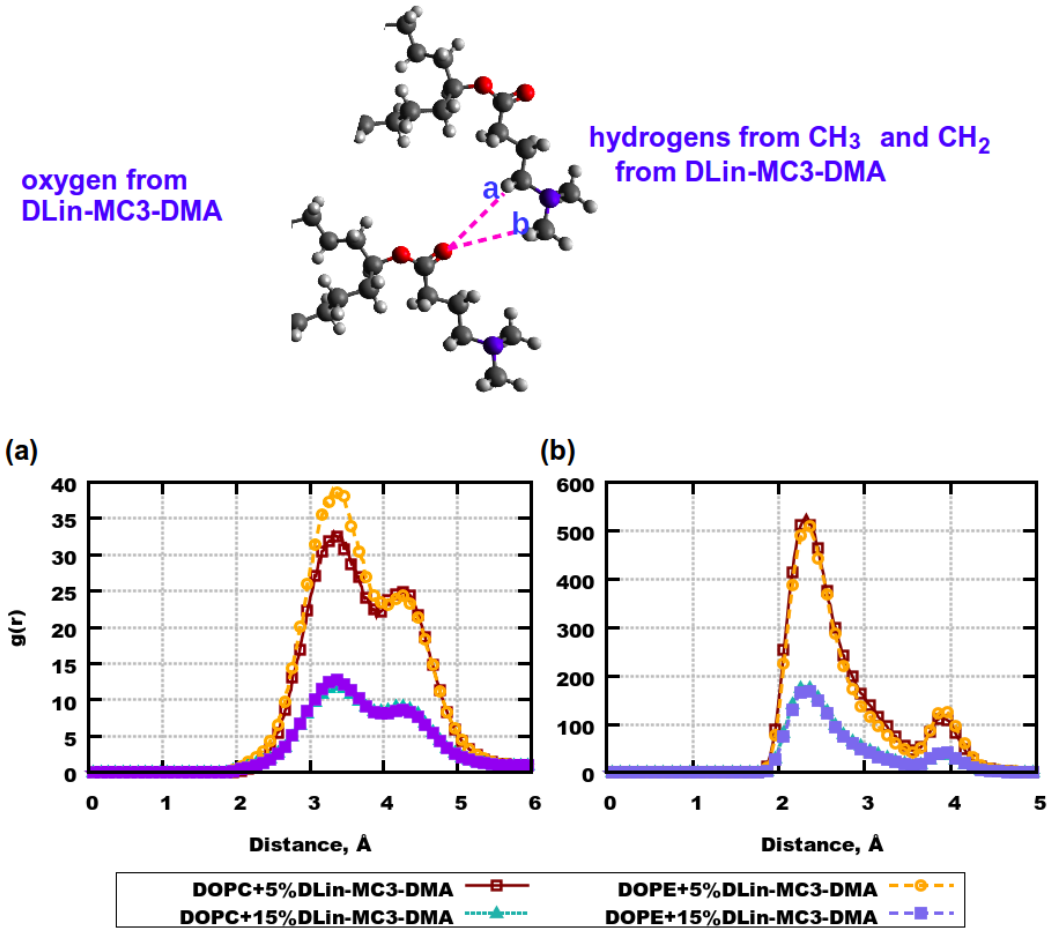

Figure S9: RDFs between pairs of atoms in the DLin-MC3-DMA head-group. (a) RDFs between hydrogensfrom the CH_2-group labeled as "a" and oxygens. (b) RDFs between hydrogens from the CH_3-group labeled as "b" and oxygens. Parts of the DLin-MC3-DMA lipid were colored in a following way: light gray color - hydrogen, dark gray - carbon, blue - nitrogen, red - oxygen.

