

Perform pure salt simulation (NH₄Cl)

1. Parameterisation methods
2. Measurements

Testing parameters

System settings: 0.15M 4-4-4 nm boxes (6 NH₄, 6 Cl, 2022 H₂O)

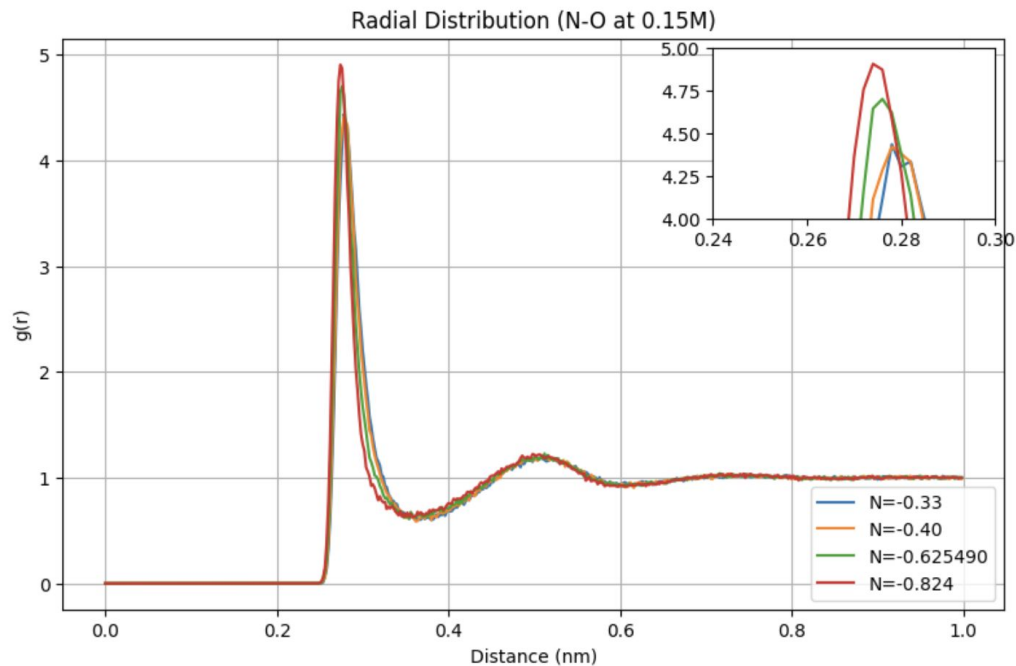
		Source
charge0	N: -0.33 H: +0.33	Original CHARMM parameters
charge1	N: -0.40 H: +0.35	NH ₄ ⁺ partial charges using OPLS charges, as OPLS and CHARMM partial charges of NH ₃ ⁺ in Lysine are nearly identical [b]
charge2	N: -0.625490 H: +0.406372	Partial charges were derived using electrostatic potential fitting. Energy constants were taken from the CHARMM, version 22, forcefield for primary amines.[h]
charge3	N: -0.824 H: +0.456	NH ₄ charges by restrained ESP-fit method using ChelpG approach [a]

RDF results (N-O)

200ns	r_max	CN	500ns	r_max	CN
0.15M, q=-0.33	0.282	6.98	0.15M, q=-0.33	0.28	7.0
0.15M, q=-0.40	0.28	7.353	0.15M, q=-0.40	0.28	6.759
0.15M, q=-0.62	0.278	6.599	0.15M, q=-0.62	0.276	6.19
0.15M, q=-0.824	0.276	6.25	0.15M, q=-0.824	0.276	6.163
1M, q=-0.33	0.282	6.377			

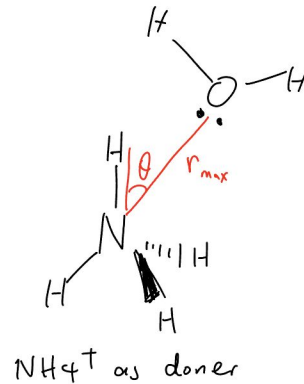
RDF results (N-O)

500ns	r_max	CN
0.15M, q=-0.33	0.282	7.0
0.15M, q=-0.40	0.28	6.759
0.15M, q=-0.62	0.278	6.19
0.15M, q=-0.824	0.276	6.163



Number of hydrogen bond

500ns	r_min	CN	Avg. no. of H-bond
0.15M, q=-0.33	0.368	7.0	12.9
0.15M, q=-0.40	0.364	6.759	13.5
0.15M, q=-0.62	0.354	6.19	15.1
0.15M, q=-0.824	0.36	6.163	12.8



Hydrogen Bonds

Help

Input options

Molecule: 0: charge3.gro

Selection 1 (Required): name NZ

Selection 2 (Optional): name CH2

NOTE: if sel1 and sel2 overlap, hbonds output is unreliable!

Frames: all (now, all, b:e, or b:s:e)

☒ Update selections every frame? ☒ Only polar atoms (N, O, S, F)?

Selection 1 is the: ☒ Donor ☐ Acceptor ☐ Both

Donor-Acceptor distance (Å): 3.6

Angle cutoff (degrees): 30

Calculate detailed info for: ☒ None ☐ All hbonds ☐ Residue pairs ☐ Unique hbond

Output options

☒ Plot the data with MultiPlot?

