

Perform pure salt simulation (NH_4Cl)

1. Parameterisation methods
2. Measurements

Testing parameters

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

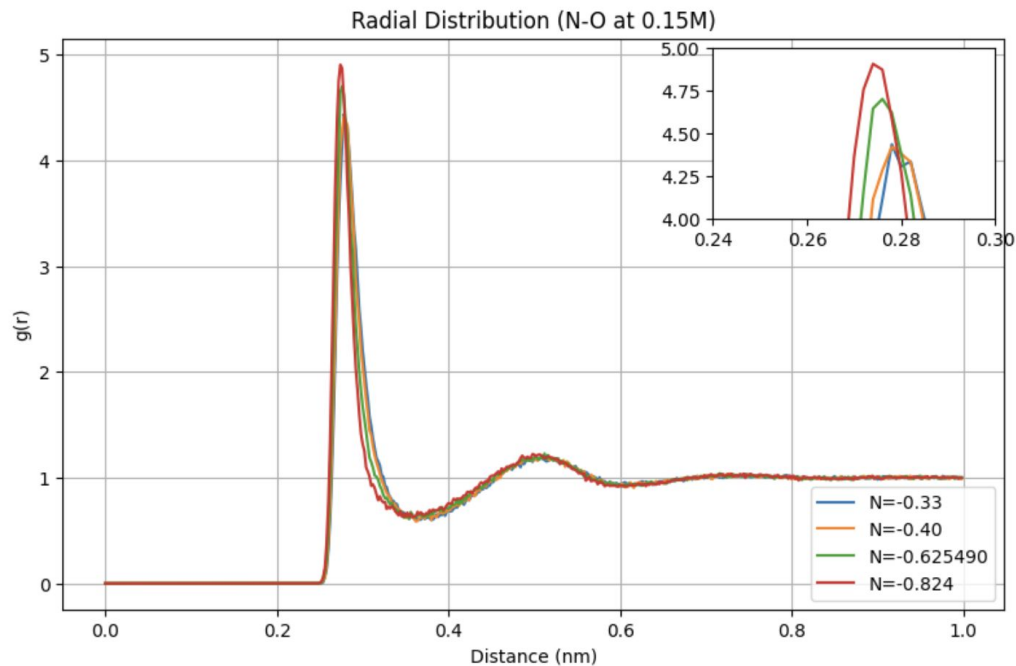
| | | Source |
|---------|------------------------------|--|
| charge0 | N: -0.33 H: +0.33 | Original CHARMM parameters |
| charge1 | N: -0.40 H: +0.35 | NH ₄ ⁺ partial charges using OPLS charges, as OPLS and CHARMM partial charges of NH ₃ ⁺ in Lysine are nearly identical [b] |
| charge2 | N: -0.625490 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)

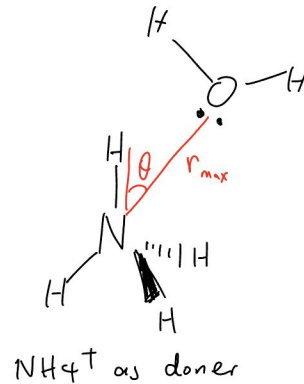
| 200ns | r_max | CN | 500ns | r_max | CN |
|-----------------|-------|-------|-----------------|-------|-------|
| 0.15M, q=-0.33 | 0.282 | 7.046 | 0.15M, q=-0.33 | 0.282 | 7.0 |
| 0.15M, q=-0.40 | 0.28 | 6.85 | 0.15M, q=-0.40 | 0.28 | 6.828 |
| 0.15M, q=-0.62 | 0.278 | 6.667 | 0.15M, q=-0.62 | 0.278 | 6.609 |
| 0.15M, q=-0.824 | 0.276 | 6.394 | 0.15M, q=-0.824 | 0.276 | 6.163 |
| 1M, q=-0.33 | 0.282 | 6.581 | | | |

RDF results (N-O)

| 500ns | r_max | CN |
|-----------------|-------|-------|
| 0.15M, q=-0.33 | 0.282 | 7.0 |
| 0.15M, q=-0.40 | 0.28 | 6.828 |
| 0.15M, q=-0.62 | 0.278 | 6.609 |
| 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 | 0.366 | 7.0 | 12.9 |
| 0.15M, q=-0.40 | 0.364 | 6.828 | 13.5 |
| 0.15M, q=-0.62 | 0.364 | 6.609 | 15.1 |
| 0.15M, q=-0.824 | 0.358 | 6.163 | 12.8 |

Hydrogen Bonds

Input options

Molecule: 0: charge3.gro

Selection 1 (Required): name NZ

Selection 2 (Optional): name OH2

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): 3.65

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/sheley/Desktop Choose

Log file:

☒ Write output to files?

