Supporting Information: Accurate binding of sodium and calcium to phospholipid bilayers by effective inclusion of electronic polarization

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S1 Simulation details

Table S1: Simulation parameters

simulation property	parameter
time-step	2 fs
equilibration time	100 ns
total simulation time	300 ns
temperature	313 K
thermostat	v-rescale[1]
barostat	Parrinello-Rahman, semi-isotropic[2]
long-range electrostatics	PME[3]
cut-off scheme	Verlet[4]
Coulomb and VdW cut-off	1.0 nm
constraints	LINCS, only hydrogen atoms[5]
constraints for water	SETTLE[6]

OpenMM simulations were run with 4 fs time step using 4 times heavier hydrogen atoms (mass subtracted from neighbouring atoms).

S2 Area per molecule and calcium binding with different water models

Table S2: Area per lipid (APL) from different models of POPC with no ions

model	APL (Å^2)	Temperature [K]
Lipid14	65.1± 0.6	300
Lipid14[7]	65.6± 0.5	303
ECC-POPC		
SPC/E	63.2± 0.6	300
SPC/E	65.1± 0.6	313
OPC3	62.2± 0.6	300
OPC3	64.2± 0.6	313
OPC	64.4± 0.6	313
TIP4p/2005	66.8± 0.6	313
TIP3p	66.2± 0.6	313
TIP3p-FB	64.8± 0.6	313
TIP4p-FB	65.6± 0.6	313
experiment[8]	62.7± 1.3	293
	64.3± 1.3	303
	67.3± 1.3	323
	68.1± 1.4	333

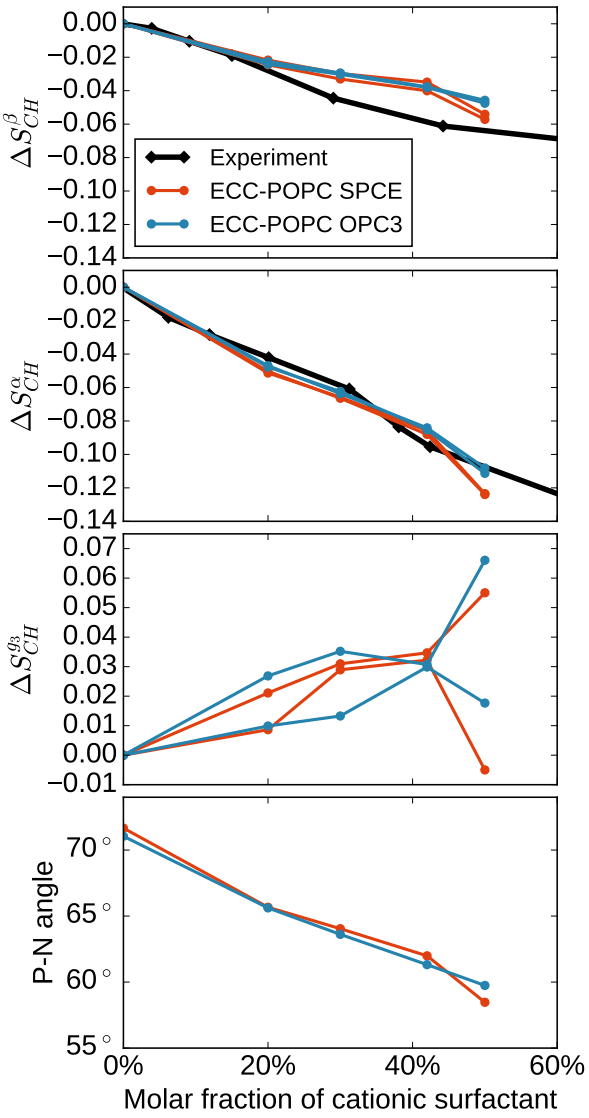

Figure S1: Changes of head group and glycerol carbon g_3 order parameters, and P-N vector orientation of POPC bilayer as a function of a molar fraction of the cationic surfactant dihexadecyldimethylammonium in a POPC bilayer from simulations with different water models (OPC3,[9] SPC/E[10]) and experiments[11] at 313 K.