Output directory: /Users/shelley Choose

Log file?

☐ Write output to files?

Frame/bond data? hbonds.dat

Detailed hbond data? hbonds-details.dat

Status

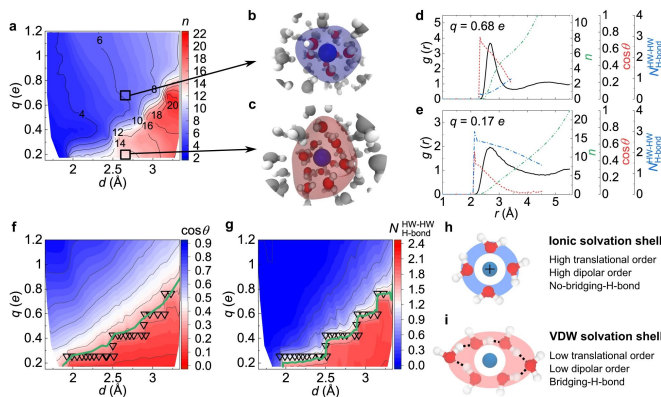
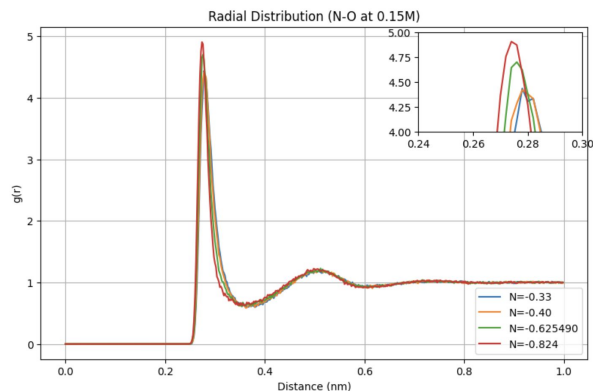
Done.

Find hydrogen bonds!

Explanation of lower CN as $|q_N|$ increases

500ns	r_max	CN
0.15M, $q=-0.33$	0.282	7.0
0.15M, $q=-0.40$	0.28	6.828
0.15M, $q=-0.62$	0.278	6.609
0.15M, $q=-0.824$	0.276	6.163

- The coordination number n drops sharply from $n \geq 12$ to $n = 4 - 8$ at $qc(d)$ as q increases (Fig. [1a](#)). This result indicates that an ion with low charge density, behaving like an electrically neutral particle, forms a thick solvation shell, whereas an ion with high charge density develops a thin, well-developed solvation shell (Fig. [1a-c](#)). We call the former the “VDW solvation shell” and the latter the “ionic solvation shell” according to their dominant interactions to form the shell.
- In the VDW solvation shell, a water molecule in the original second shell location penetrates the open space between the first and the second shell while stabilised through its H-bonding with two molecules in the first shell (Fig. [1d, e](#)).
- As q increases, the ion-induced water dipole reorientation destroys these bridging H-bonds, kicking the penetrating water out from the first shell. We have confirmed this mechanism in Supplementary Fig. [3](#) by directly monitoring the water dipole ordering and H-bonding in a non-equilibrium simulation.



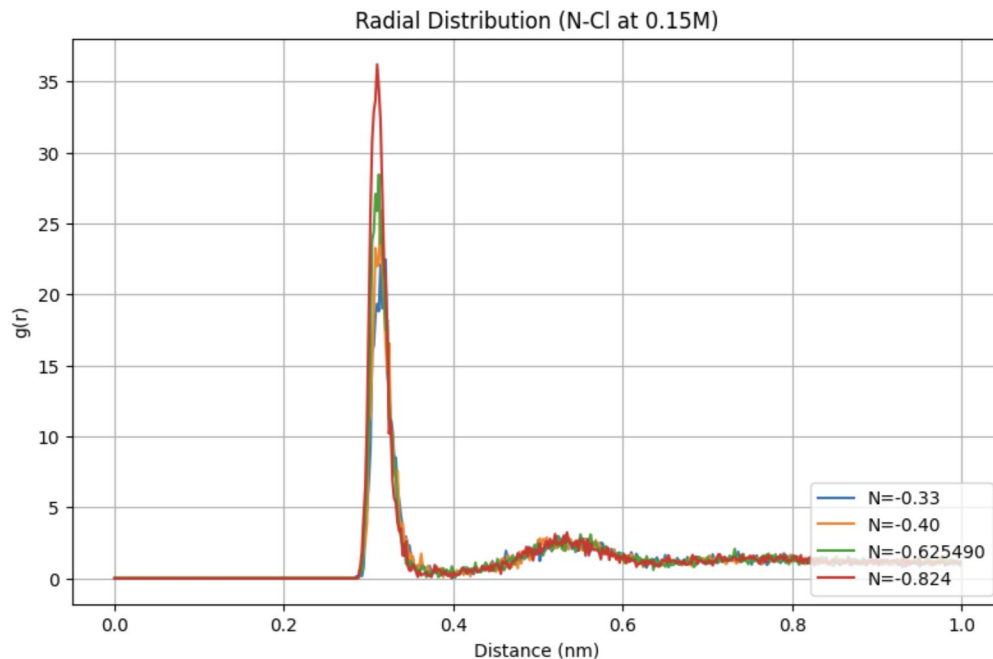
Shi, R., Cooper, A.J. & Tanaka, H. Impact of hierarchical water dipole orderings on the dynamics of aqueous salt solutions. *Nat Commun* 14, 4616 (2023). <https://doi.org/10.1038/s41467-023-40278-x>