6 Evolution of the CV for well-tempered metadynamics simulations

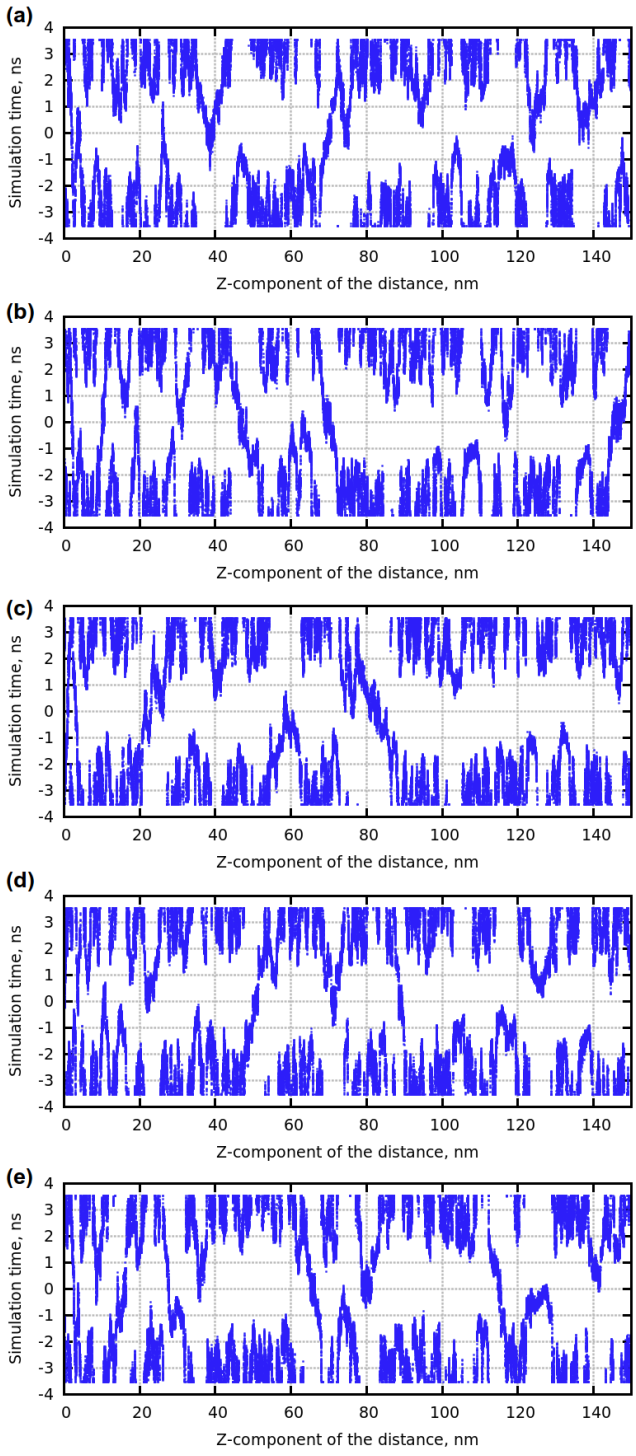

Figure S10: Evolution of the CV in 5 well-tempered metadynamics simulations (a, b, c, d, e) for DOPC with 5% of DLin-MC3-DMA.