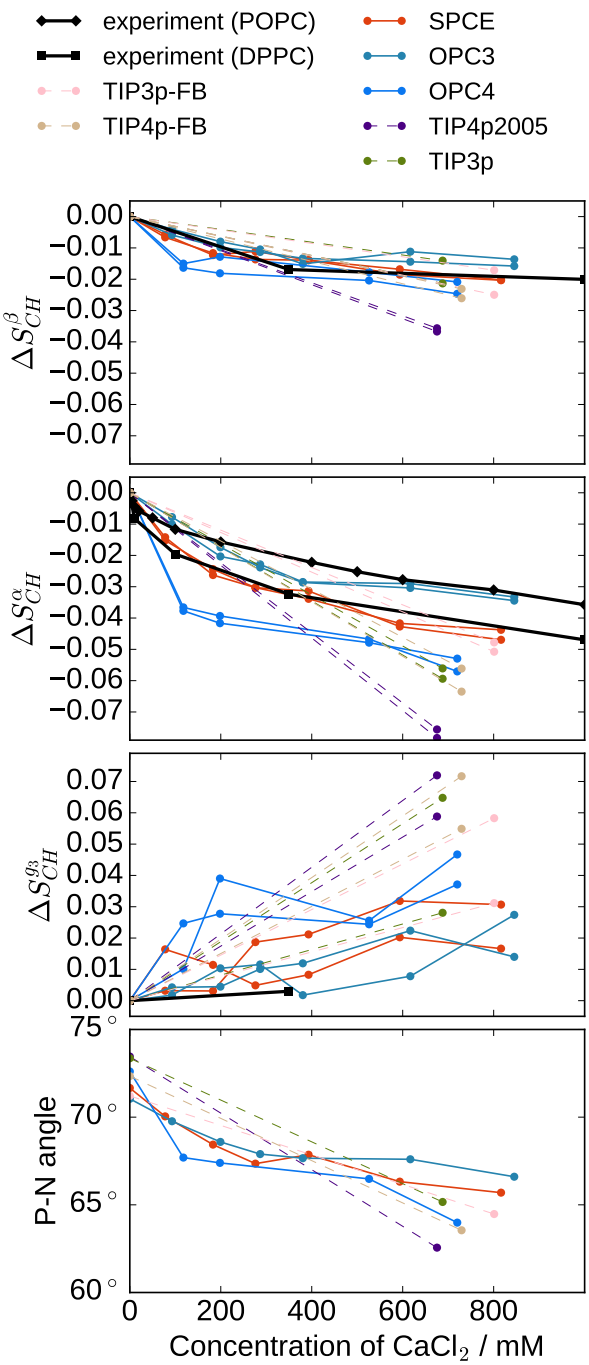

Figure S2: Changes of head group and glycerol carbon g_3 order parameters, and P-N vector orientation of POPC bilayer as a function of $CaCl_2$ concentrations in bulk (C_{ion}) from ECC-POPC simulations at 313K with different water models (SPC/E,[10] OPC,[12] OPC3,[9] TIP3P,[13] TIP3p-FB and TIP4p-FB,[14] and TIP4p/2005[15]) together with experimental data (DPPC (323 K)[16] and POPC (313 K)[17]). Ion concentrations (C_{ion}) are calculated from the cation number density C_{np} at the farthest point from the lipid bilayer in the aqueous phase as [ion]=C_{np}/0.602.