Frame/bond data? /Users/sheley/Desktop/hbonds3.dat

Detailed hbond data? /Users/sheley/Desktop/hbonds3-details.dat

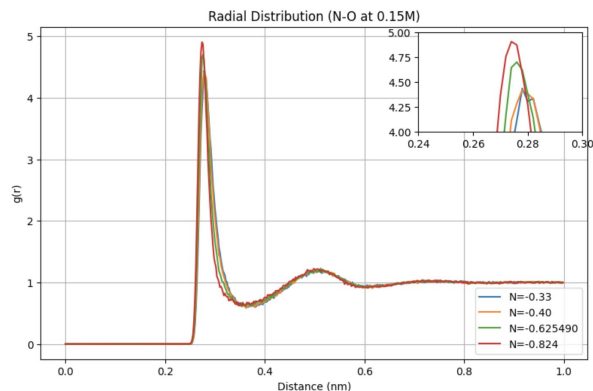
Status

Done.

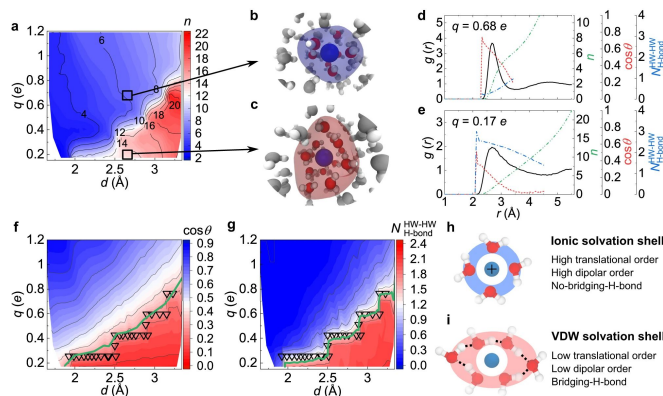
Find hydrogen bonds!

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.



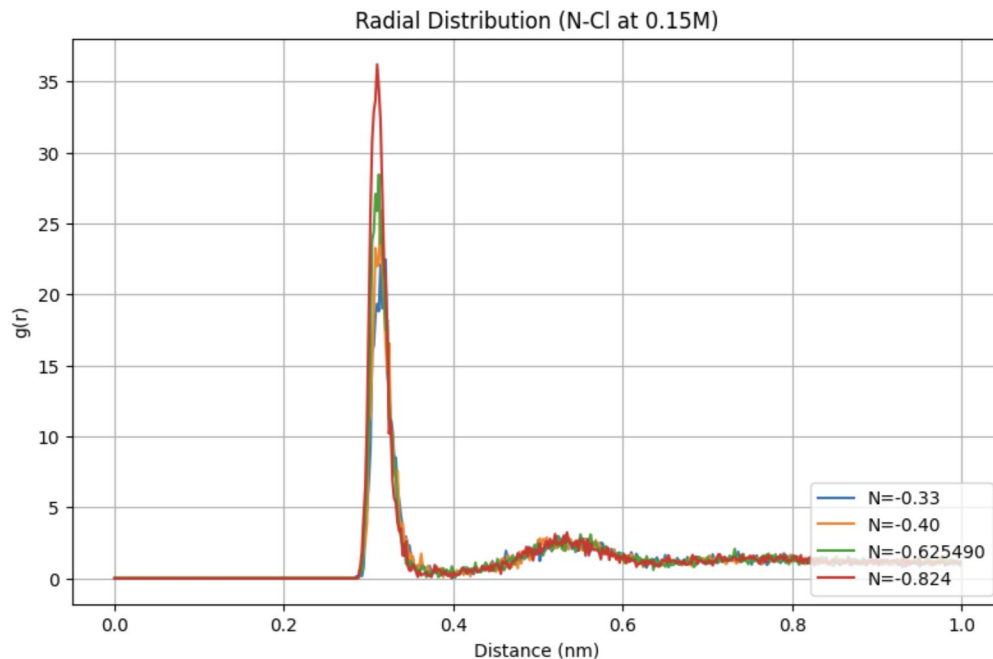
Shi, R., Cooper, A.J. & Tanaka, H. Impact of hierarchical water dipole orderings on the dynamics of aqueous salt solutions. *Nat Commun* 14, 4616 (2023). <https://doi.org/10.1038/s41467-023-40278-x>