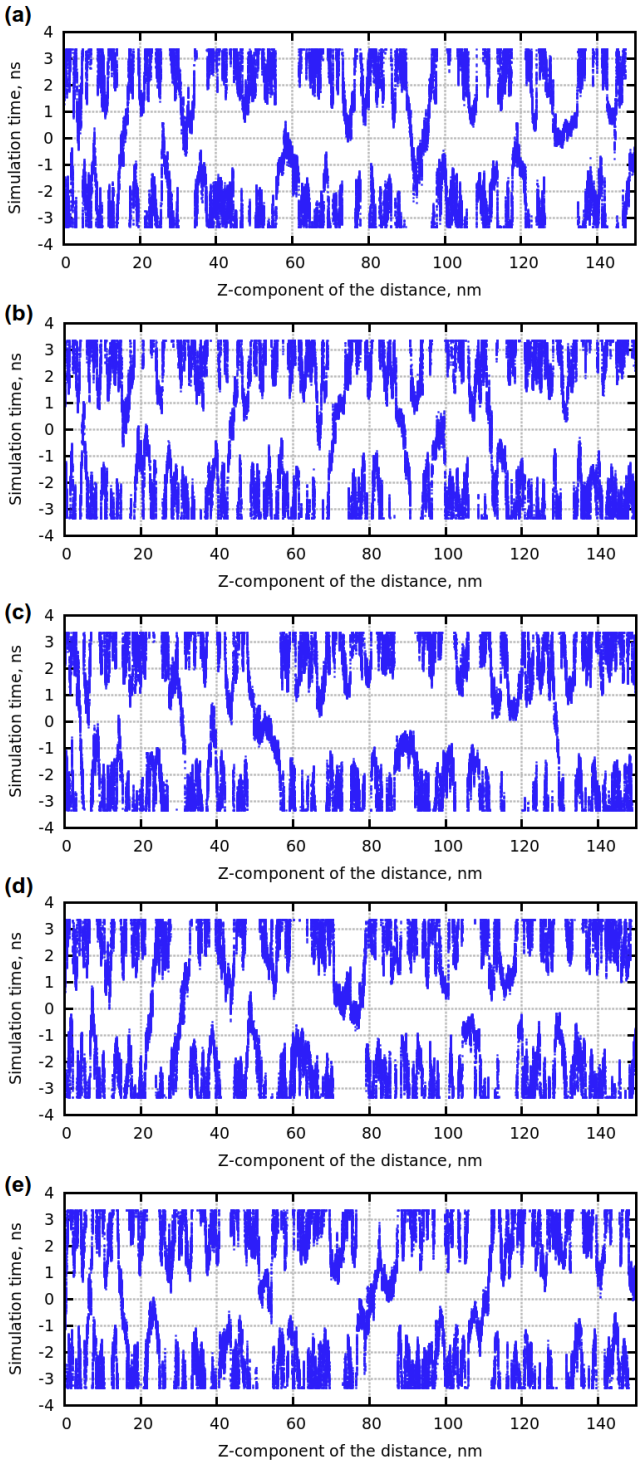

Figure S11: Evolution of the CV in 5 well-tempered metadynamics simulations (a, b, c, d, e) for DOPC with 15% of DLin-MC3-DMA.