RDF results (N-CI)

200ns	r_max	CN	500ns	r_max	CN
0.15M, q=-0.33	0.314	0.078	0.15M, q=-0.33	0.316	0.078
0.15M, q=-0.40	0.314	0.08	0.15M, q=-0.40	0.314	0.083
0.15M, q=-0.62	0.312	0.091	0.15M, q=-0.62	0.312	0.087
0.15M, q=-0.824	0.31	0.102	0.15M, q=-0.824	0.31	0.102
1M, q=-0.33	0.314	0.429			

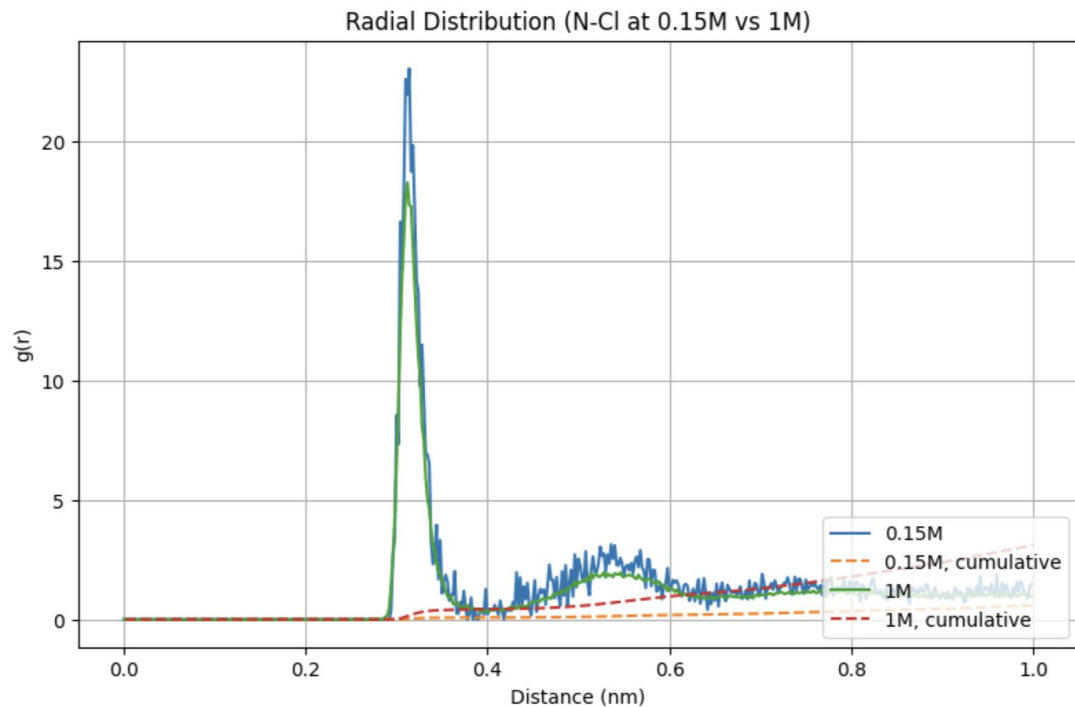
RDF results (N-Cl)

500ns	r_max	CN
0.15M, q=-0.33	0.316	0.078
0.15M, q=-0.40	0.314	0.083
0.15M, q=-0.62	0.312	0.087
0.15M, q=-0.824	0.31	0.102



RDF results (N-Cl)

200ns	r_max	CN
0.15M, q=-0.33	0.314	0.078
1M, q=-0.33	0.314	0.429



Research on NH₄ conduction in ion channel

[a] Detailed Mechanism for AmtB Conducting NH₄ /NH₃: Molecular Dynamics Simulations

- Optimised charges by restrained ESP-fit method using ChelpG approach
 - N: -0.824; H: +0.456

[b] Ammonium Recruitment and Ammonia Transport by E. coli Ammonia Channel AmtB

- NH₄⁺ partial charges using OPLS charges
- NH₄⁺ bond and bond angle using CHARMM27 parameters, same as NH₃ moiety of Lysine

[c] Molecular Dynamics Simulations on the Escherichia coli Ammonia Channel Protein AmtB: Mechanism of Ammonia/ Ammonium Transport

- Apply Mulliken charges at the HF/6-31G(d)
- LJ parameters same as amide groups

[d] Ammonium Transporters Achieve Charge Transfer by Fragmenting Their Substrate

- NH₄⁺ and surrounding water molecules and protein side chains are described by a polarizable force field based on the classical Drude oscillator, (62-65) and parametrized to reproduce both the free energy of hydration and the ion–protein interactions
- Pair-specific LJ parameters between the ions and atoms of the ligands are adjusted to reproduce the ab initio interaction energies
- Full geometry optimizations of the complexes between these ligands and the three cations Na⁺, K⁺, and NH₄⁺ are performed at the MP2(FC)/6-311++G(d,p) level using Gaussian 09 program