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 | | | |

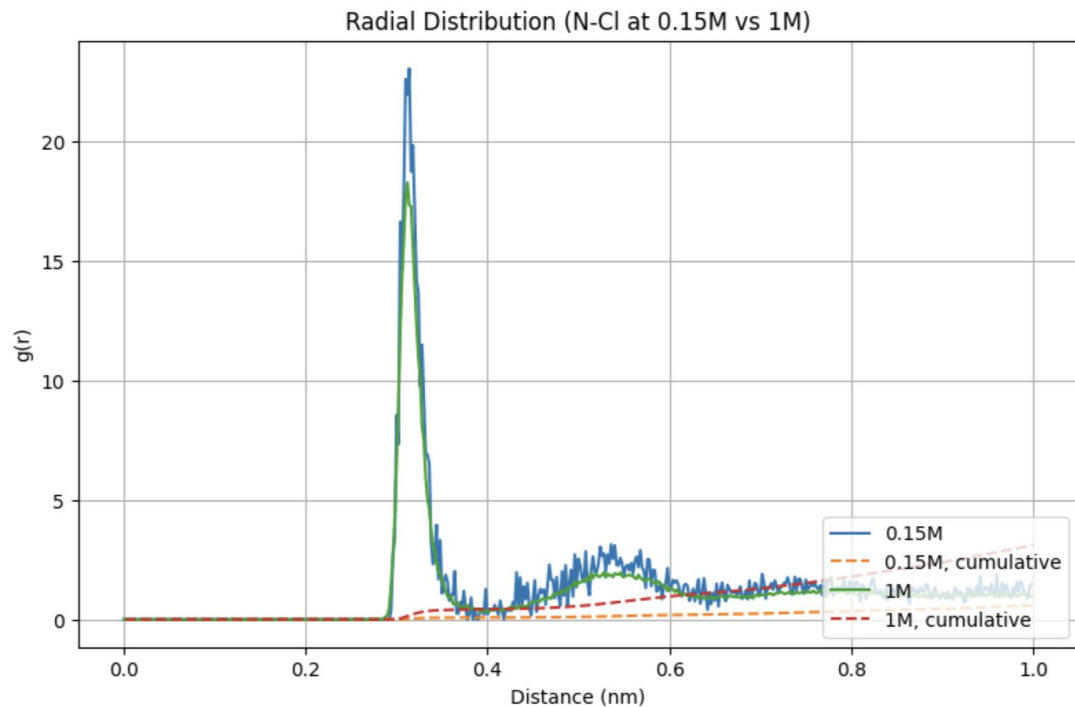
RDF results (N-Cl)

| 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_{θ}) ^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 | Partial charge -0.625490 | |
| | H | +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]

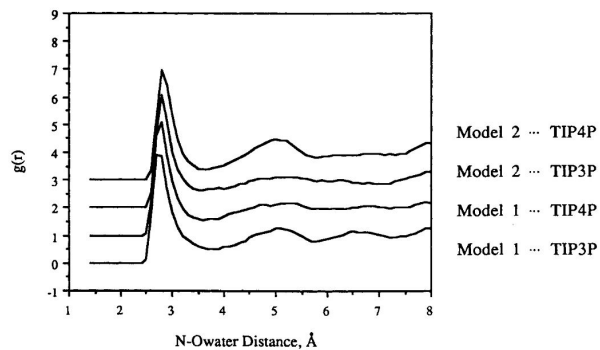
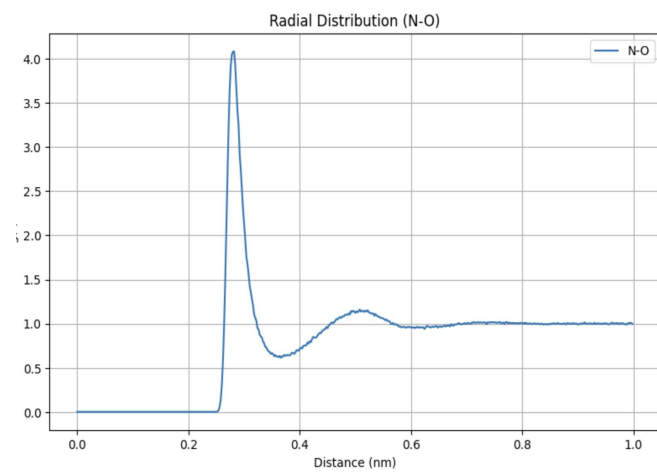
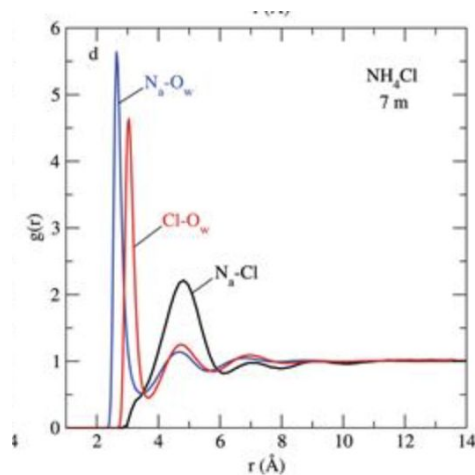