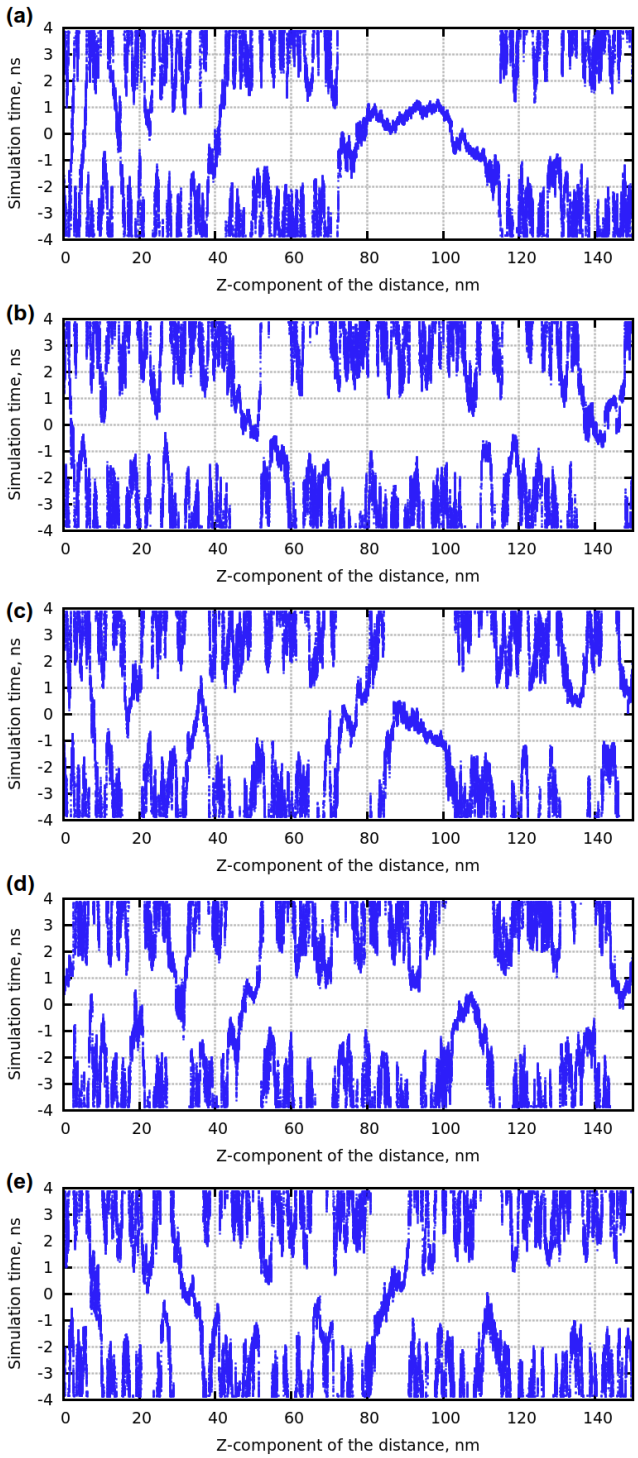

Figure S12: Evolution of the CV in 5 well-tempered metadynamics simulations (a, b, c, d, e) for DOPE with 5% of DLin-MC3-DMA.

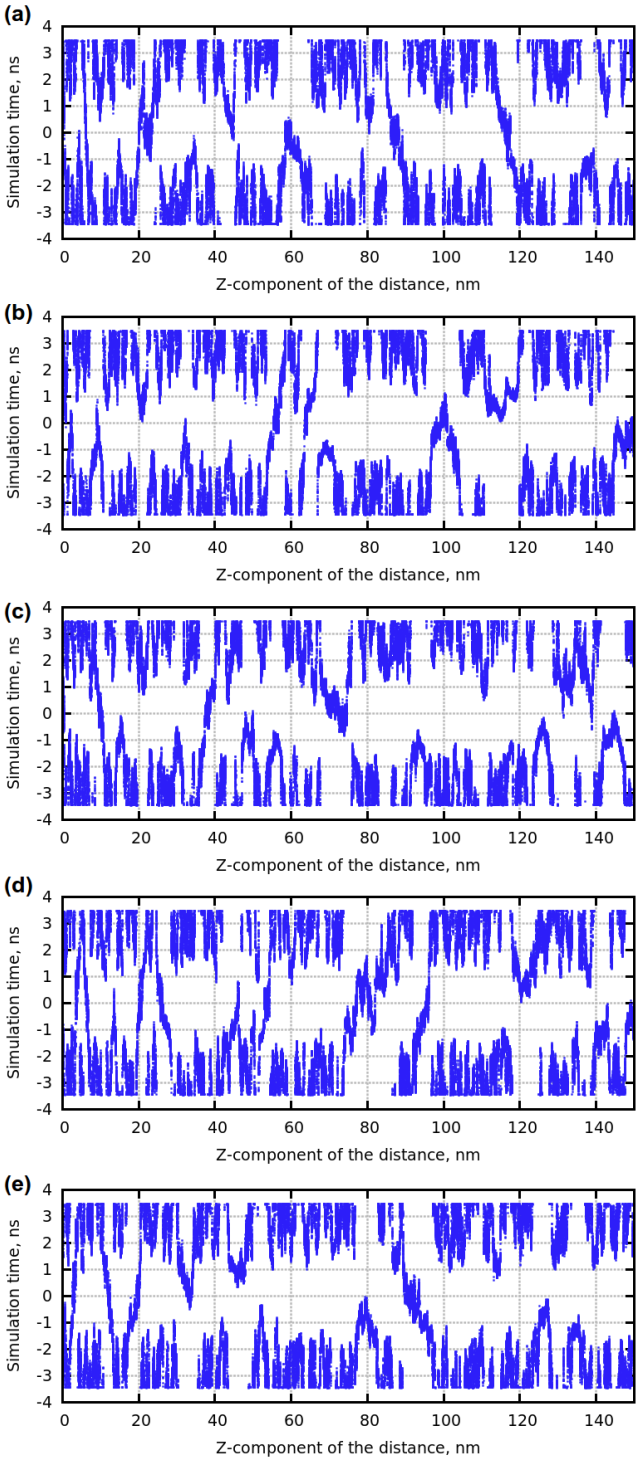

Figure S13: Evolution of the CV in 5 well-tempered metadynamics simulations (a, b, c, d, e) for DOPE with 15% of DLin-MC3-DMA.

