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	NH4+ partial charges using OPLS charges, as OPLS and CHARMM partial charges of NH3+ 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	NH4 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

Radial Distribution (N-O at 0.15M)
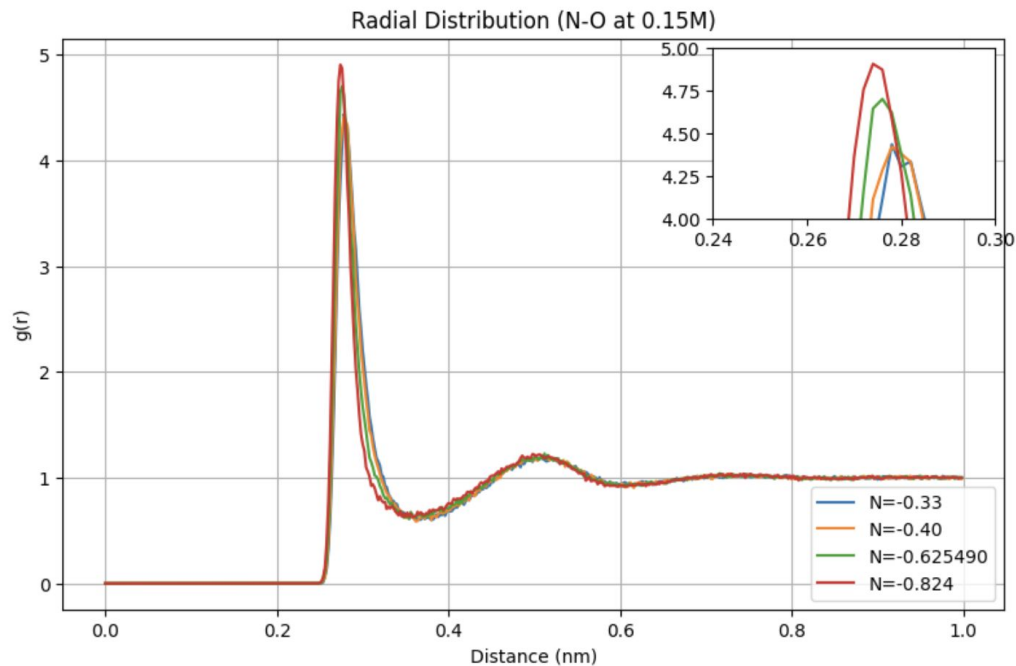
Number of hydrogen bond
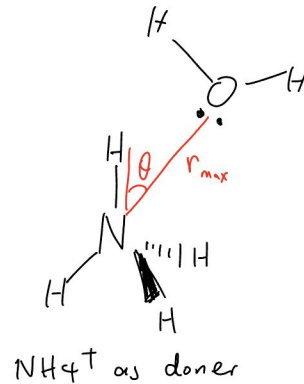
500ns	r_min	CN	Avg. no. of H-bond	Avg. occupancy (%)
0.15M, q=-0.33	0.368	7.0	12.9	0.107
0.15M, q=-0.40	0.364	6.759	13.5	0.111
0.15M, q=-0.62	0.354	6.19	15.1	0.124
0.15M, q=-0.824	0.36	6.163	12.8	0.106