Figure 2. $\text{N}-\text{O}_{\text{water}}$ radial distribution functions for model 1 and 2 in TIP3P and TIP4P.

[5]



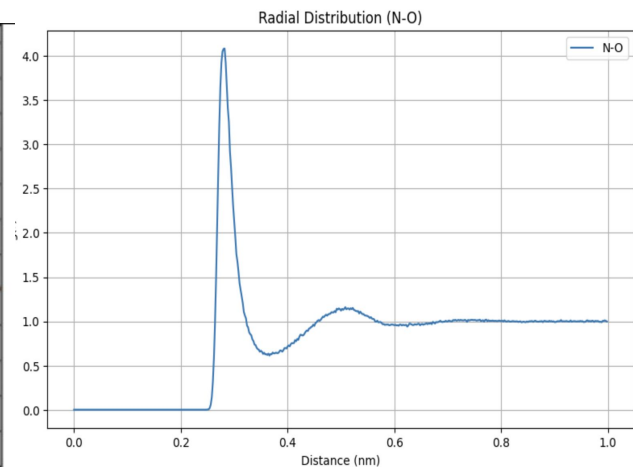
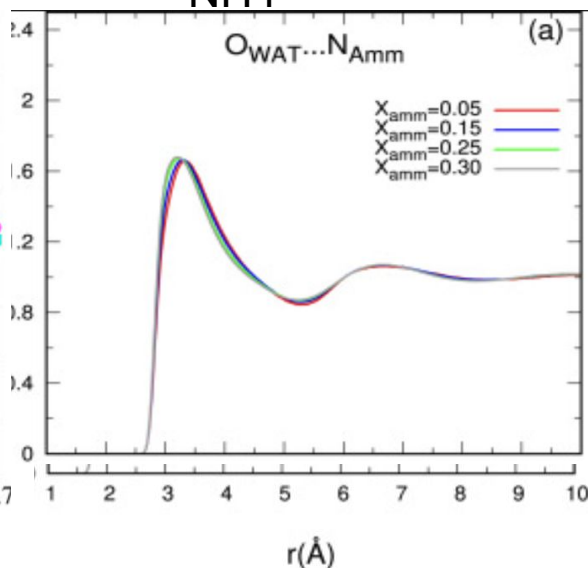
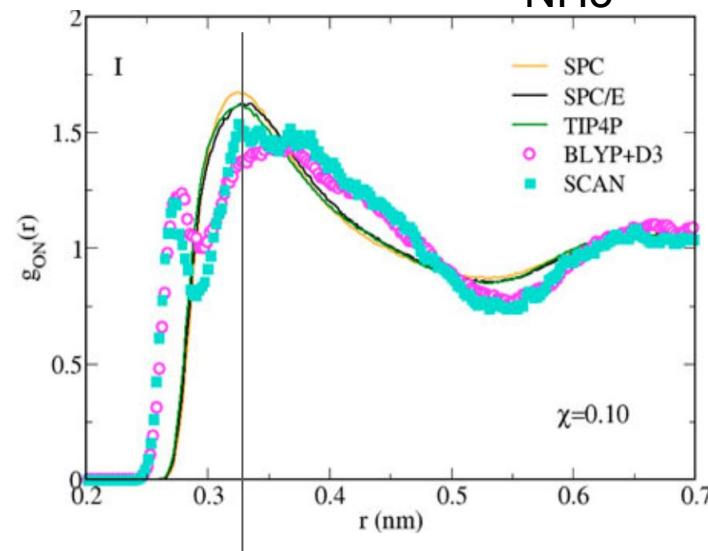
NH_4 :

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

Coordination number = 6.581

$\chi = 0.02$

RDF plots of $N_{NH_3}-O$ and $N_{NH_4}-O$



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]