7 Evolution of Gaussian heights (HILLS) for well-tempered metadynamics simulations

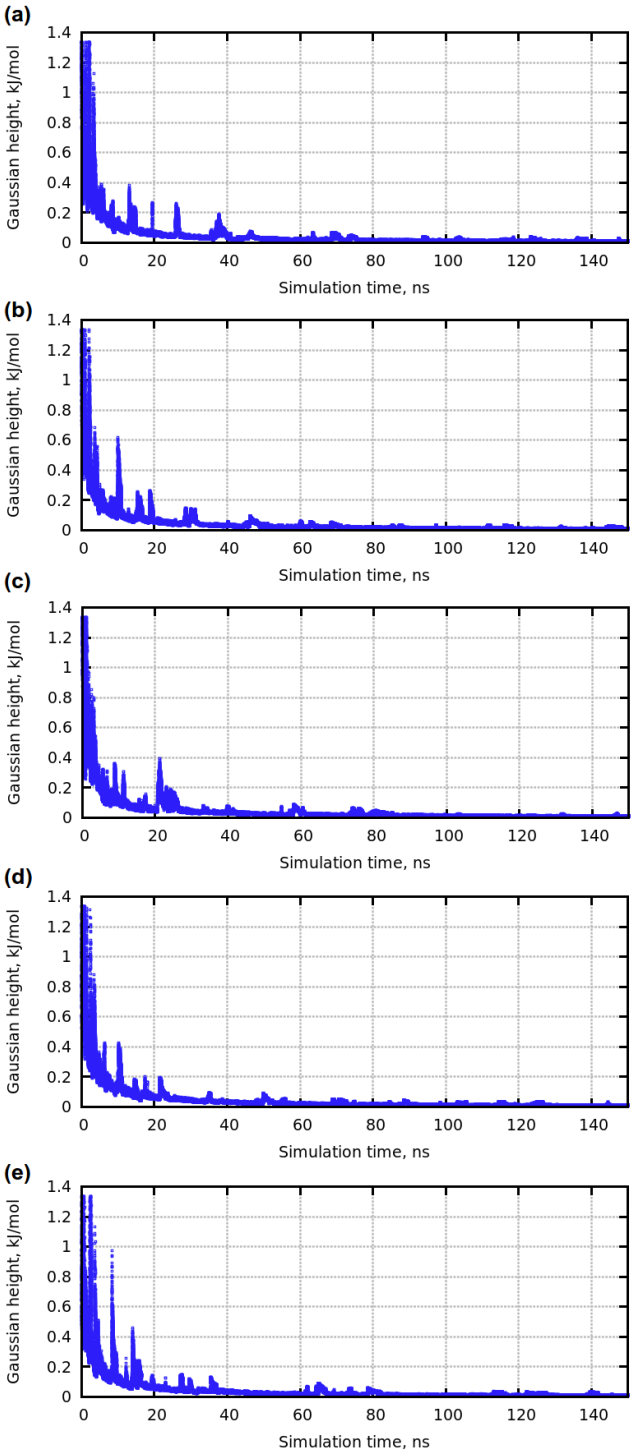

Figure S14: Evolution of the Gaussian heights in 5 well-tempered metadynamics simulations (a, b, c, d, e) for DOPC with 5% of DLin-MC3-DMA.

