1. CHARMM functional form

$$U = \sum_{bonds} K_b(b-b_0)^2 + \sum_{angles} K_\theta(\theta-\theta_0)^2 + \sum_{dihedrals} K_\phi(1+\cos(n\phi-\delta))$$

$$+ \sum_{\substack{improper \\ dihedrals}} K_\varphi(\varphi-\varphi_0)^2 + \sum_{\substack{Urey- \\ Bradley}} K_{UB}(r_{i,3}-r_{r3;0})^2$$

$$+ \sum_{\substack{non- \\ bonded}} \frac{q_i q_j}{4\pi D r_{ij}} + \varepsilon_{ij}\left[\left(\frac{R_{min,ij}}{r_{ij}}\right)^{12} - 2\left(\frac{R_{min,i,j}}{r_{ij}}\right)^{6}\right]$$

Bonded parameters   Non-bonded parameters

2. Parameters defined for NaCl and NH4Cl (forcefield.itp, cgenff.prm)

①	NaCl : ╱
	NH4Cl : N–H $\longrightarrow$

N	CP3	1	1.955000e-01	2.677700e+05
NG3P3	HGP2	1	1.040000e-01	3.372304e+05
NH1	C	1	1.345000e-01	2.405160e+05

$b_0 \qquad K_b$

②, ⑤	NaCl ╱
	NH4Cl : H–N–H $\longrightarrow$

HGA2	CRL2	HGA2	5	1.090000e+02	3.780480e+02	1.008200e-01	1.313720e+04
HGP2	NG3P3	HGP2	5	1.0950000e+02	3.6819200e+02	0.0000000e+00	0.0000000e+00

$\theta_0 \qquad K_\theta \qquad K_{UB}$

⑥, ⑦	NaCl : Na $\longrightarrow$
	Cl $\longrightarrow$

SOD	11	22.9898	1.000	A	2.51367073323e-01	1.962296e-01
CLA	17	35.4500	-1.000	A	4.044680180036e-01	6.276000e-01

$q \qquad\qquad \sigma_i \qquad\qquad \varepsilon_i$

NH4Cl N $\longrightarrow$
H $\longrightarrow$

NG3P3	7	14.007000	0.000	A	0.329632525712	0.8368000
HGP2	1	1.008000	0.000	A	0.040001352445	0.1924640

$\sigma_i \qquad \varepsilon_i$

$$\varepsilon_{ij} \ (\text{Default}) = \sqrt{\varepsilon_i \times \varepsilon_j} \qquad R_{min}^{ij} \ (\text{Default}) = \frac{R_{min,i} + R_{min,j}}{2}$$

$$= \frac{1}{2}\left[(2^{1/6}\sigma_i) + (2^{1/6}\sigma_j)\right]$$

· NBFIX overwrites default ε_{ij} and R_{min}^{ij}

NaCl

CLA	SOD	1	3.32394311738e-01	3.51037600000e-01

$\sigma'_{ij} \qquad\qquad \varepsilon_{ij}$

NH4Cl : ╱

3. Bonded parameters (①-⑤)

Step 1: Geometric data

- Fitting to gas-phase structures (Microwave, electron diffraction) & crystal structures (X-ray)
- Adjust geometries manually

CGenff:
heterocycles & simple functional groups

Step 2: Force Constant

- Fitting to vibrational data (gas-phase infrared, Raman data/Solution, crystal data) for model systems
- Supplement with ab initio calculations (assignment of experimental vibrational frequencies to internal coordinates, obtain values for low-frequency torsional modes, determination of intermolecular interaction contributions to vibrational spectra)

Step 3: Optimisation

- Introduce Urey-Bradley terms for in-plane deformations and separating symmetric and asymmetric bond stretching modes
- Introduce improper dihedral terms to reproduce out-of-plane modes
- optimised at MP2/6-31G(d) level (frequencies and PED of vibrational spectrum, potential energy surface)

Step 4: Potential energy scans

- Important for backbone and side chain conformers to describe energy barriers and minimum-energy structures
- Use experimental gas-phase data and ab initio calculations to obtain energy surface
- Test the accuracy of potential function to reproduce structural distortions

[1],[2]