NH_4^+ as doner

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
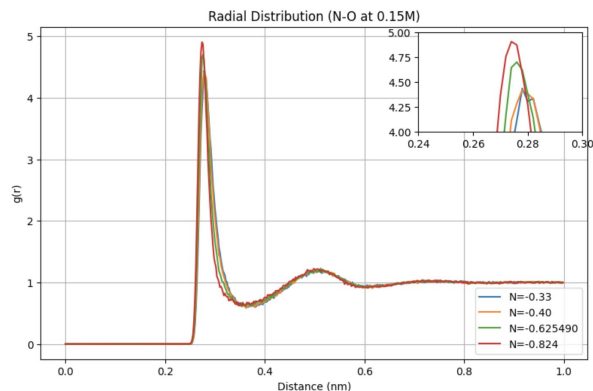
- The coordination number n drops sharply from $n \geq 12$ to $n = 4 - 8$ at $qc(d)$ as q increases (Fig. 1a). This result indicates that an ion with low charge density, behaving like an electrically neutral particle, forms a thick solvation shell, whereas an ion with high charge density develops a thin, 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.
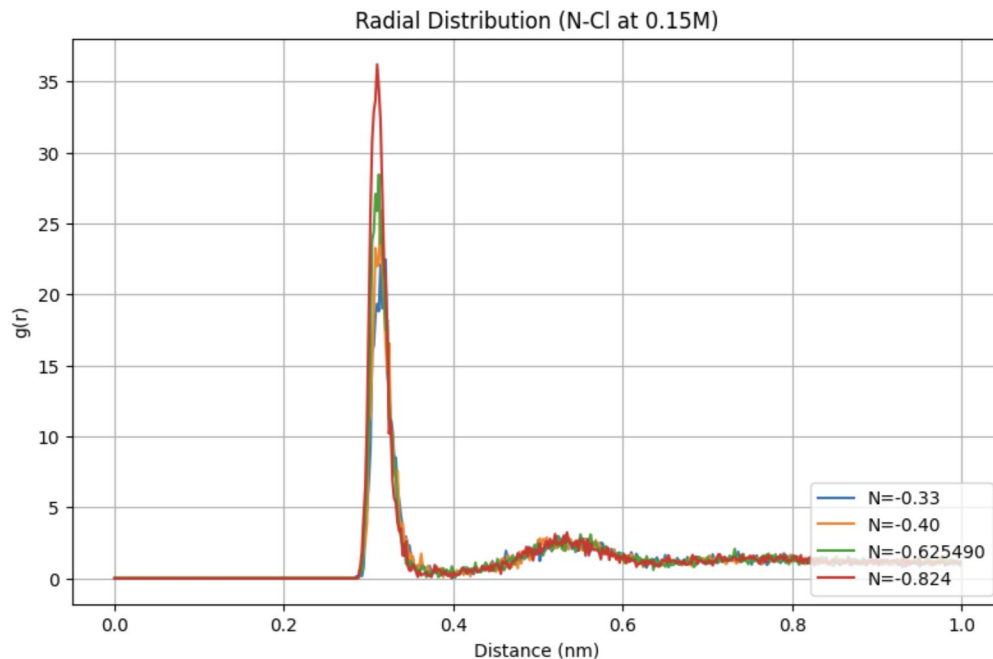

Radial Distribution (N-O at 0.15M)
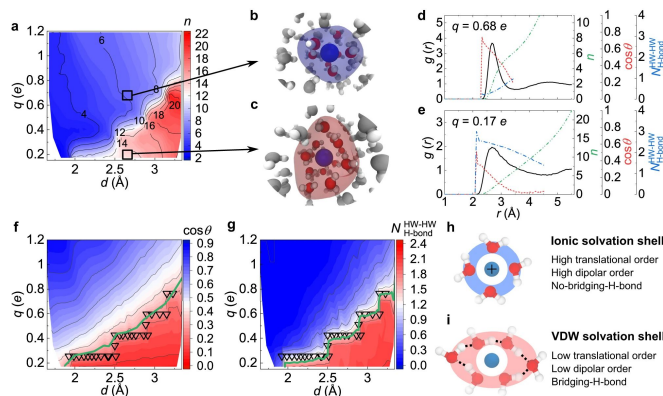
Shi, R., Cooper, A.J. & Tanaka, H. Impact of hierarchical water dipole orderings on the dynamics of aqueous salt solutions. *Nat Commun* 14, 4616 (2023). https://doi.org/10.1038/s41467-023-40278-x

RDF results (N-Cl)