S3 Sodium binding to POPC with the glycerol carbon g_3 order parameters and the head group orientation

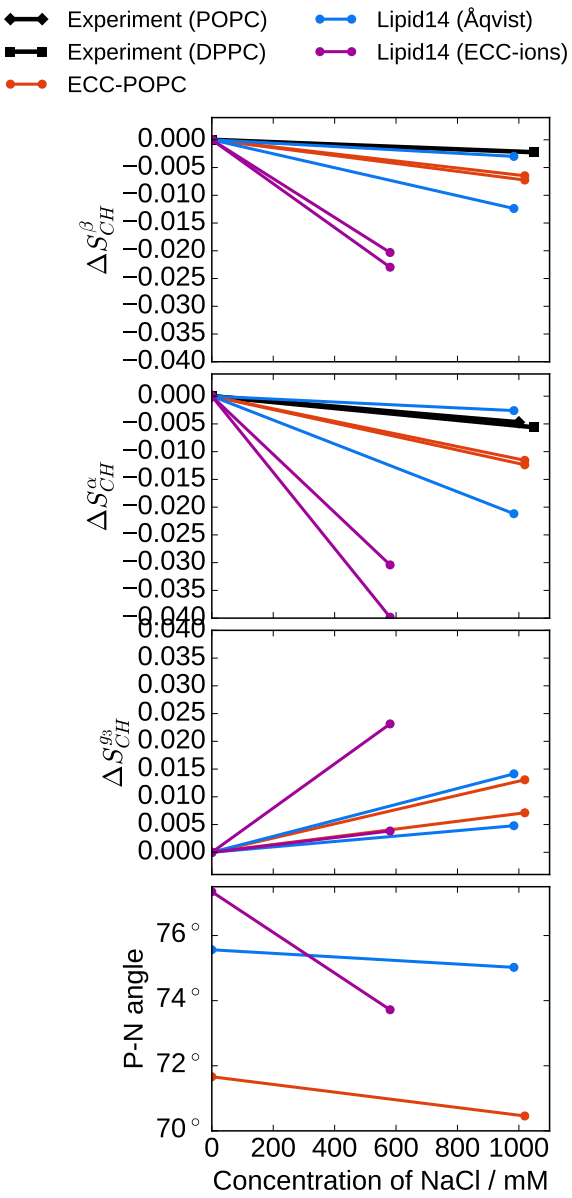

Figure S3: Changes of head group and glycerol carbon g_3 order parameters, and the P-N vector orientation of POPC bilayer as a function of NaCl concentrations in bulk (C_{ion}) from simulations with different force fields at 313 K together with experimental data (DPPC (323 K)[16] and POPC (313 K)[17]). Simulation data with Lipid14 and Åqvist ion parameters at 293 K is taken directly from Refs. 18–20.

S4 Ternary complex model in simulations

The NMR data about PC headgroup order parameters and atomic absorption spectroscopy data were previously best explained using a ternary complex binding model.[17] In this model, one calcium is assumed to form complexes with two lipids, i.e. with the binding stoichiometry of 1 Ca^{2+}:2 POPC. The model predicts a linear relationship between quantities C_b and $\sqrt{C_b/C_I}$, where C_b is the mole fraction of bound Ca^{2+} per POPC and C_I is the concentration of free cations at the plane of ion binding.[17] Experimentally detemined C_b from NMR measurements and atomic absorption spectroscopy together with C_I calculated from the Poisson-Boltzmann equation gave a good agreement with the predictions of the ternary complex model.[17]

To compare ECC-POPC simulations to the ternary complex model, we calculated C_b from simulations (as defined in the main text), and C_I from the minimum $CaCl_2$ concentration at membrane-water interface, locating around 2.6 nm from the membrane center in the density profiles in Fig. 5 in the main text.

The results from simulations are shown in Fig. S4 together with the line fitted to experimental data by Altenbach and Seelig.[17] Both results are in agreement with the prediction of the ternary complex model. The small discrepancy between the results from experiments and simulations probably arise from difference in the evaluation of the concentrations and inaccuracy of Poisson-Boltzmann theory for divalent cations like Ca^{2+}.[21] In conclusion, the results suggest that the almost equal probabilities for Ca^{2+} to form complexes with one to three lipids detailed in the main text is in line with an averaged interpretation of the experimental observations which supported the ternary complex model.