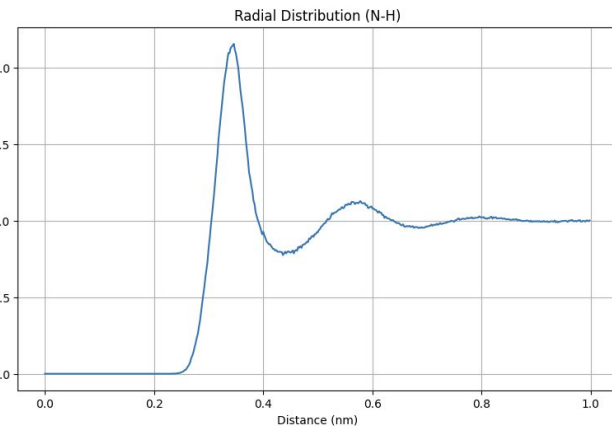
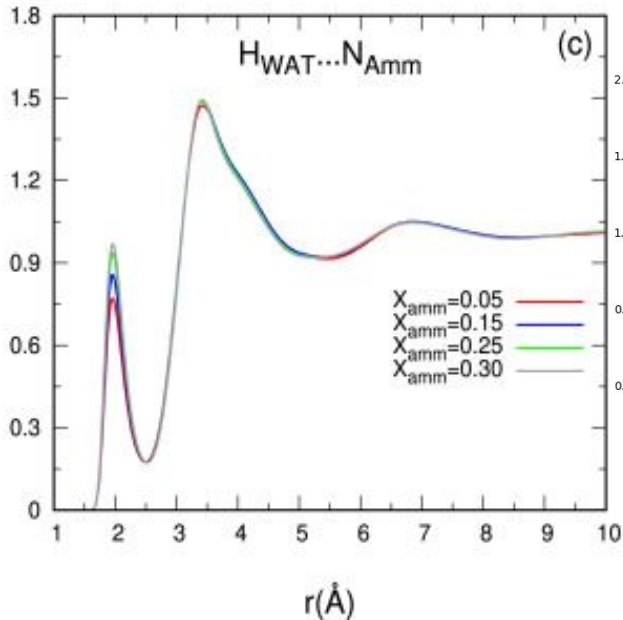
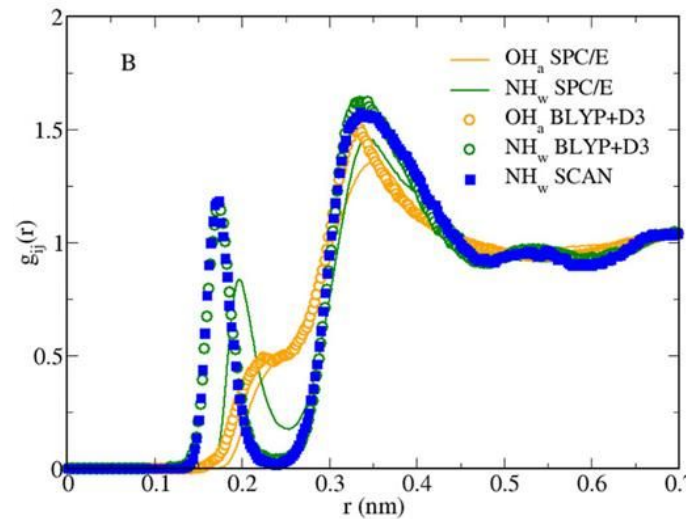
NH3:

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 $N_{NH_3}-H$ and $N_{NH_4}-H$



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 $\chi = 0.05-0.30$ [17]

NH4 from original simulation:
First maximum found at $r = 0.344$ 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