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

Radial Distribution (N-Cl at 0.15M)

https://github.com/Heiley-W/project/blob/main/RDF-analysis.ipynb

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

Radial Distribution (N-Cl at 0.15M vs 1M)
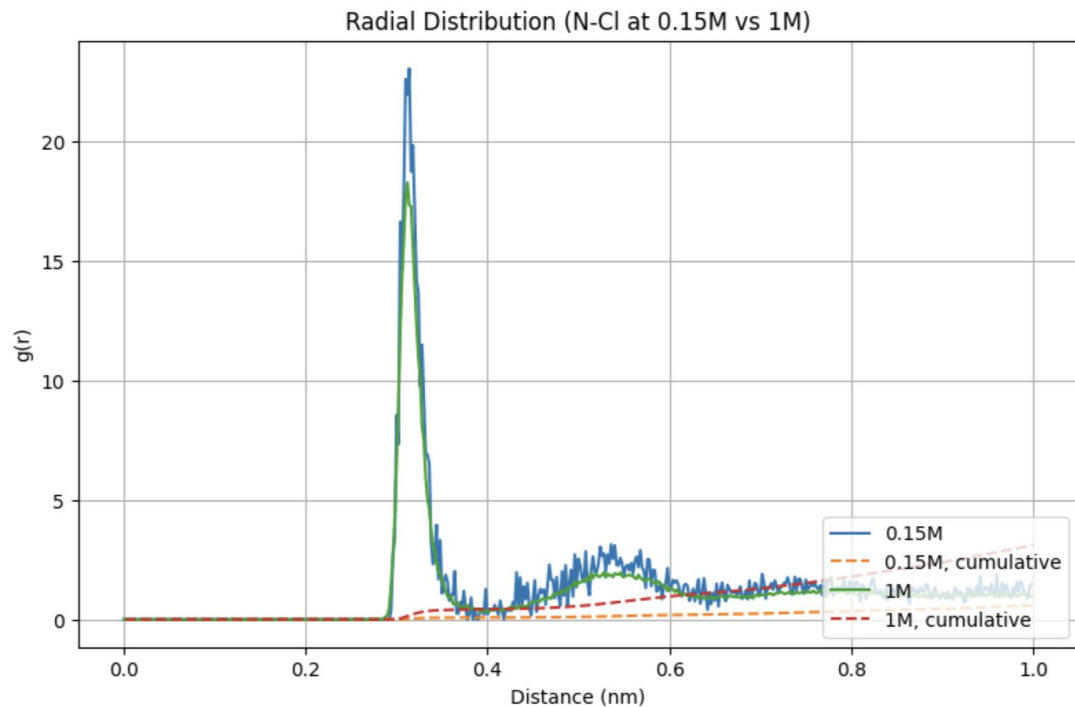
Research on NH4 conduction in ion channel

[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 NH3+, phosphatidylethanolamine	CHARMM36, TIP3P	N: -0.33 H: +0.33
[a]	NH4 charges by restrained ESP-fit method using ChelpG approach	GROMOS87, SPC	N: -0.824 H: +0.456
[b]	NH4+ partial charges using OPLS charges, as OPLS and CHARMM partial charges of NH3+ 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]	- 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]	- Parameters of ammonia from server SwissParam - Validated with salvation free energy of ammonia in water using free energy perturbation	CHARMM27, TIP3P	
[h]	- 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 $(K_b)^a$ [kcal/(mol Å^2)]	Bond length (Å)
Stretching	N—H	403.0	1.003
		Energy constant $(K_\theta)^a$ [kcal/(mol rad^2)]	Bond angle (°)
Bending	H—N—H	44.0	109.471
		Partial charge	
Electrostatic	N	−0.625490	
	H	+0.406372	

Other NH4 parameterisations

	Method	Force field, water	Charges
Default	N from primary NH3+, 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 OH2 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 OH2 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	
NH3 MD [16]		3.25	
NH3 Ab Initio [16]		2.75	

