Supporting Information

for

Isothermal Titration Calorimetry of Be^{2+} and Ca^{2+} with Phosphatidylserine Models Guides All-Atom Force Field Development for Lipid-Ion Interactions

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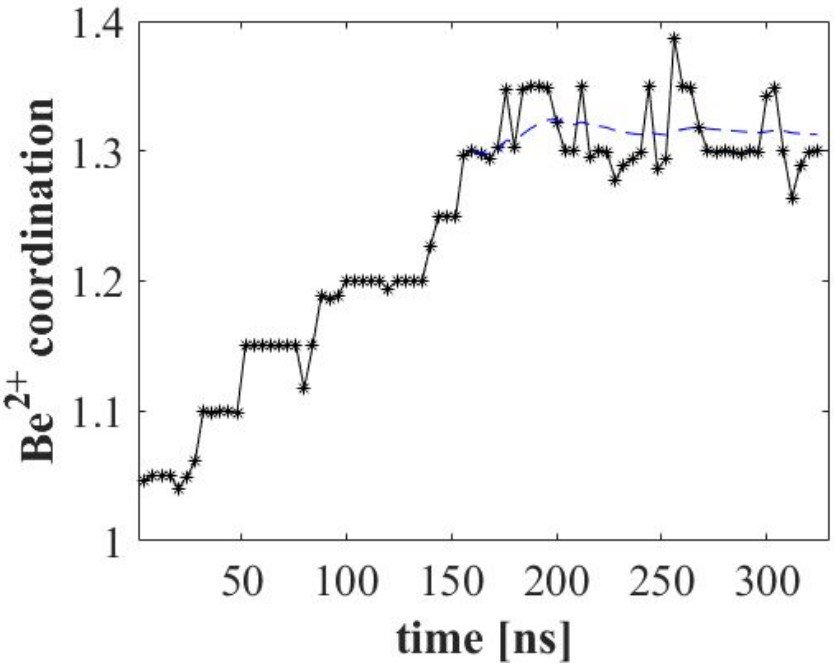

Figure S1. Be^{2+} coordination by dimethyl phosphate. Each point represents $N_{\mathrm{ion}\ -\ \mathrm{O_{dp}}}$ averaged over 4-ns blocks. Equilibration is seen around 100 ns, and tight binding restricts fluctuations.

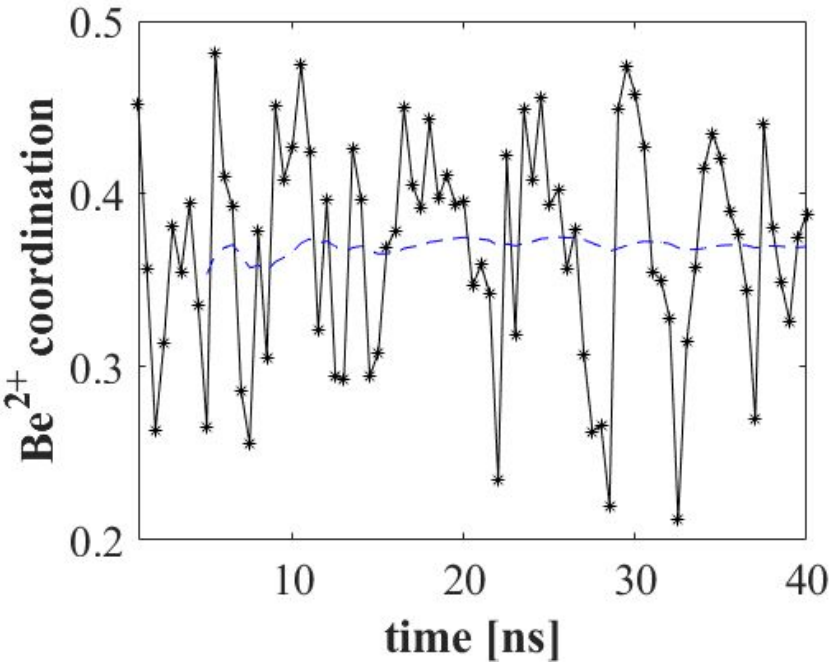

Figure S2. Be^{2+} coordination by acetate, revised lipid FF. Each point represents $N_{\mathrm{ion}\ -\ \mathrm{O_{dp}}}$ averaged over 0.5-ns blocks. Blue dashed line is the accumulated average as a function of time from 5 ns forward.