4. Non-bonded parameters (⑥ ~ ⑦)

- Calculate minimum interaction energies and solvation structure for experimental thermodynamic parameters and molecular volumes with TIP3P water model

- Optimise partial atomic charges and interaction distance or angle at HF/6-31G(d) level (compound-water interactions and dipole moment)   and MP2[1]

- Perform condensed-phase simulations to compare heats of vaporization and molecular volumes with experimental data

- Perform crystal simulations to compare heats of sublimation and unit cell parameters
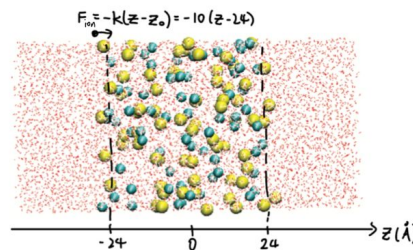
[1],[2]

5. Optimisation of non-bonded parameters $(\textcircled{R}, \textcircled{E})$ using osmotic pressure (·NBFIX Parameters)

R_{min}^{ii} E_{min}^{ii} → (Default) Lorentz-Berthelot combination rule

→ NBFIX

			σ_{ij}	ε_{ij}
CLA	SOD	1	3.32394311738e-01	3.51037600000e-01

$R_{ij} = \sigma_{ij} * 2^{1/6} = 0.3726574\ \text{Å}$

Step 1 : System setup

· Introduce flat-bottom half-harmonic planar restraint on ions

$F_{ion} = -k(z-z_0) = -10(z-24)$

Step 2 : Measurement

· Measure mean force on ions by 'membrane'

$$\langle F_{wall} \rangle = k \frac{1}{N} \sum_{iN} \sum_i (|z_i - z_{wall}|)$$

k = force constant ($10\ \text{kcal/mol/Å}^2$)
N = number of steps
i = index of ion
z = z-coordinate of ion

A = cross-sectional area ($48 \times 48\ \text{Å}^2$)

· Calculate osmotic pressure Π

$$\Pi = \frac{\langle F_{wall} \rangle}{A}$$

Step 3 : Calibration of R_{min}

· Sample Π at different R_{min} and obtain best-fit line by linear regression

Experimental Π
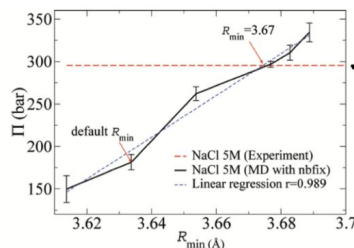
Table 2. Modified Ion−Ion LJ Parameters

ion pair	R_{min}^{ij} Å	
	combination rule	NBFIX
Na^{+a} − Cl$^-$	3.633	3.676
Na^{+b} − Cl$^-$	3.680	3.731
K$^+$−Cl$^-$	4.033	4.081

[a] Parameterization of Na$^+$ in 1994 from ref 2. [b] Reparameterization of Na$^+$ in 2008 from ref 39.

[3]

6. Optimisation using hydration free energy

A. Ion hydration free energies

- Real hydration free energy ΔG_{hyd}^{real} : reversible work to move an ion from vacuum to interior of pure water phase at 298.15 K and 1 atm

$$\Delta G_{hyd} = \Delta G_{hyd}^{intr} + Z F \Phi + C$$

Intrinsic bulk-phase value = $\Delta G_{elec} + \Delta G_{disp} + \Delta G_{rep}$
(electrostatic) (attractive) (repulsive)

Two-stage
1. charge neutralisation
2. v.d.W removal / disappear

- ΔG_{hyd}^{intr} found by Free-Energy Perturbation

- Difference in hydration free energy relative to immediate neighbours in series $\Delta\Delta G_{hyd}$: based on Thermodynamic Integration

$$V(\lambda) = (1-\lambda)^k V_0 + [1-(1-\lambda)^k] V_1 \qquad V_0, V_1 = \text{unperturbed / perturbed Hamiltonians}$$