[g] Ammonium Transport Proteins with Changes in One of the Conserved Pore Histidines Have Different Performance in Ammonia and Methylamine Conduction

- The force field parameters of ammonia and methylamine were obtained from server SwissParam. [52]
- In order to validate the force field parameters, the salvation free energy of ammonia and methylamine in water was calculated using free energy perturbation (detailed protocol shown in Text S1).
- The calculated solvation free energies for ammonia and methylamine are -5.00 ± 0.24 and -4.49 ± 0.18 kcal/mol (Figure S1) respectively, very similar to the experiment values (-4.31 kcal/mol for ammonia and -4.57 kcal/mol for methylamine [53]).
- Therefore the parameters used here should be suitable for simulations.

Research on NH₄ conduction in ion channel

	Method	Force field, water	Charges
Default	Parameters same as methylammonium MAMM N from primary NH ₃ ⁺ , phosphatidylethanolamine	CHARMM36, TIP3P	N: -0.33 H: +0.33
[a]	NH ₄ charges by restrained ESP-fit method using ChelpG approach	GROMOS87, SPC	N: -0.824 H: +0.456
[b]	NH ₄ ⁺ partial charges using OPLS charges, as OPLS and CHARMM partial charges of NH ₃ ⁺ in Lysine are nearly identical	CHARMM27, H atoms were added to crystal waters using PSFGEN in NAMD	N: -0.40 H: +0.35
[c]	N, H charges using Mulliken charges at the HF/6-31G(d)	CHARMM, TIP3P	Not specified
[d]	<ul style="list-style-type: none"> - NH₄⁺ and surrounding water molecules and protein side chains are described by a polarizable force field based on the classical Drude oscillator, and parametrised to reproduce both the free energy of hydration and the ion–protein interactions. - Pair-specific LJ parameters between the ions and atoms of the ligands are adjusted to reproduce the ab initio interaction energies. - Full geometry optimizations of the complexes between these ligands and the three cations Na⁺, K⁺, and NH₄⁺ are performed at the MP2(FC)/6-311++G(d,p) level using Gaussian 09 program. 	CHARMM27, TIP3P	/
[e]		CHARMM36, TIP3P	Adapted from [a]

Research on NH4 conduction in ion channel (2)

	Method	Force field, water	Charges
Default	Parameters same as methylammonium MAMM N from primary NH3+, phosphatidylethanolamine	CHARMM36, TIP3P	N: -0.33 H: +0.33
[g]	<ul style="list-style-type: none">- Parameters of ammonia from server SwissParam- Validated with salvation free energy of ammonia in water using free energy perturbation	CHARMM27, TIP3P	
[h]	<ul style="list-style-type: none">- Parameters were obtained using the Extensible Computational Chemistry Environment (ECCE)49 after performing quantum mechanics calculations using NWChem- Geometrically optimised at RHF level with 6-31111G(3df,3pd)basis set with Pople(3df,3pd) as a polarization function,and with Pople-style as a diffusion function- Partial charges were derived using electrostatic potential fitting. Energy constants were taken from the CHARMM, version 22, forcefield for primary amines.	CHARMM, TIP3P	N: -0.625490 H: +0.406372

	Elements	Energy constant (K _p) ^a [kcal/(mol Å ²)]	Bond length (Å)
Stretching	N—H	403.0	1.003
		Energy constant (K _θ) ^a [kcal/(mol rad ²)]	Bond angle (°)
Bending	H—N—H	44.0	109.471
Electrostatic	N H	Partial charge −0.625490 +0.406372	

Other NH₄ parameterisations

	Method	Force field, water	Charges
Default	N from primary NH ₃ ⁺ , phosphatidylethanolamine H from polar H ⁺	CHARMM36, TIP3P	N: -0.33 H: +0.33
Madrid [5]	N, H charges using OPLS-based model, scaled by 0.85	Madrid-2019, TIP4P/2005	N: -0.3400 H: +0.2975

RDF data (Na-O)

	No. of OH ₂ in first hydration shell	First peak	First minimum
Simulation [1]	5.702	2.36	3.18
Literature [2]	4.0-8.0	2.36	
MC in TIP4P [3]	6.2	2.50	
Madrid [6]	5.4	2.33	

RDF data (N-O)

	No. of OH ₂ in first hydration shell	First peak	First minimum
Simulation [1]	6.581	2.82	3.66
Literature [2]	8.1-10.0	2.6-3.05	
MC in TIP4P [3]	7.3	2.90	
MC in TIP3P [4]	7.0-7.1	2.63-2.70	
Madrid [5]	5.5	2.66	
NH ₃ MD [16]		3.25	
NH ₃ Ab Initio [16]		2.75	

RDF plots of $\text{N}_{\text{NH}_4}-\text{O}$

[4]

