Adsorption modes of Na$^+$, Li$^+$, and Mg^{2+} to model zwitterionic lipid bilayers: Supporting Information

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We followed the method outlined in Saunders *et al.* 2022[1] to obtain the non-aqueous parameters listed in table S1 for Li$^+$, and the gas phase results are shown in figures S1 and S2.

Table S1: Lennard-Jones cross-terms used in each simulation. We have computed LB-terms using Lorentz-Berthelot (LB) mixing rules, starting with the self-terms for Li$^+$ from Joung and Chetatham III*et al.* [2] ϵ are presented in units of / Kj/mol and σ are presented in units of /nm.

| Atom type | Li$^+$ | | | |
| | LB-Rules | | MB-NB-fix | |
	ϵ	σ	ϵ	σ
CH3	1.07485	0.25797	0.99872	0.30898
CH2	0.75411	0.27432	1.05729	0.20001
OA	1.09408	0.21821	2.91925	0.20020
P	1.85667	0.23975	6.99324	0.21844
OM*	1.19328	0.21400	0.23749	0.20015
CO*	0.35344	0.29727	0.48204	0.35920
O*	1.19328	0.21400	0.06248	0.20068
OW	0.95709	0.22875	0.95709	0.22875

Table S2: Fractions per lipid of anions perfectly adsorbed, imperfectly adsorbed, sterically adsorbed, and non-adsorbed anions in each simulation, defined in the same way as we define adsorption of cations. These are computed by counting the number of waters in the first-coordination shell of every anion in the simulation box in every frame. For the total number of adsorbed anions, we only check if the anion is within the hydration boundary of the bilayer. We then subtract the number within this region that are completely dehydrated – these are the perfectly adsorbed anions. We futher subtract any ions that have lost one or more waters – the imperfectly adsorbed ions. The remaining are considered sterically adsorbed. We indicate each system by the cation name, as the anion in the system is always Cl⁻. We note that the anion binding fractions follow the trend seen in the total number of cations bound for each system, due to the formation of the ionic double-layer at the bilayer-water interface. Most anions adsorb sterically in each system, with some adsorbing imperfectly as they approach the positively charged choline trimethylammonium in the lipid headgroup.

Adsorbed anions / lipid	Cl⁻ in Na^+ System	Cl⁻ in Li^+ System	Cl⁻ in Mg^{2+}-Li *et al.* System	Cl⁻ in Mg^{2+}-Grotz *et al.* System
Total θ	0.423	0.463	0.186	0.208
Steric θ_s	0.209	0.213	0.107	0.126
Imperfect θ_I	0.214	0.250	0.079	0.082
Perfect θ_P	0.000	0.000	0.0	0.0