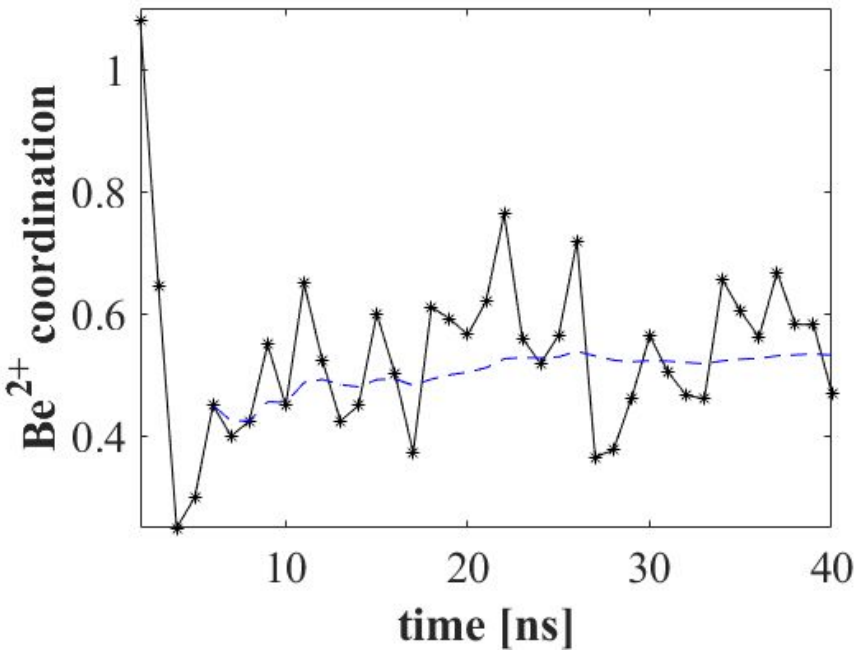

Figure S3. Be^{2+} coordination by acetate, revised CGENFF. Each point represents $N_{\mathrm{ion}\ -\ \mathrm{O_{dp}}}$ averaged over 2-ns blocks. Equilibration is seen around 5 ns, after which coordination fluctuates. Blue dashed line is the accumulated average as a function of time from 5 ns forward.

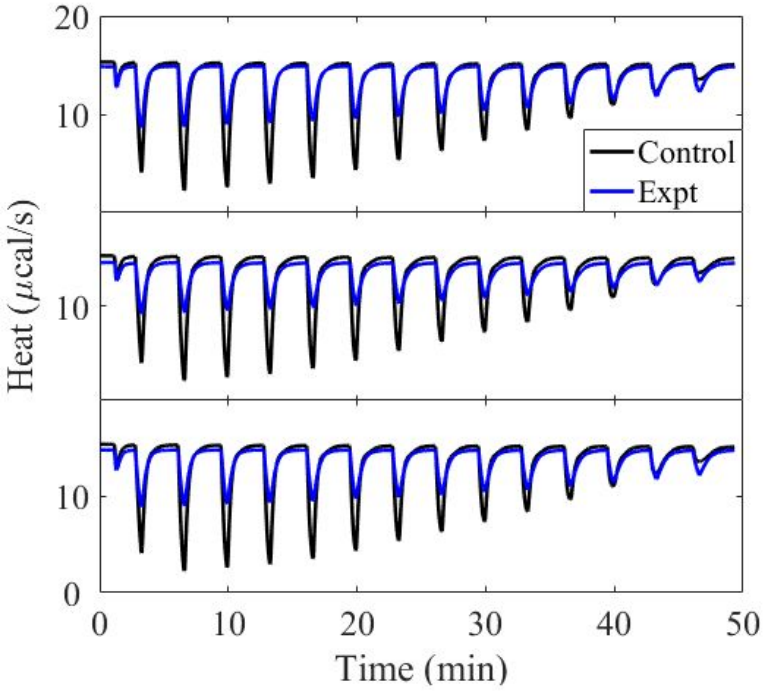

Figure S4. ITC data for Be^{2+} with dimethyl phosphate (DMP). Concentrations were 4 mM DMP in the syringe and 2 mM Be^{2+} in the cell.