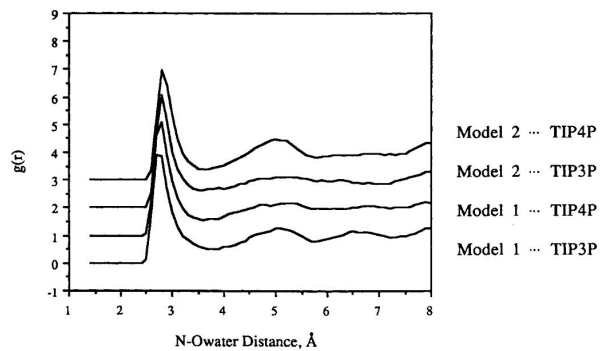
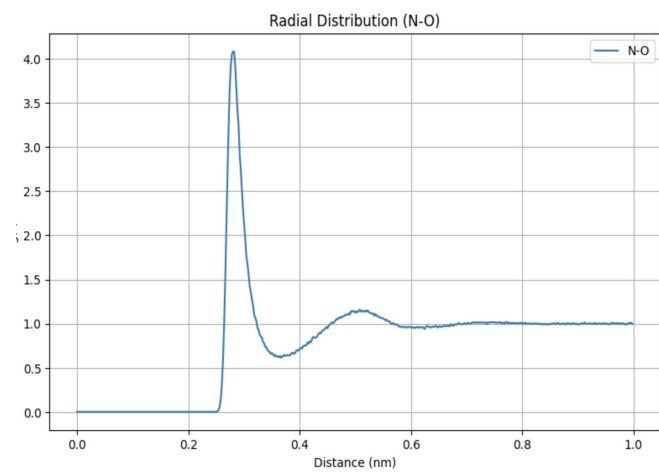
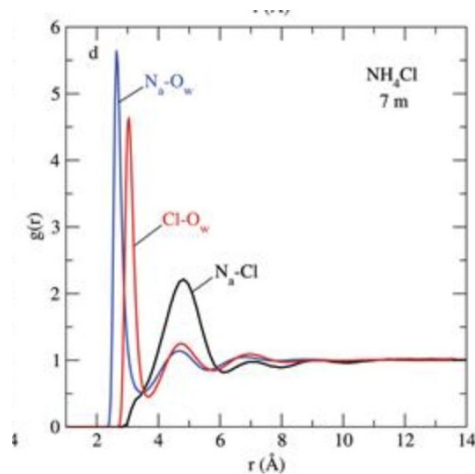


Figure 2. $\text{N}-\text{O}_{\text{water}}$ radial distribution functions for model 1 and 2 in TIP3P and TIP4P.

[5]



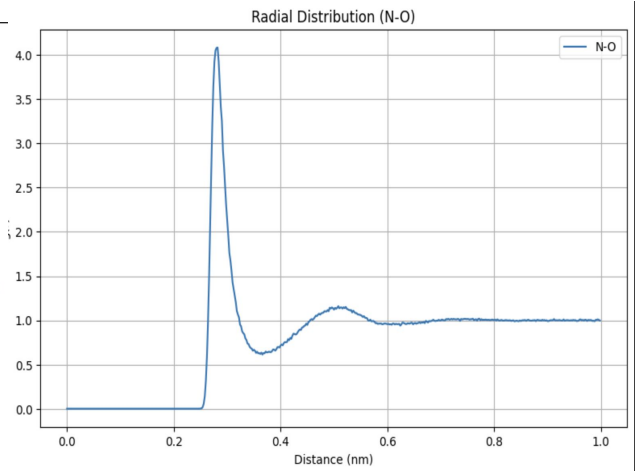
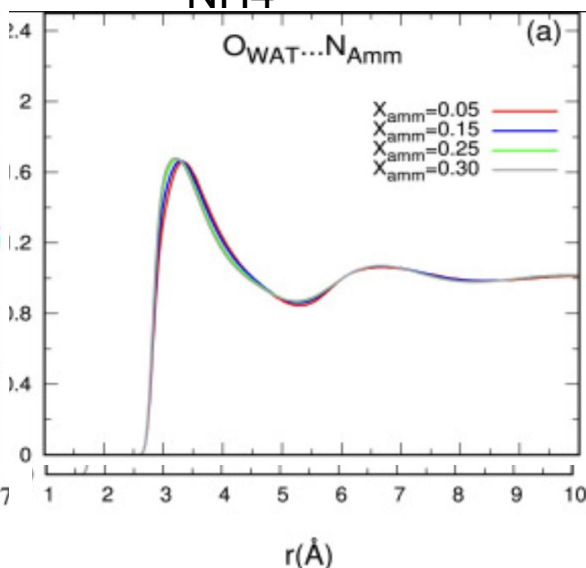
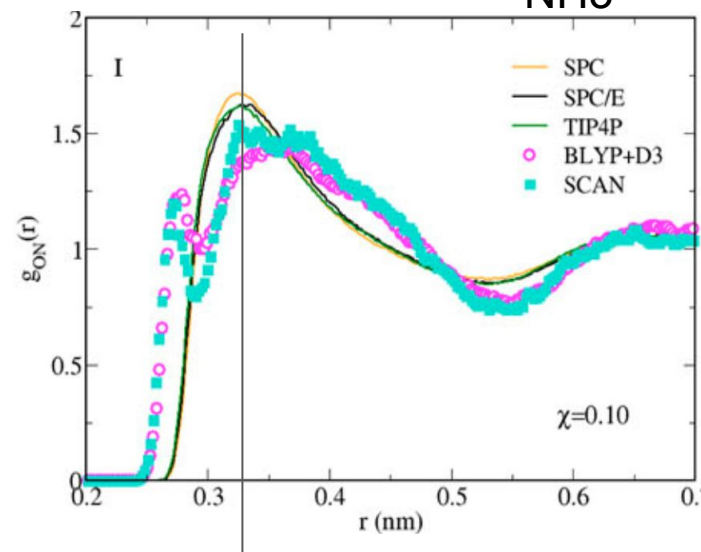
NH_4 :