- Change in free energy for alchemical A→B mutation $\Delta G_{mut} = \Delta G_{hyd}(B) - \Delta G_{hyd}(A) = \Delta\Delta G_{hyd}(A \to B)$

ion	ΔG_{elec} (kcal/mol)	ΔG_{disp} (kcal/mol)	ΔG_{rep} (kcal/mol)	$\Delta G_{hyd}^{intr\,a}$ (kcal/mol)	$\Delta G_{hyd}^{real\,b}$ (kcal/mol)	$\Delta G_{hyd}^{expt\,c}$ (kcal/mol)	$\Delta\Delta G_{hyd}^{real\,d}$ (kcal/mol)	$\Delta\Delta G_{hyd}^{expt\,c}$ (kcal/mol)
F^-	−124.1	−1.5	5.0	−120.6	−107.2	−99.1 to −121.6	29.1	28.0 to 30.6
Cl^-	−95.8	−3.7	7.3	−92.2	−78.8	−70.7 to −91.0	6.3	3.3 to 6.5
Br^-	−89.1	−4.9	8.0	−86.0	−72.6	−64.9 to −84.6	8.7	7.7 to 11.1
I^-	−79.7	−7.2	9.7	−77.2	−63.8	−57.2 to −76.2		
Li^+	−114.6	−0.2	2.0	−112.8	−122.4	−113.8 to −128.4	23.3	23.9 to 27.5
Na^+	−91.6	−1.0	3.1	−89.5	−99.1	−88.7 to −103.2	18.4	17.0 to 17.6
K^+	−73.7	−1.9	4.5	−71.1	−80.7	−71.2 to −86.0	6.6	5.1 to 5.6
Rb^+	−67.2	−2.7	5.4	−64.5	−74.1	−66.0 to −80.6	6.5	5.5 to 7.7
Cs^+	−60.8	−3.6	6.5	−58.0	−67.6	−60.5 to −75.1		

experiment

B. Hydration Free energy of alkali halides

- Total hydration free energy of neutral alkali halides, $\Delta G_{hyd}(MX) = \Delta G_{hyd}(M^+) + \Delta G_{hyd}(X^-)$

Table 4. Calculated (and Experimental) Hydration Free Energy of the Alkali Halides[a]

	Hydration Free Energy (kcal/mol)				
	Li^+	Na^+	K^+	Rb^+	Cs^+
F^-	−229.6 (−229.0)	−206.3 (−203.8)	−187.9 (−186.6)	−181.3 (−181.2)	−174.8 (−173.8)
Cl^-	−201.2 (−199.3)	−177.9 (−174.0)	−159.5 (−156.8)	−152.9 (−151.4)	−146.4 (−144.0)
Br^-	−195.0 (−192.9)	−171.7 (−167.6)	−153.3 (−150.4)	−146.7 (−145.0)	−140.2 (−137.6)
I^-	−186.2 (−183.9)	−162.9 (−158.7)	−144.5 (−141.5)	−137.9 (−136.1)	−131.4 (−128.7)

[a]Experimental hydration free energies (in kcal/mol) for LiX, NaX, KX, and RbX are from ref 65 and for CsX are from ref 63.

[5] [4]

→ $\Delta G_{hyd} = f(R_{min}, \varepsilon)$ hypersurface can be mapped from TI calculations

ε is dependent on R_{min} for given hydration free energy
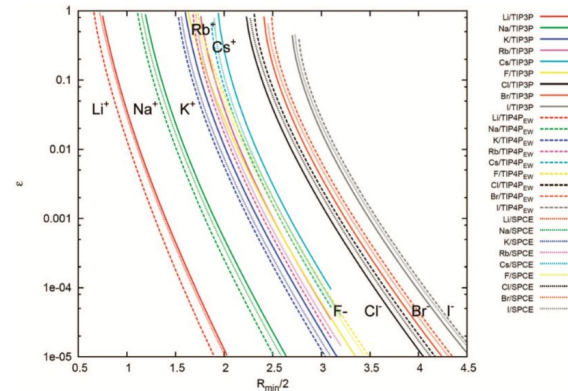

Figure 3. Correlations between R_{min} and ε for a given free energy of hydration by using the Schmid values. Shown are the correlations in R_{min} and ε from the $\Delta G_{hydration} = f(R_{min}, \varepsilon)$ hypersurface at a given value of the hydration free energies. The chosen values are those from Schmid and co-workers (see Table 10).[117] Points on the same line have equivalent hydration free energies. The solid lines are for TIP3P water, the dashed lines are for TIP4P$_{EW}$ water, and the dotted lines are for SPC/E water; each ion is represented by a different color. The units for the x and y axes are Angstroms and kcal/mol, respectively.