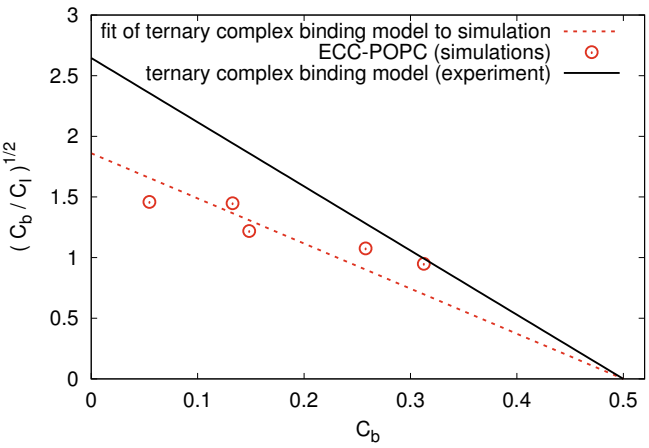

Figure S4: Fits of experimental[17] and ECC-POPC simulation data to the prediction of the ternary complex model.

S5 Histograms of residence times

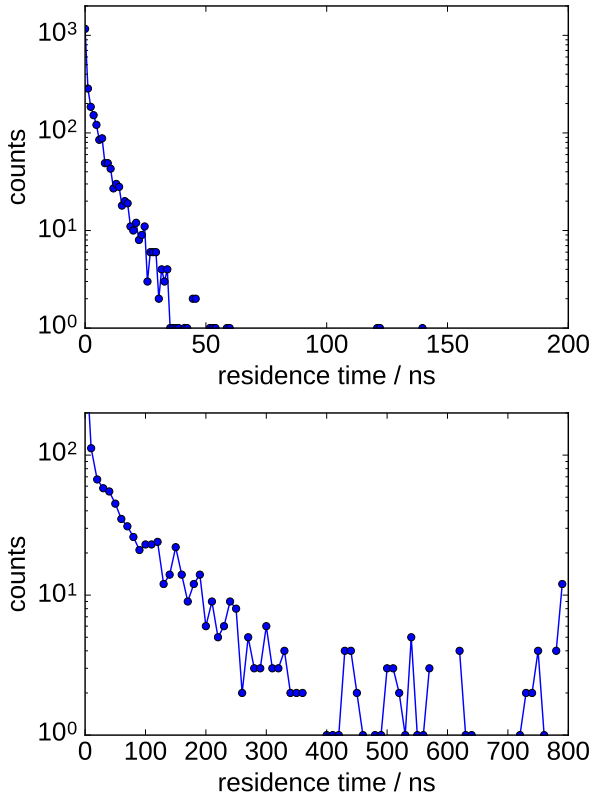

Figure S5: Histograms of residence times of Ca^{2+} in a POPC bilayer from ECC-POPC (top) and CHARMM36 (bottom) simulations with ECC-ions. Both simulations had the same concentration of $CaCl_2$ respect to water (C'_{ion}= 450 mM). CHARMM36 simulation was directly taken from Refs. 22,23. Scales of x-axes represent the lengths of the simulations used for analysis. In ECC-POPC simulation, 90% of the residence times are shorter than 60 ns, with the longest observed residence time being 141 ns, which is well below the total length of the simulation (200 ns). This is, however not the case in CHARMM36 simulation, where residence times of several calcium cations are apparently limited by the length of the simulation. Less than 60% of the residence times are shorter than the half of the simulation length (400 ns) in CHARMM36 simulation.