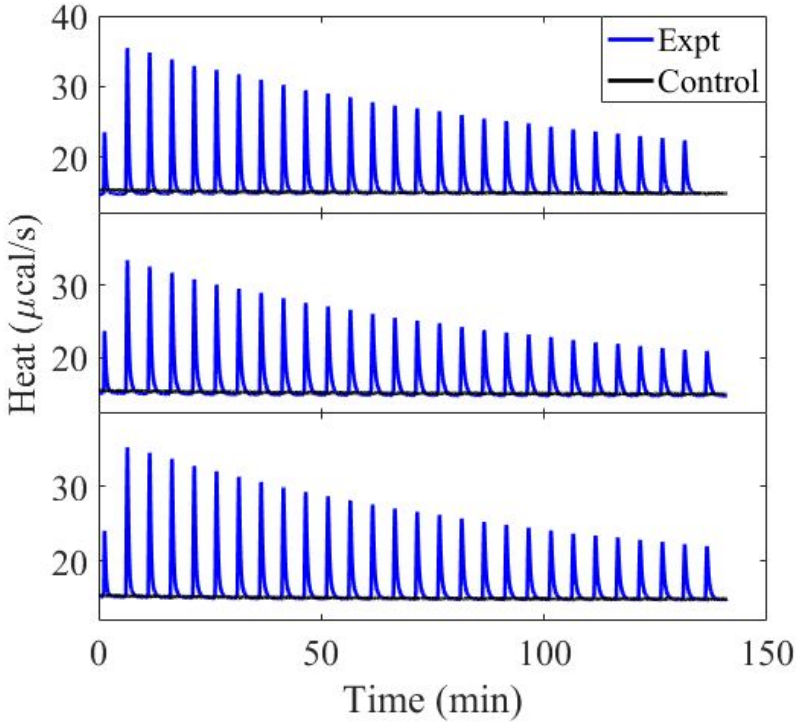

Figure S5. ITC data for Be^{2+} with Na^{+1}-acetate. Concentrations were 20 mM Na^{+1}-acetate in the syringe and 5 mM Be^{2+} in the cell.

Table S1. Values of $r_{ij}^{\min}$ [Å] used in FEP simulations to calculate free energy of association ΔG_c.

Small Molecule	CHARMM Atom Types	$r_{ij}^{\min}$ Tested/ # of Trials
DMP Lipid FF	O2L	2.51*/2
		2.8/2
		2.82/2
		2.84/4
		2.86/3
		2.88/3
		2.9/3
		2.92/3
		2.95/3
		3.0/1
acetate CGEN FF	OG2D2	2.51*/2
		2.6/2
		2.8/2
		3.0/2
		3.20/3
		3.23/2
		3.25/2
acetate Lipid FF**	OCL	2.51*/2
		3.0/3
		3.07/3
		3.1/4
		3.2/3

*Default values for $r_{ij}^{\min}$, calculated using Eq. [6] and Be^{2+} LJ parameters developed in this study.
**New soluble acetate model for Lipid FF. See supplemental information section S2.