RDF plots of N_{NH4}-O

[4]
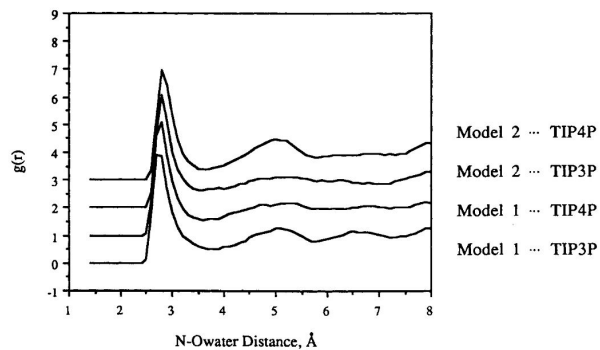
Figure 2. N—O$_{water}$ radial distribution functions for model 1 and 2 in TIP3P and TIP4P.

[5]
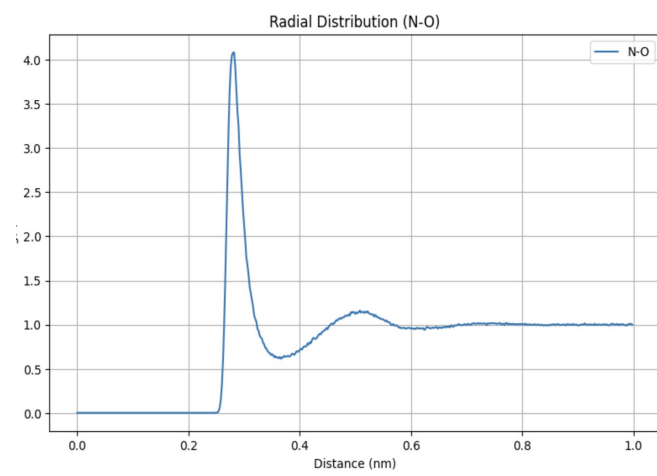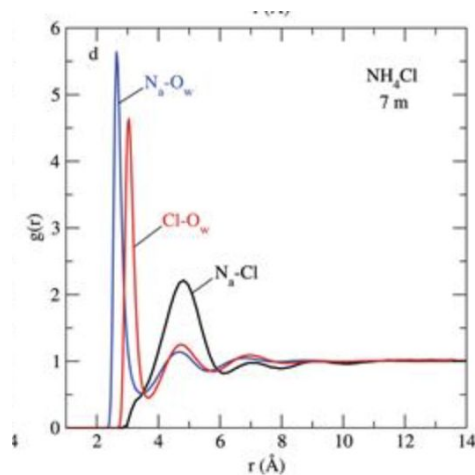
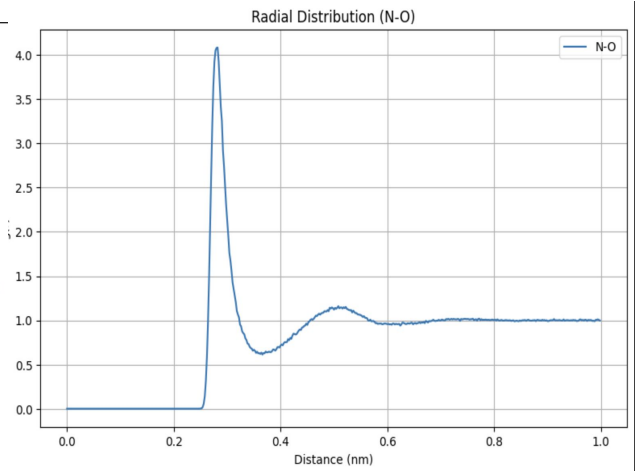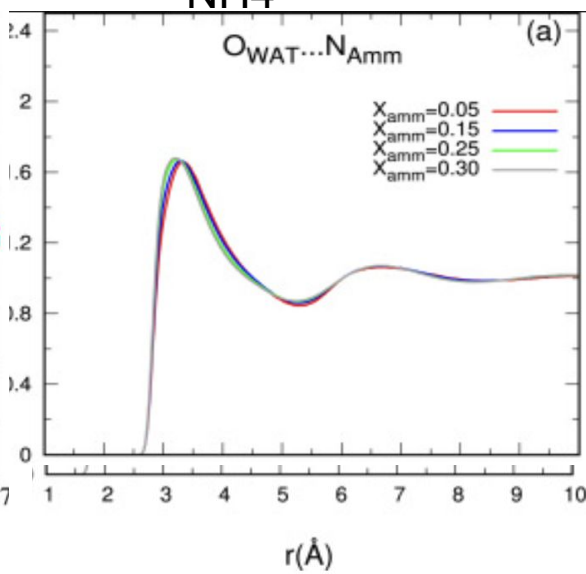