S6 Comparison between Gromacs and openMM

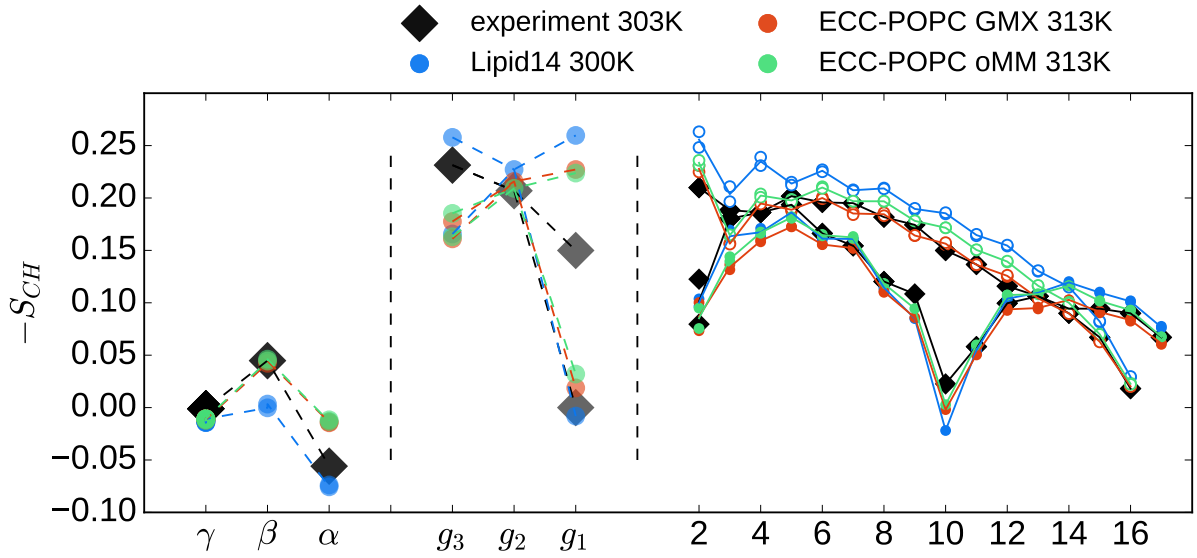

Figure S6: Order parameters of POPC head group, glycerol backbone and acyl chains from Lipid14[7] and ECC-POPC simulations ran with GROMACS 5.1.4[24] and openMM 7[25] together with experiments.[26] The size of the markers for the head group order parameters correspond to the error estimate ±0.02 for experiments,[27,28] while the error estimate for simulations is ±0.005. The size of the points for acyl chains are decreased by a factor of 3 to improve the clarity of the plot.