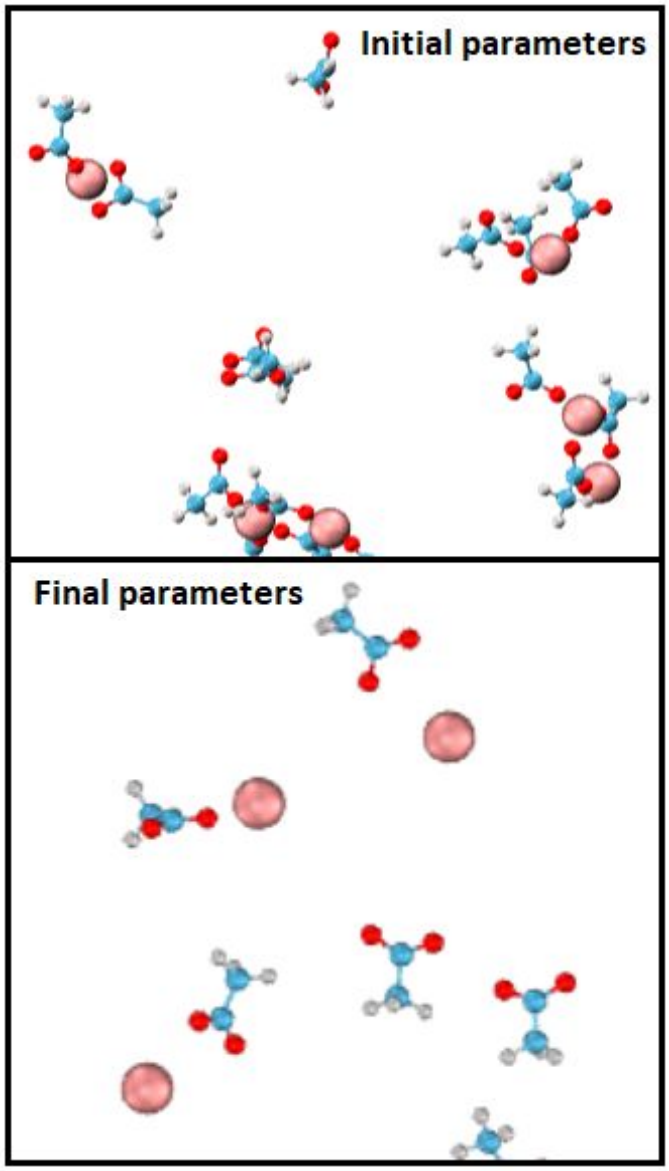

Figure S6. Be^{2+} in solution with acetate. Default (top) and adjusted (bottom) LJ interaction parameters for Lipid FF. Colors: Be^{2+}, pink; O, red; C, blue; H, gray. Water and Na^{+} ions not shown.

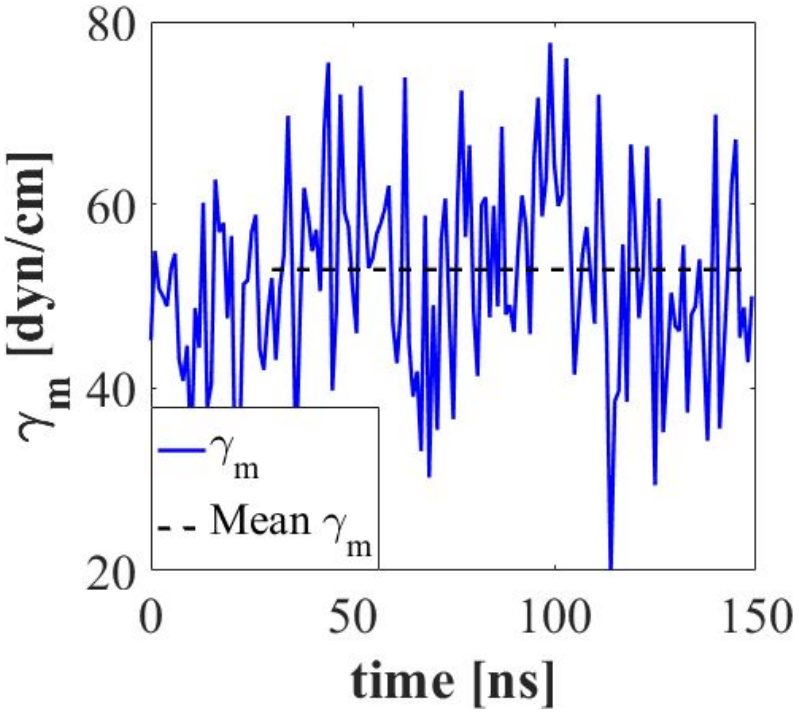

Figure S7. Equilibration of DOPS monolayer surface tension (γ_m). γ_m of Be^{2+}-bound DOPS monolayer, $A_l = 65.3$ Å^2, as a function of simulation time, calculated in 1-ns blocks. Mean computed from 30 – 150 ns.