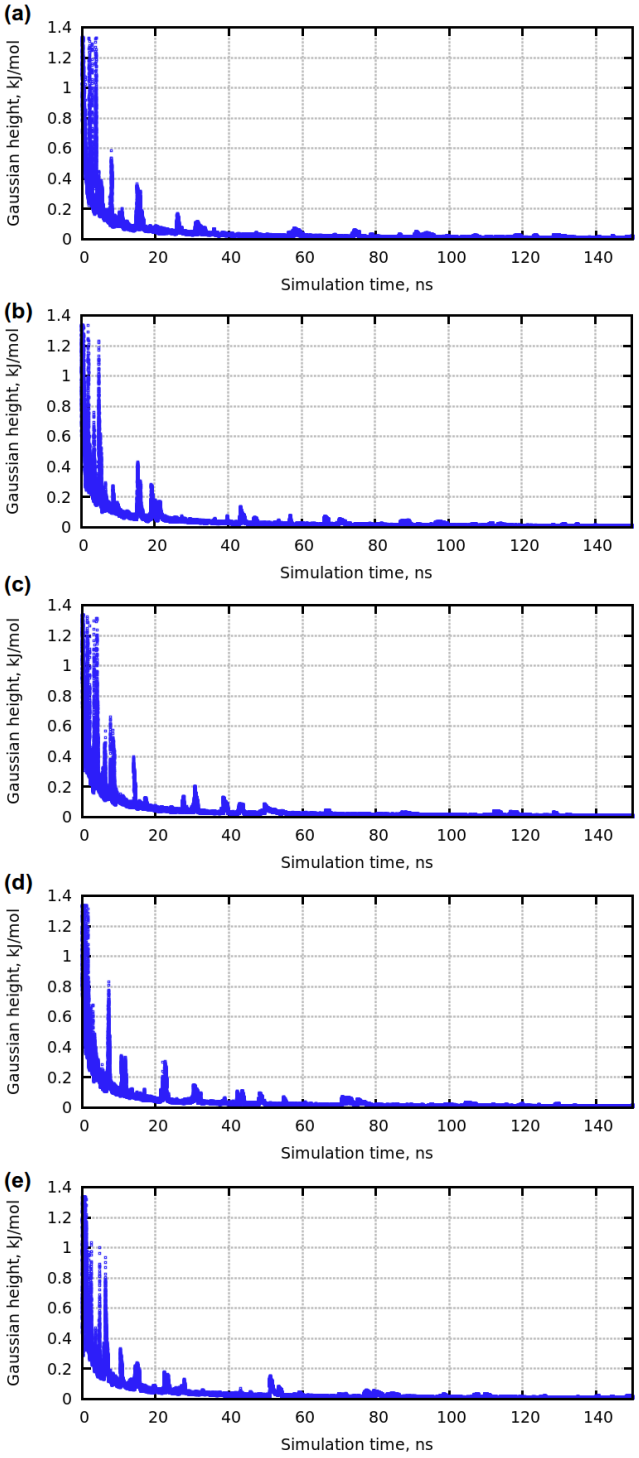

Figure S15: Evolution of the Gaussian heights in 5 well-tempered metadynamics simulations (a, b, c, d, e) for DOPC with 15% of DLin-MC3-DMA.