Figure S1: Substitution energies of Li^+ from clusters of solvent to clusters of methyl-acetate and diethyl-phosphate. The *ab initio* substitution energies in black were used as the target for the optimization of the non-aqueous ion cross-terms. The blue line is the result of the Lorentz-Berthelot mixing rules, and the red line is the result of our optimized parameters. We see a substantial improvement in the substitution energies for both methyl-acetate clusters and diethyl-phosphate clusters.
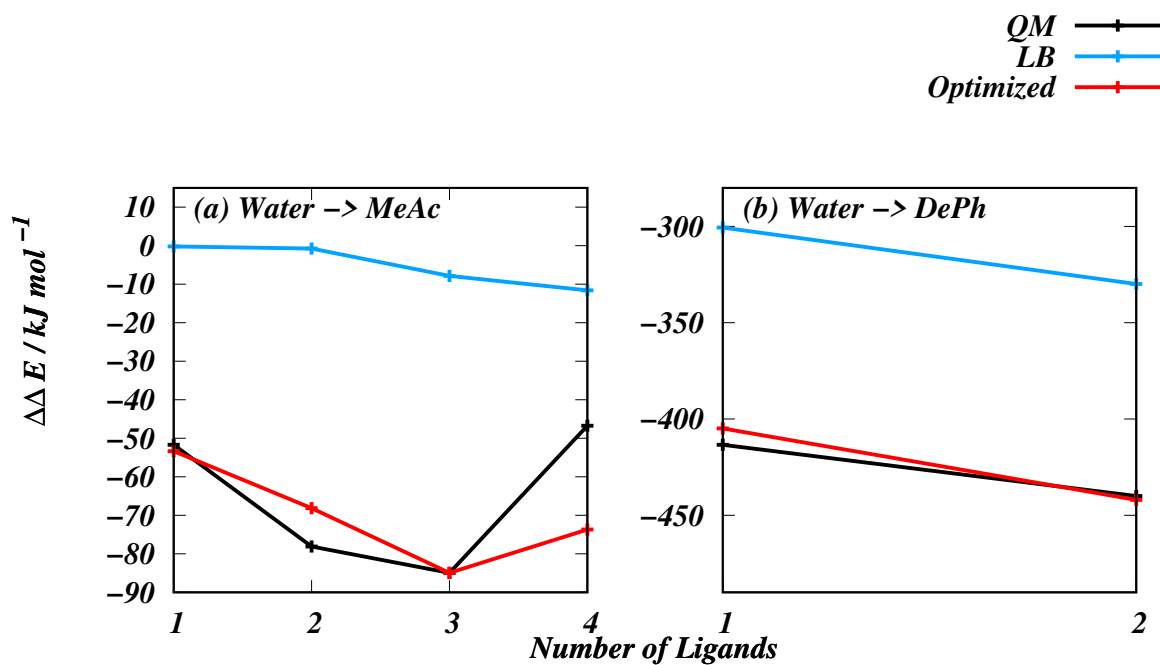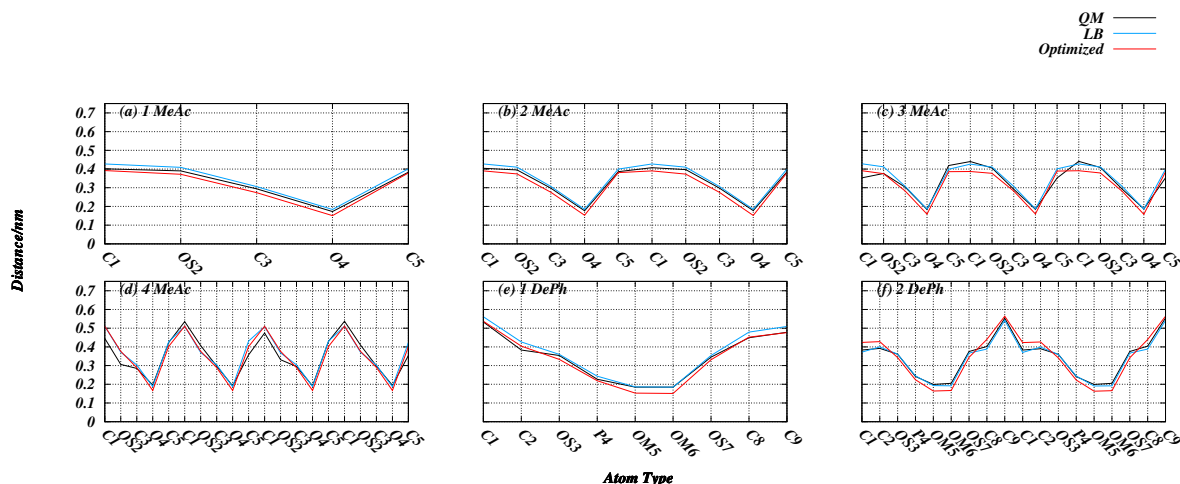
Figure S2: Distances of all ligand atoms from ion, for each cluster. Lorentz-Berthelot parameters result in geometries that are very similar to the target data – in general, the optimized parameters result in the ion being slightly closer to the electronegative oxygens in each cluster.

References

(1) Saunders, M.; Wineman-Fisher, V.; Jakobsson, E.; Varma, S.; Pandit, S. A. High-dimensional parameter search method to determine force field mixing terms in molecular simulations. *Langmuir* **2022**, *38*, 2840–2851.

(2) Joung, I. S.; Cheatham III, T. E. Determination of alkali and halide monovalent ion parameters for use in explicitly solvated biomolecular simulations. *The journal of physical chemistry B* **2008**, *112*, 9020–9041.