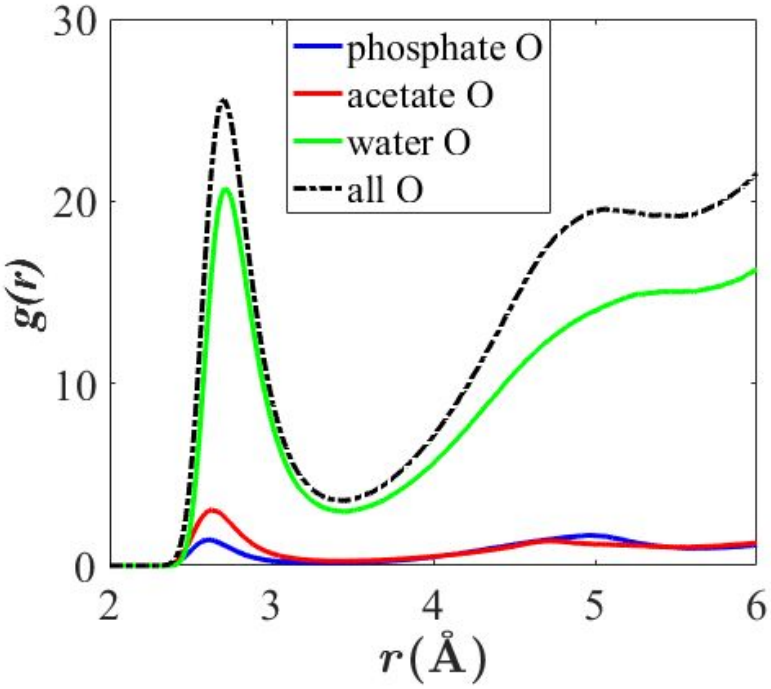

Figure S8. Pair correlation functions of K^+ with various oxygens. $A_l =$ 65.3 Å^2/lipid. For comparison, $g(r)$ are not normalized. See Fig. 11 to compare with Be^{2+}.

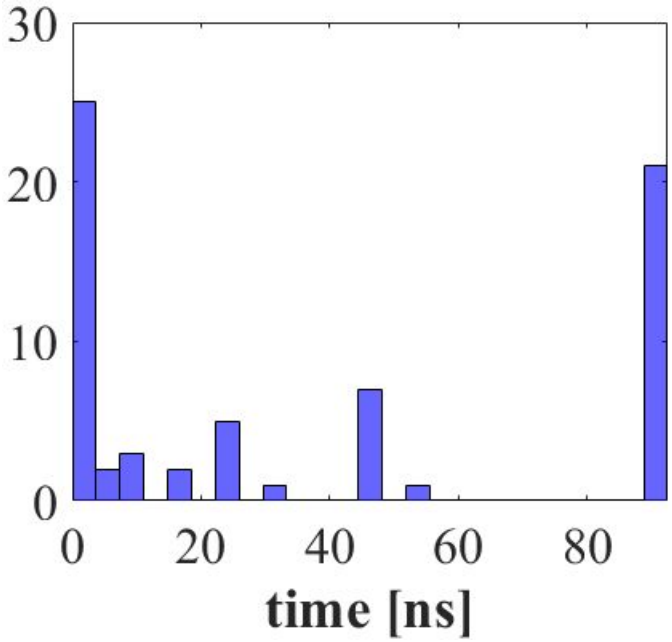

Figure S9. Histogram of Be^{2+}-phosphate association times. A_l = 65.3 Å^2, computed from 30 – 120 ns. Associations < 20 ps not shown.

S2. Soluble acetate models. Residue "ACE" below is compatible with the C36 lipid FF.[1] Partial charges (column 4) were borrowed from residue DOPS. Atom names and types are columns 2 and 3, respectively. Where necessary, additional parameters listed were adapted from methyl acetate[1] and are also listed below. Parameters not listed were not changed.

Residue "ACET" is part of the CGEN FF.[2] Only partial charges are shown.

```
RESI ACE         -1.00 !
GROUP                  !
ATOM C2  CCL      0.34 !          H1    O1 (-)
ATOM O1  OCL     -0.67 !          |    /
ATOM C1  CTL3    -0.27 !      H2--C1--C2
ATOM O2  OCL     -0.67 !          |    \\
ATOM H1  HAL3     0.09 !          H3    O2
ATOM H2  HAL3     0.09 !
ATOM H3  HAL3     0.09 !
BOND C1 H1  C1 H2  C1 H3
BOND C1 C2  C2 O1
DOUBLE  C2 O2
IMPR C2 O2 O1 C1
```

Additional parameters for "ACE":

BONDS

```
CTL3  CCL   200.0       1.522
```

ANGLES

```
OCL  CCL  CTL3    55.0     109.0    20.00   2.3260
HAL3 CTL3 CCL     33.00    109.50   30.00   2.163
```

DIHEDRDALS

```
OCL  CCL  CTL3  HAL3     0.00    6   180.0
```

IMPROPERS

```
CCL  OCL  OCL   CTL3    96.00    0     0.00
```

```
RESI ACET         -1.00 ! C2H3O2 acetate, K. Kuczera
GROUP
ATOM  C1  CG331   -0.37
ATOM  C2  CG2O3    0.62 !     H1    O1 (-)
ATOM  H1  HGA3     0.09 !     |    /
ATOM  H2  HGA3     0.09 ! H2--C1--C2
ATOM  H3  HGA3     0.09 !     |    \\
ATOM  O1  OG2D2   -0.76 !     H3    O2
ATOM  O2  OG2D2   -0.76
BOND C1 H1  C1 H2  C1 H3
BOND C1 C2  C2 O1
DOUBLE  C2 O2
IMPR C2 O2 O1 C1
```