First maximum found at $r = 0.282\text{nm}$

Coordination number = 6.581

$\chi = 0.02$

RDF plots of N_{NH3}-O and N_{NH4}-O

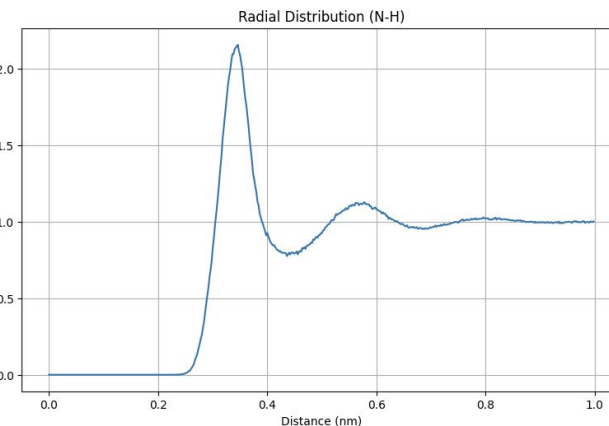
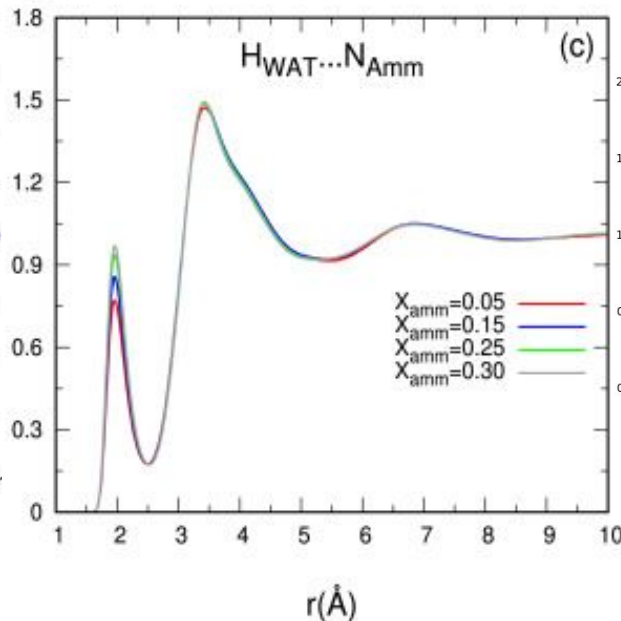
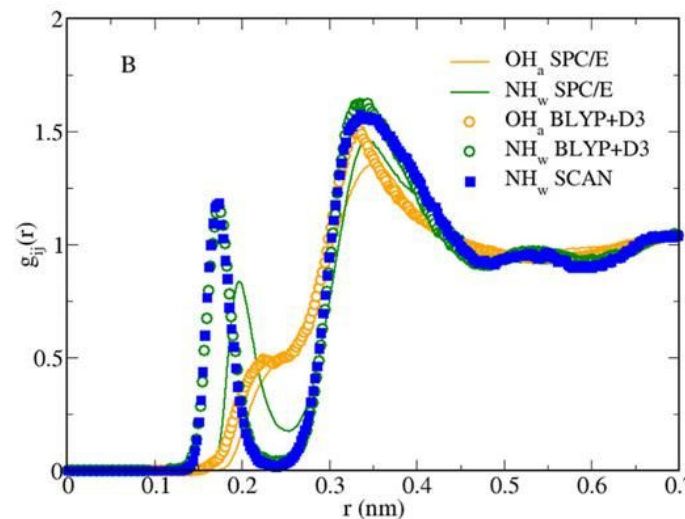


NH₃:
MD (lines) and AIMD (symbols) at $\chi = 0.1$ (NH₃:H₂O). The three different force fields used for water are represented by orange (SPC), black (SPC/E), and green (TIP4P) lines, while ab initio BLYP+D3 and SCAN correlations are indicated as magenta circles and cyan squares, respectively. [16]

NH₃:
MD simulation at $\chi = 0.05-0.30$ [17]

NH₄:
First maximum found at $r = 0.282$ nm
Coordination number = 6.581
 $\chi = 0.02$

RDF plots of $N_{\text{NH}_3}\text{-H}$ and $N_{\text{NH}_4}\text{-H}$



NH3:

Comparison between SPC/E (lines), BLYP+D3 (circles), and SCAN (squares) radial distributions functions involving hydrogen atoms for $T = 295$ K and $\chi = 0.10$. Correlations between atoms of the same molecule type are reported in (a), whereas cross-correlations are shown in (b). [16]