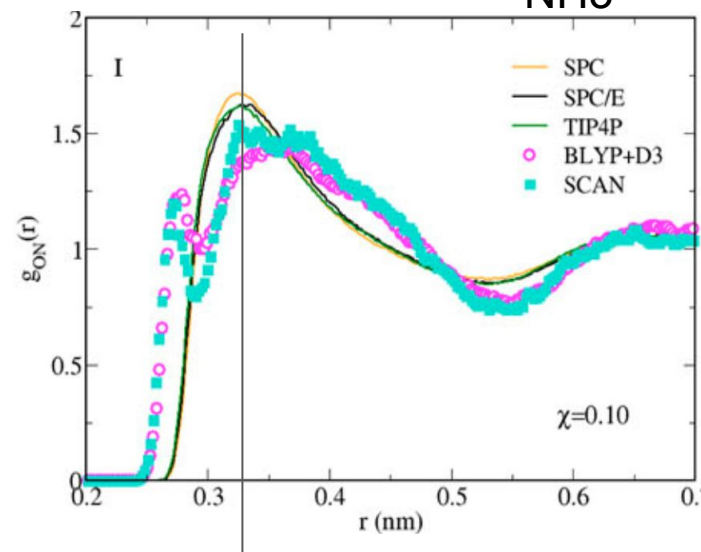NH4:
First maximum found at r = 0.282nm
Coordination number = 6.581
χ =0.02

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


NH3:
MD (lines) and AIMD (symbols) at χ = 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 χ = 0.05-0.30 [17]