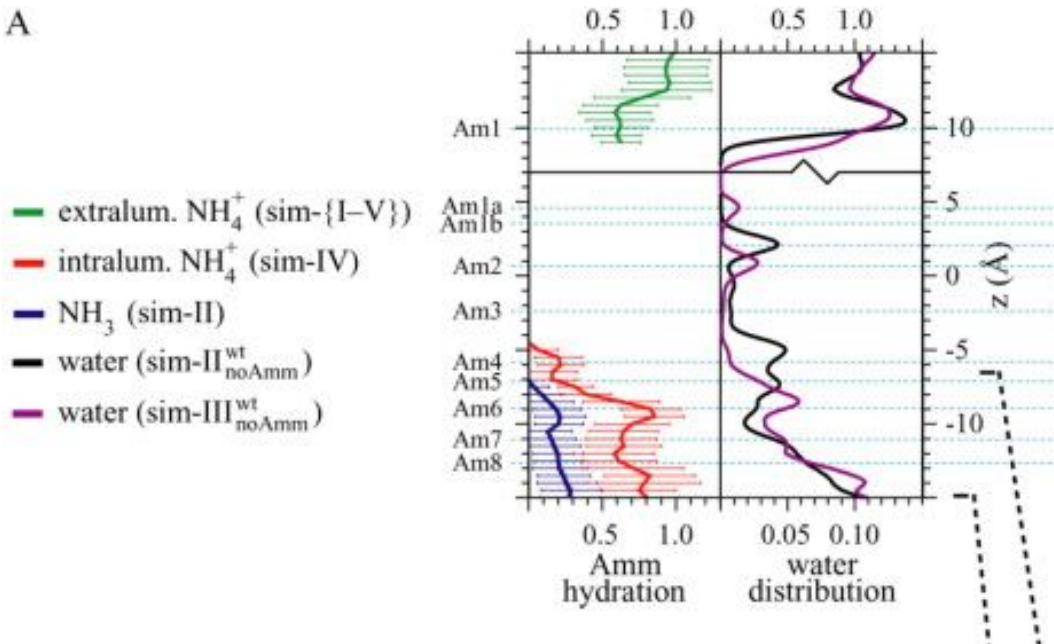
- [1] <https://github.com/Heiley-W/project/blob/main/RDF-analysis.ipynb>
- [2] Ionic radii in aqueous solutions <https://doi.org/10.1021/cr00090a003>
- [3] Halide, Ammonium, and Alkali Metal Ion Parameters for Modeling Aqueous Solutions <https://doi.org/10.1021/ct600252r>
- [4] Free Energy Calculations 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>

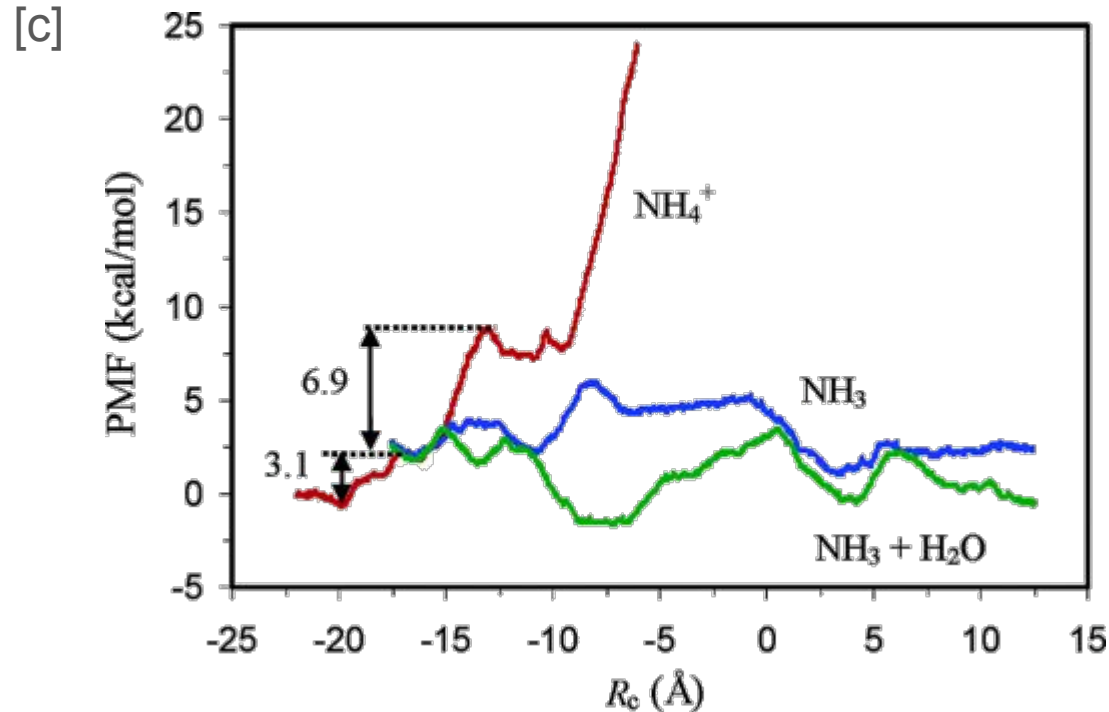
References

- [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 NH₄ conduction in ion channel

[f] Experiment