NH3:

MD simulation at $\chi = 0.05\text{-}0.30$ [17]

NH4 from original simulation:

First maximum found at $r = 0.344\text{nm}$

Coordination number = 20.891

$\chi = 0.02$

RDF data (Cl-O)

	No. of OH ₂ in first hydration shell	First peak	First minimum
Simulation, NaCl [1]	7.911	3.16	3.84
Simulation, NH ₄ Cl [1]	7.227	3.16	3.80
Literature [2]	5.9-8.5	3.1-3.3	
MC in TIP4P [3]	7.6	3.25	
Madrid [6]	5.9	3.05	

Free energy calculations

	Absolute hydration energy of NH ₄	Absolute hydration energy of Na	Relative hydration energies between NH ₄ ⁺ and Na ⁺
Experiment [7]	-78.6		-21.7 kcal/mol
Free energy perturbation [4]	-79.55 (+ Born) -98.85		-28.87 kcal/mol
Empirical model [8]	-68.1	-87.2	-19.1 kcal/mol
MC simulation [3]	-73.1	-92.3	-19 kcal/mol

Osmotic coefficient at 1M/1m

	NH ₄ Cl	NaCl
Isopiestic vapour pressure method [9]	0.897	
MC simulations [10]		0.91-0.92
Experiment [11]		0.94
MD simulations [12]		0.93
Experiment [13]	0.927	
Hückel equation calculation [14]	0.902	
Experiment [15]	0.9671	

References

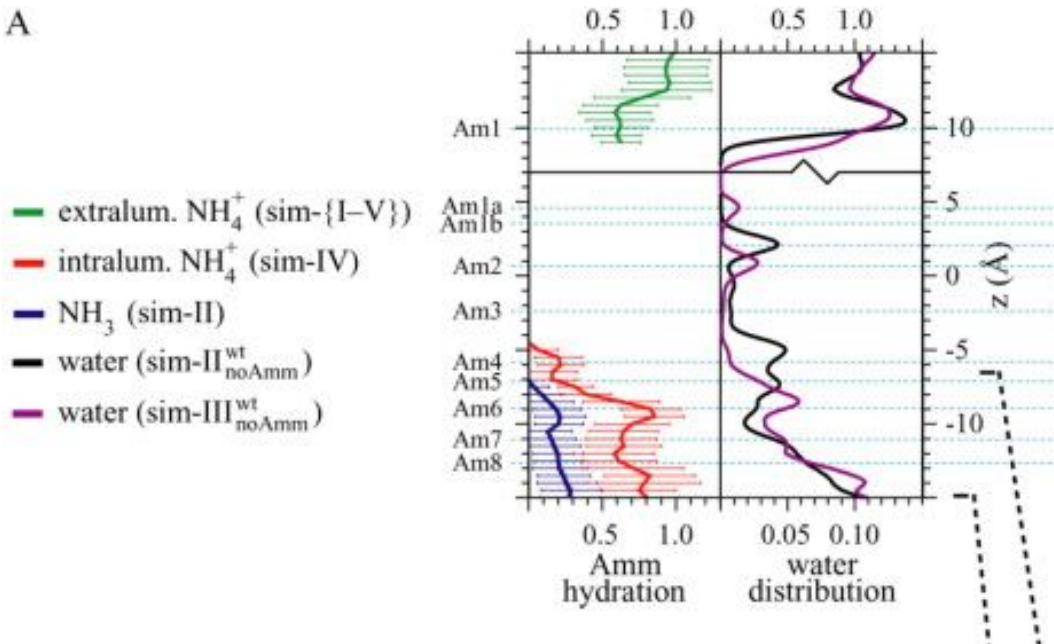
- [1] <https://github.com/Heiley-W/project/blob/main/RDF-analysis.ipynb>
- [2] Ionic radii in aqueous solutions <https://doi.org/10.1021/cr00090a003>
- [3] Halide, Ammonium, and Alkali Metal Ion Parameters for Modeling Aqueous Solutions <https://doi.org/10.1021/ct600252r>
- [4] Free Energy Calculations Involving NH_4^+ in Water <https://doi.org/10.1002/jcc.540120106>
- [5] Further extension of the Madrid-2019 force field: Parametrization of nitrate and ammonium ion <https://doi.org/10.1063/5.0177363>
- [6] A force field of Li^+ , Na^+ , K^+ , Mg^{2+} , Ca^{2+} , Cl^- , and in aqueous solution based on the TIP4P/2005 water model and scaled charges for the ions <https://doi.org/10.1063/1.5121392>
- [7] Ref 33 and 22 of [4] respectively
- [8] A simple empirical model describing the thermodynamics of hydration of ions of widely varying charges, sizes, and shapes [https://doi.org/10.1016/0301-4622\(94\)00051-4](https://doi.org/10.1016/0301-4622(94)00051-4)
- [9] The osmotic and activity coefficients of aqueous solutions of ammonium chloride and ammonium nitrate at 25° <https://doi.org/10.1039/TF9534900027>
- [10] Osmotic and activity coefficients from effective potentials for hydrated ions <https://doi.org/10.1103/PhysRevE.55.5689>
- [11] Ref 20 of [10]
- [12] Osmotic coefficients of atomistic NaCl (aq) force fields <https://doi.org/10.1063/1.2185105>
- [13] The Osmotic and Activity Coefficients of Some Salts Having Relatively Large Molar Volumes <https://doi.org/10.1021/je60071a020>
- [14] Mean Activity Coefficients and Osmotic Coefficients in Aqueous Solutions of Salts of Ammonium Ions with Univalent Anions at 25 °C <https://doi.org/10.1021/je300474k>
- [15] The Vapor Pressures and Activity Coefficients of Aqueous Solutions of Ammonium Chloride at 25° <https://doi.org/10.1021/ja01286a019>
- [16] The structure of water-ammonia mixtures from classical and ab initio molecular dynamics <https://doi.org/10.1063/5.0220328>
- [17] Effects of concentration and pressure on the aqueous solvation structure of ammonia and composition dependent ion solvation scenario in water-ammonia mixtures <https://doi.org/10.1016/j.fluid.2020.112507>