7. Optimisation using RDF

- Radial distribution function $g(r) = \dfrac{\rho(r)}{\rho}$ $\rho = $ density until r_{max}

- Integration up to first minimum = coordination numbers (CNs)

$$CNs = \int_0^{r\text{-}min} g(r)\, dr$$
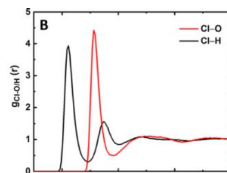
	Hydration Number			
	F$^-$	Cl$^-$	Br$^-$	I$^-$
this work	6.7	7.7	8.0	8.7
experiment	6.9[a]	5.3–7.3[b]	6.3–8.9[c]	6.7–9.1[d]
polarizable MM	5.1–6.7[e]	6.0–8.4[f]	6.6–9.0[g]	6.7–9.2[h]
QM	4.9–5.0[i]	5.5–6.5[j]	5.6–6.5[k]	6.6–8.5[l]
QM/MM	5.7[m]	5.9–6.6[n]	–	–
nonpolarizable MM	6.0–6.9[o]	7.0–7.6[p]	7.2–7.7[q]	7.3–9.7[r]

ion	atom-type pair (MX)[a]	NBFIX[b]	
		ϵ_{MX} (kcal/mol)	$R_{min,MX}$ (Å)
F$^-$	FLA-LIT	−0.032	3.2125
	FLA-SOD	−0.069	3.32575
	FLA-POT	−0.090	3.67875
	FLA-RUB	−0.100	3.8150
	FLA-CES	−0.120	4.015
Cl$^-$	CLA-LIT	−0.046	3.5675
	CLA-SOD	−0.083875	3.7310
	CLA-POT	−0.114236	4.0810
	CLA-RUB	–	–
	CLA-CES	−0.140	4.370

- Potential of mean Force $W(r) = -k_B T \ln(g(r))$

- Radius of first hydration shell = First minimum

TABLE 13: Radii of the First Hydration Shell[a]

	this research	Jensen and Jorgensen	Smith−Dang− Garrett	Beglov and Roux	Åqvist	Marcus[185]
			TIP3P			
Li$^+$	1.96	2.04	1.97		2.03	2.08
Na$^+$	2.38	2.49	2.37	2.31	2.41	2.356
K$^+$	2.75	2.86	2.83	2.71	2.72	2.798
Rb$^+$	2.92	3.00	2.93		2.85	2.89
Cs$^+$	3.11	3.19	3.11		3.05	3.139
F$^-$	2.63	2.80	2.70			2.63
Cl$^-$	3.13	3.29	3.24	3.12		3.187
Br$^-$	3.29	3.41				3.373
I$^-$	3.51	3.65	3.64			3.647
rms	0.07	0.09	0.05	0.07	0.06	

[4]

8. Optimisation using crystal properties (LE, LC)

- **LE:** loss in the total lattice potential energy when crystal structure transforms into gas phase, listed in CRC handbook

- **LC:** length of the edge of the unit crystals / cation-anion distances

- Rmin is chosen to minimise the overall deviation with literature cation-anion distances and LE at given ΔG_{hyd}

$$\sqrt{\sum_{\substack{ion \\ pair}} \left((\delta_{dis} W_{dis})^2 + (\delta_{LE} W_{LE})^2 \right)}$$

deviation — weight

- Choose solutions that lead to stable crystals

TABLE 2: LE (kcal/mol) of Crystals of Alkaline Halide Salts as Obtained from the CRC Handbook,[163] Including both the Theoretical LEs Estimated from the Kapustinskii Equation (Top Half) and the Empirical/Experimental LEs Calculated from a Born–Fajans–Haber Cycle (Bottom Half)

	Li	Na	K	Rb	Cs
			Theory		
F	246.2	217.5	193.1	185.0	177.8
Cl	199.3	183.8	167.5	162.5	157.0
Br	188.3	175.0	160.4	155.6	151.1
I	174.5	163.0	151.1	147.5	143.4
			Experiment		
F	250.7	222.3	198.1	190.0	181.4
Cl	206.5	188.8	172.1	166.1	160.1
Br	196.0	180.2	165.2	159.7	154.6
I	182.6	168.5	155.4	151.1	146.5