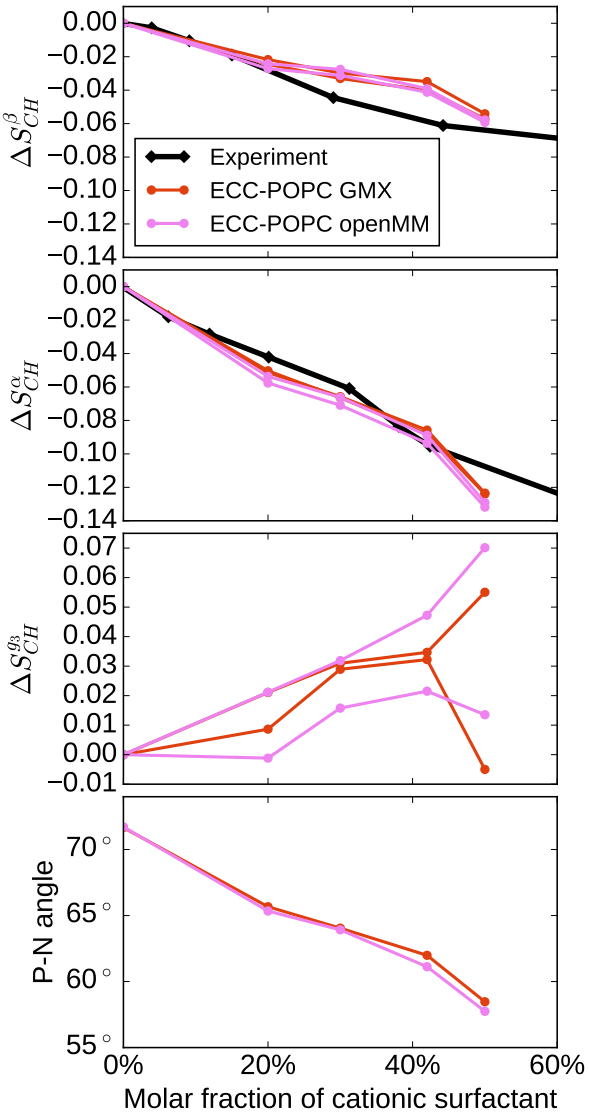

Figure S7: Changes of headgroup and glycerol carbon g_3 order parameters, and P-N vector orientation as a function of a molar fraction of the cationic surfactant dihexadecyldimethylammonium in a POPC bilayer from simulations with the ECC-POPC model simulated with GROMACS 5.1.4[24] and openMM 7[25] compared with the experimental values from.[11] The size of the markers for the head group order parameters correspond to the error estimate ±0.02 for experiments,[27,28] while the error estimate for simulations is ±0.005.

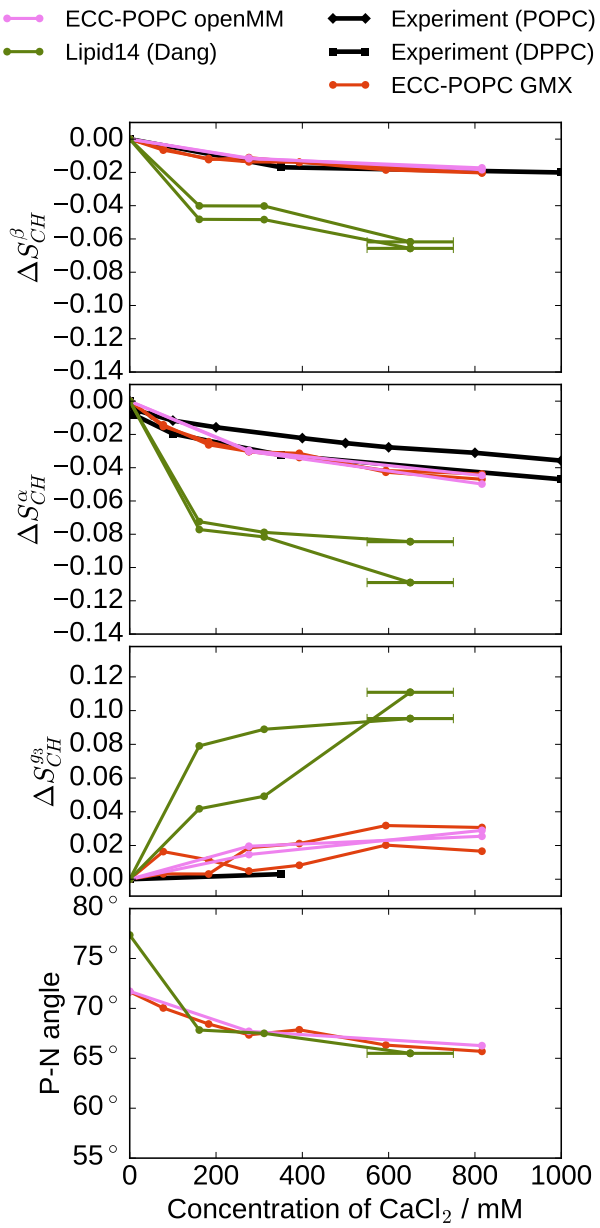

Figure S8: Changes of the head group and glycerol carbon g_3 order parameters, and P-N vector orientation of a POPC bilayer as a function of the $CaCl_2$ concentration in bulk (C_{ion}) from Lipid14[7] and ECC-POPC simulations ran with GROMACS 5.1.4[24] and openMM 7[25] at 313 K together with experiments (DPPC (323 K)[16] and POPC (313 K)[17]). Bulk concentrations from simulations are calculated from the farthest point from the lipid bilayer in the aqueous phase with an error estimate of 10 mM.

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