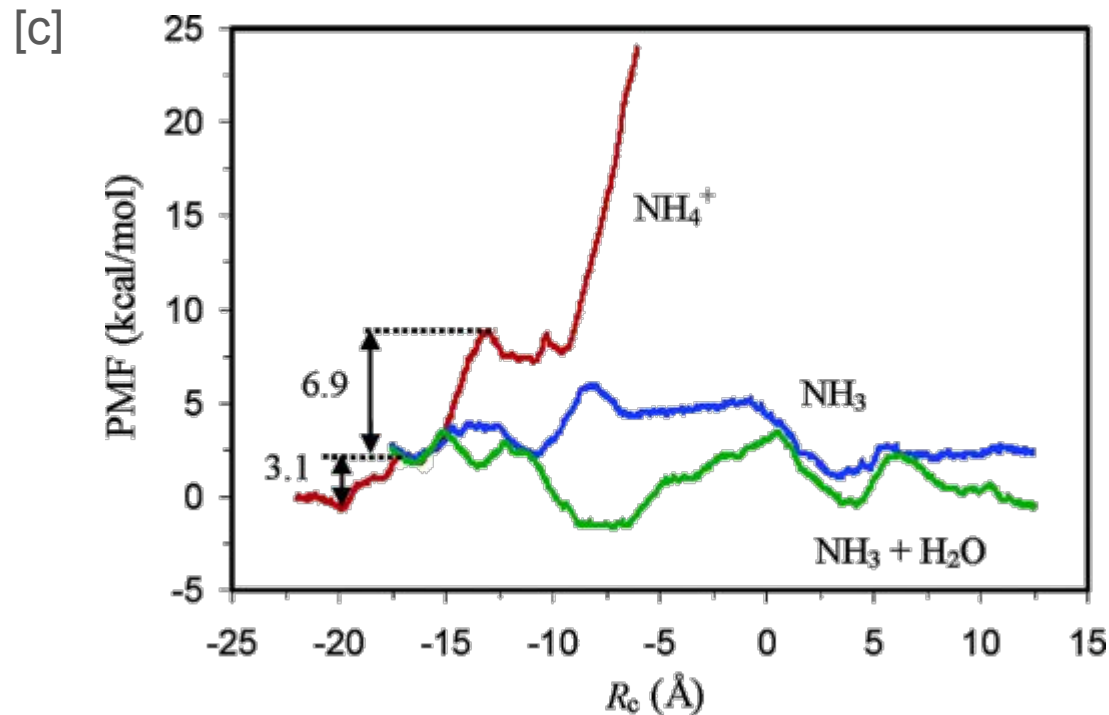
References

- [a] Detailed Mechanism for AmtB Conducting $\text{NH}_4^+/\text{NH}_3$: Molecular Dynamics Simulations <https://doi.org/10.1529/biophysj.106.090191>
- [b] Ammonium Recruitment and Ammonia Transport by E. coli Ammonia Channel AmtB <https://doi.org/10.1529/biophysj.106.089714>
- [c] Molecular Dynamics Simulations on the Escherichiacoli Ammonia Channel Protein AmtB: Mechanism of Ammonia/Ammonium Transport <https://doi.org/10.1021/ja0631549>
- [d] Ammonium Transporters Achieve Charge Transfer by Fragmenting Their Substrate <https://doi.org/10.1021/ja300129x>
- [e] A two-lane mechanism for selective biological ammonium transport <https://doi.org/10.1101/849562>
- [f] The mechanism of ammonia transport based on the crystal structure of AmtB of Escherichia coli <https://doi.org/10.1073/pnas.0406475101>
- [g] Ammonium Transport Proteins with Changes in One of the Conserved Pore Histidines Have Different Performance in Ammonia and Methylamine Conduction <https://doi.org/10.1371/journal.pone.0062745>
- [h] Free-energy profiles for ions in the influenza M2-TMD channel <https://doi.org/10.1002/prot.22376>

Research on NH4 conduction in ion channel

[b]



Research on NH_4 conduction in ion channel

Research on NH_4 conduction in ion channel

[f] Experiment