NH4:
First maximum found at r = 0.282nm
Coordination number = 6.581
χ =0.02

RDF plots of N_{NH3}-H and N_{NH4}-H
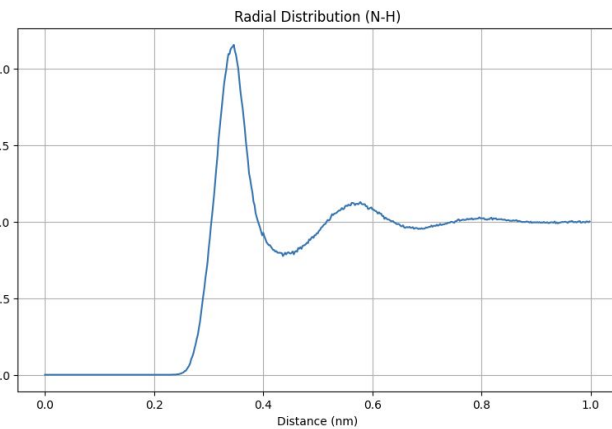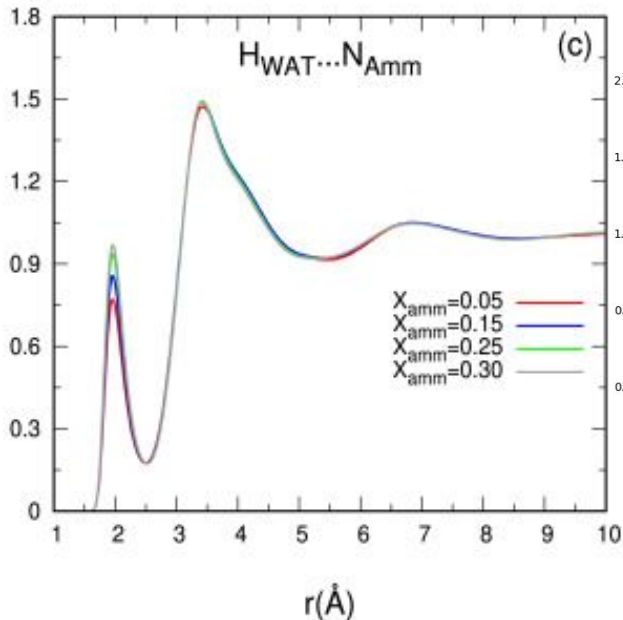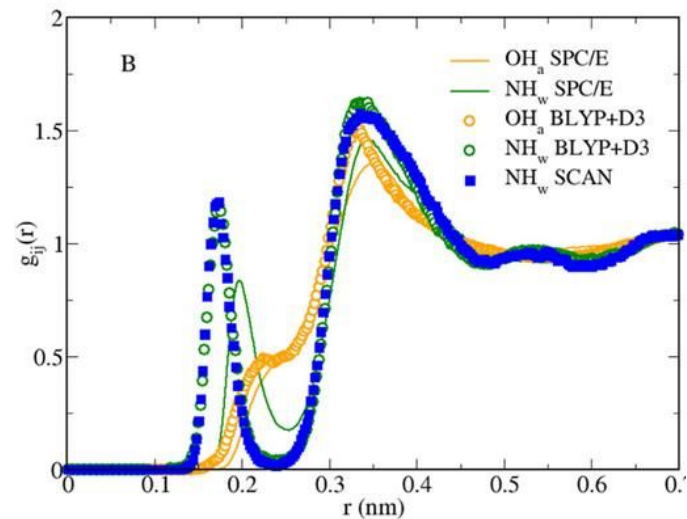
NH3:
Comparison between SPC/E (lines), BLYP+D3 (circles), and SCAN (squares) radial distributions functions involving hydrogen atoms for T = 295 K and χ = 0.10. Correlations between atoms of the same molecule type are reported in (a), whereas cross-correlations are shown in (b). [16]

NH3:
MD simulation at χ = 0.05-0.30 [17]

NH4 from original simulation:
First maximum found at r = 0.344nm
Coordination number = 20.891
χ =0.02

RDF data (Cl-O)

	No. of OH2 in first hydration shell	First peak	First minimum
Simulation, NaCl [1]	7.911	3.16	3.84
Simulation, NH4Cl [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 NH4	Absolute hydration energy of Na	Relative hydration energies between NH4+ 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

	NH4Cl	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 NH4+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+, Mg2+, Ca2+,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

[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 NH4+/NH3: 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 NH4 conduction in ion channel