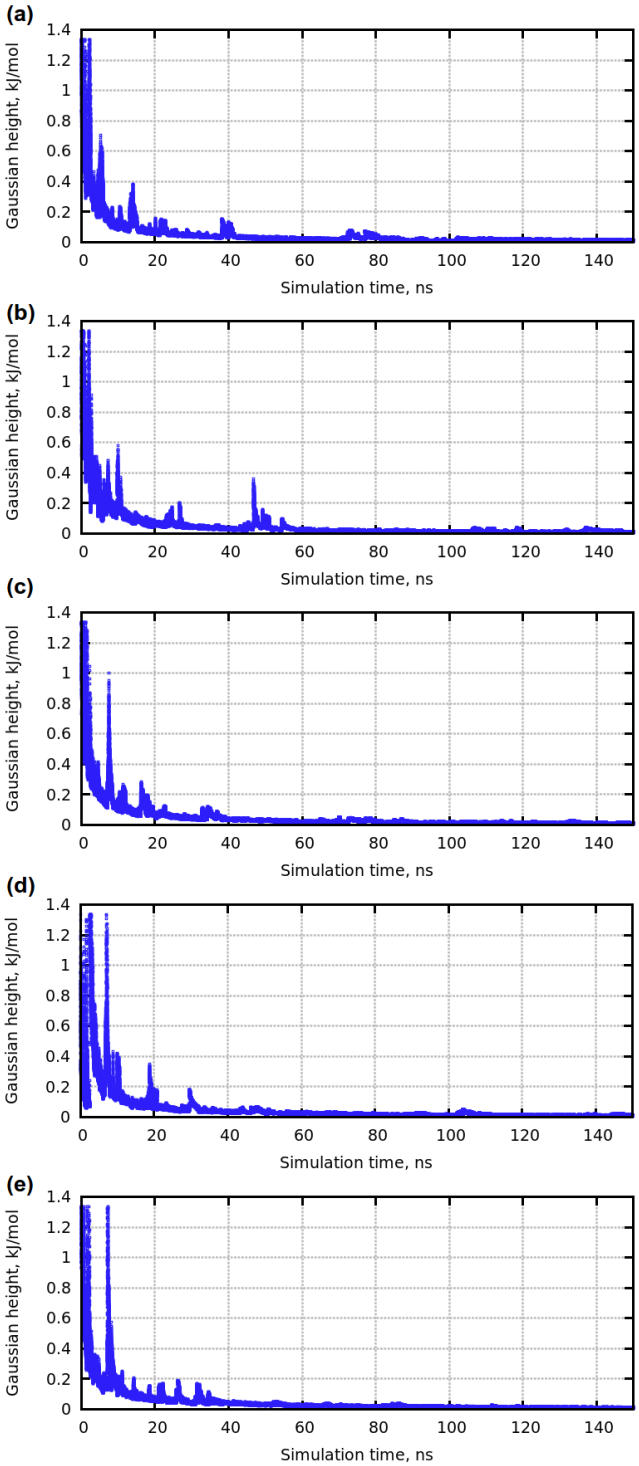

Figure S16: Evolution of the Gaussian heights in 5 well-tempered metadynamics simulations (a, b, c, d, e) for DOPE with 5% of DLin-MC3-DMA.

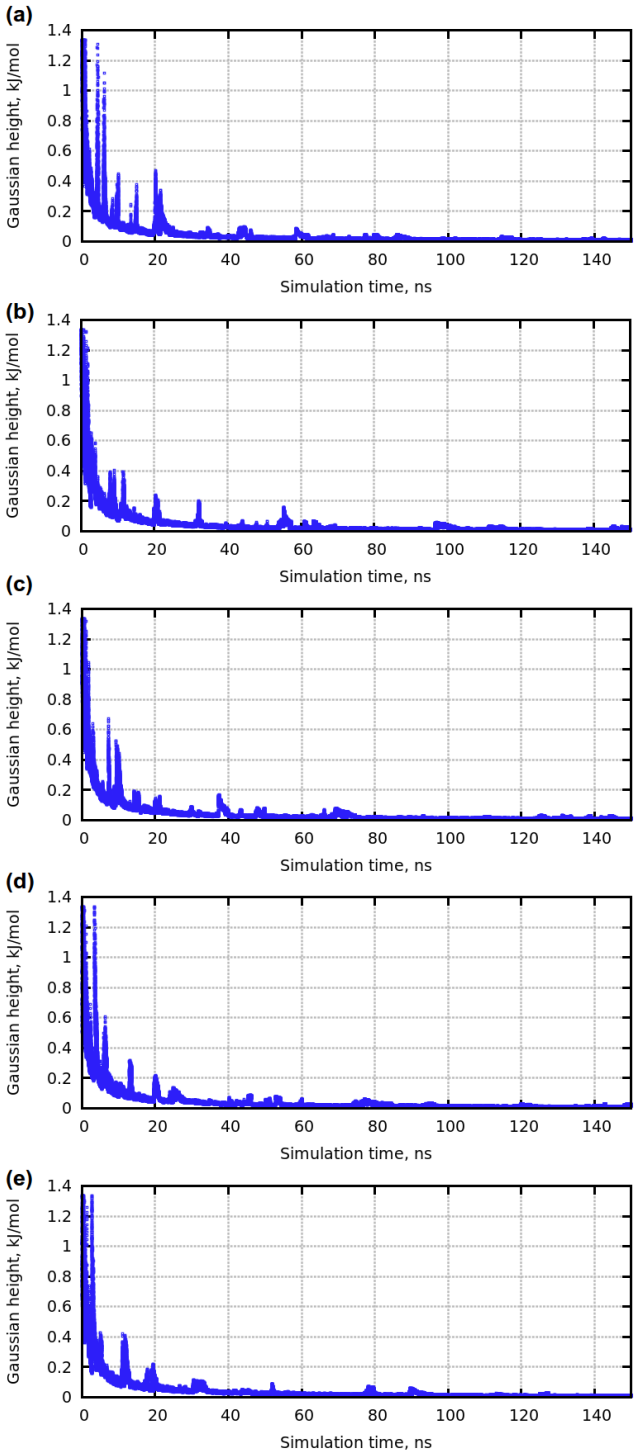

Figure S17: Evolution of the Gaussian heights in 5 well-tempered metadynamics simulations (a, b, c, d, e) for DOPE with 15% of DLin-MC3-DMA.

References

[1] W. Humphrey, A. Dalke, K. Schulten *et al.*, *J. Mol. Graph.*, 1996, **14**, 33–38.