TABLE 3: LC (Angstroms) of Crystals of Alkaline Halide Salts (Top Half) and Interionic Distance (Angstroms) Calculated from the LC at Room Temperature (Bottom Half)[a]

	Li	Na	K	Rb	Cs
			LC		
F	4.027	4.634	5.347	5.652	6.014
Cl	5.140	5.640	6.293	6.581	4.123
Br	5.501	5.977	6.600	6.889	4.295
I	6.023	6.473	7.066	7.342	4.568
			Distance		
F	2.014	2.317	2.674	2.826	3.007
Cl	2.570	2.820	3.147	3.291	3.571
Br	2.751	2.989	3.300	3.445	3.720
I	3.011	3.236	3.533	3.671	3.956

[a] The data were obtained from the first column of Table 1.2 from Sirdeshmukh et al.[164]

TABLE 4: Range of Acceptable Solutions at Different Ratios of Weights on Interionic Distance and LE on the Ion Radii Optimization ($W_{LE} = 1$)[a]

	$W_{dis} = 107$	$W_{dis} = 150$	$W_{dis} = 200$	$W_{dis} = 250$	$W_{dis} = 300$
			$R_{min}/2$		
Li$^+$	0.886	0.986	1.079	1.078	1.078
Na$^+$	1.325	1.361	1.379	1.384	1.387
K$^+$	1.687	1.702	1.709	1.712	1.713
Rb$^+$	1.803	1.811	1.815	1.817	1.818
Cs$^+$	1.968	1.974	1.978	1.979	1.980
F$^-$	2.377	2.346	2.259	2.180	2.144
Cl$^-$	2.614	2.526	2.500	2.498	2.497
Br$^-$	2.657	2.616	2.602	2.602	2.601
I$^-$	2.876	2.862	2.856	2.855	2.855
			rms (Distance)		
	0.028	0.022	0.018	0.018	0.017
			rms (LE)		
	3.28	3.97	4.49	4.62	4.68

[a] By using eq 3, the radii of the ions (R_{min}) were optimized at various ratios of the respective weights on the inter-ionic distance (W_{dis}) and LE (W_{LE}). Displayed are the different $R_{min}/2$ values optimized for the Schmid hydration free energy target values with TIP3P water. Acceptable solutions were those that led to stable crystals (as per Figure 5), maintained size consistency across the monovalent ion series, and had Cs$^+$ < 2.5 Å and I$^-$ < 3.5 Å. The units of the weights are kcal^{-1}mol (W_{dis}) and Å^{-1} (W_{LE}). The same data for the TIP4P$_{EW}$ and SPC/E models are shown in the Supporting Information, Tables S4 and S5.
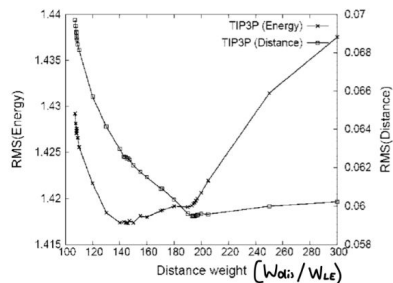
Figure 7. rms deviations of single water–ion binding energies and distances. The rms deviations are plotted as a function of the weight on interionic distance (Å^{-1}) with a fixed weight on the LE (1 kcal^{-1}mol) over the range of acceptable weight ratios (as per Table 4). The units are kcal/mol for the energy and Angstrom for the distance. TIP3P ions have the minimal rms in energy at a weight ratio of 146:1, whereas the minimal rms in distance occurs at 195:1. TIP4P$_{EW}$ ions have the minimal rms deviation for both the energy and the distance at a weight ratio of 50.36:1. SPC/E is somewhat anomalous because the rms of the energy keeps increasing as the rms of the distance decreases. With the SPC/E model, because the minima are not colocalized, the weight ratio was taken at the middle point of both curves or at 27:1. Plots of the rms deviations for TIP4P$_{EW}$ and SPC/E are shown in the Supporting Information.

[5]

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