[c]
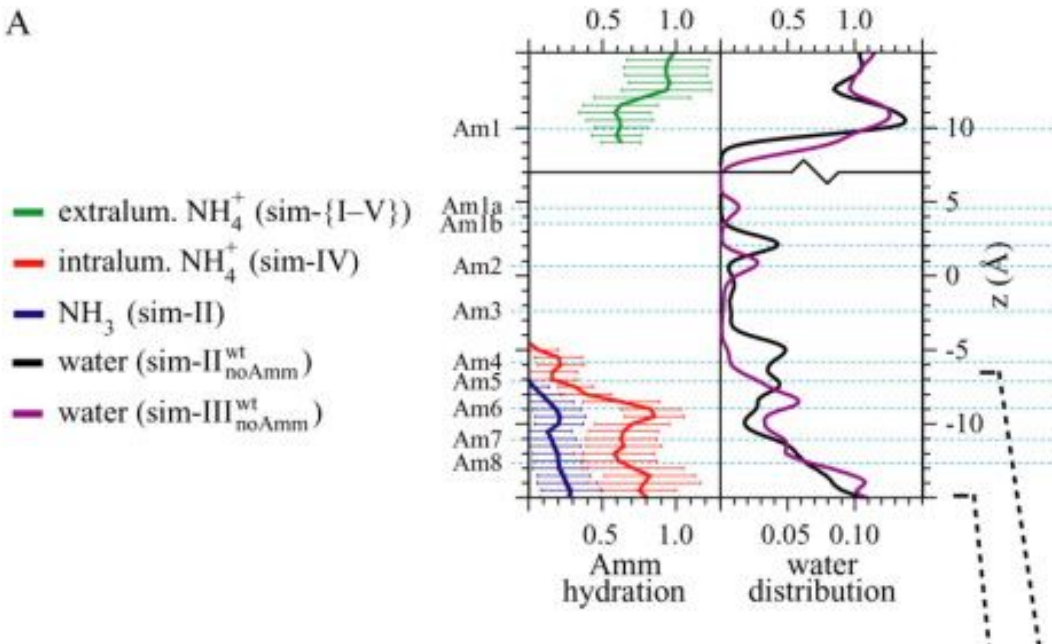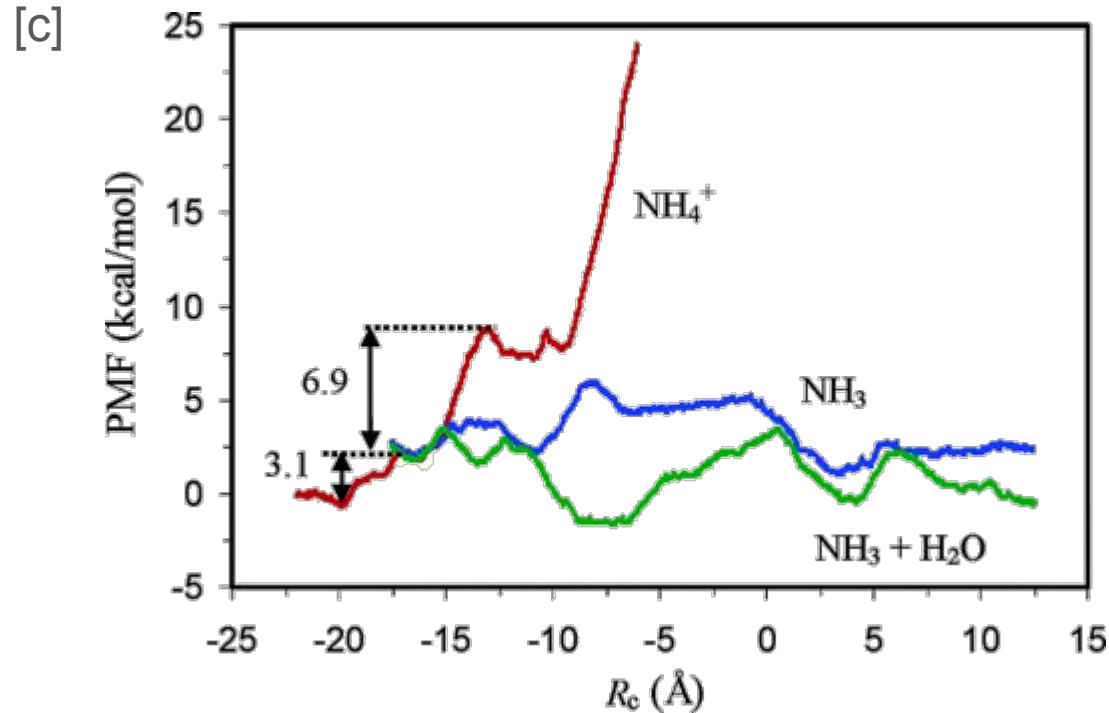
Research on NH4 conduction in ion channel

[f] Experiment