Perform pure salt simulation (NH_4Cl)

1. Parameterisation methods
2. Measurements

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_θ)[a] [kcal/(mol rad^2)]	Bond angle (°)
Bending	H—N—H	44.0	109.471

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]

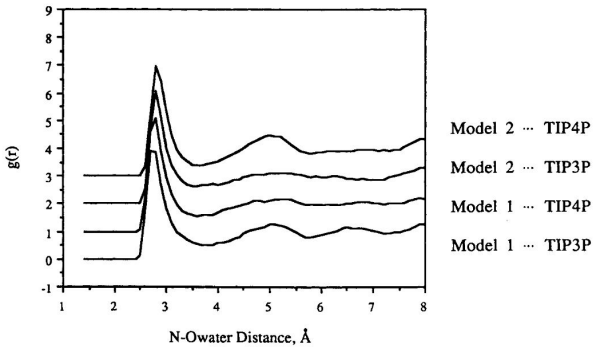
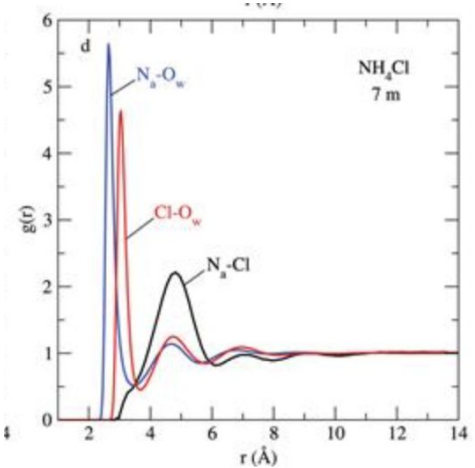
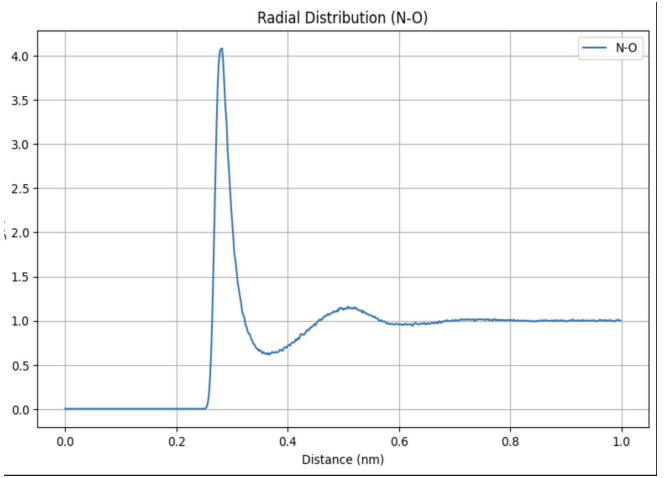


Figure 2. $N—O_{water}$ radial distribution functions for model 1 and 2 in TIP3P and TIP4P.

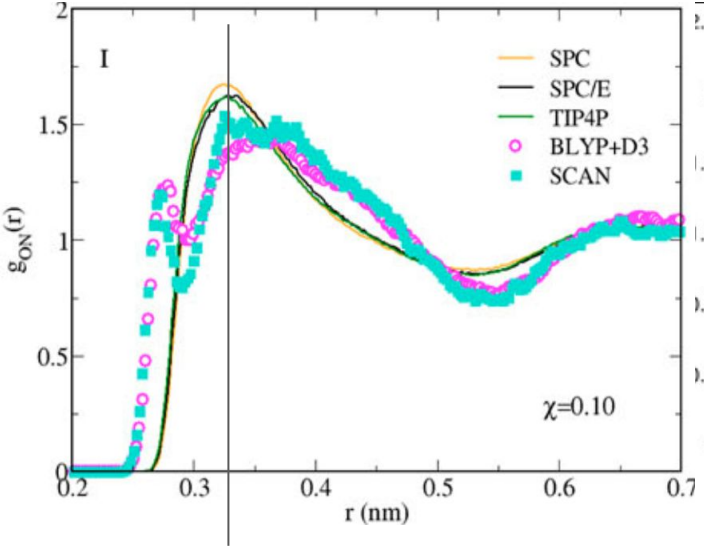
[5]

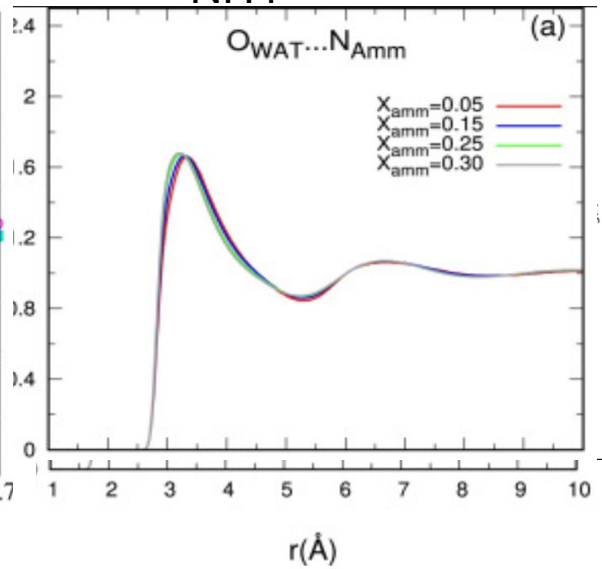


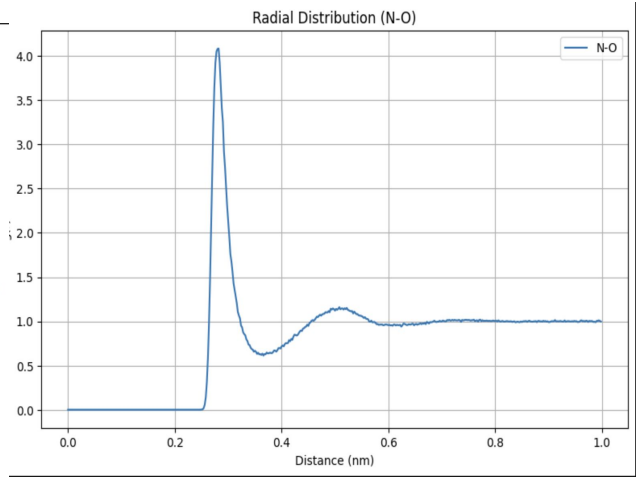


NH4:
First maximum found at r = 0.282nm
Coordination number = 6.581
χ =0.02

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





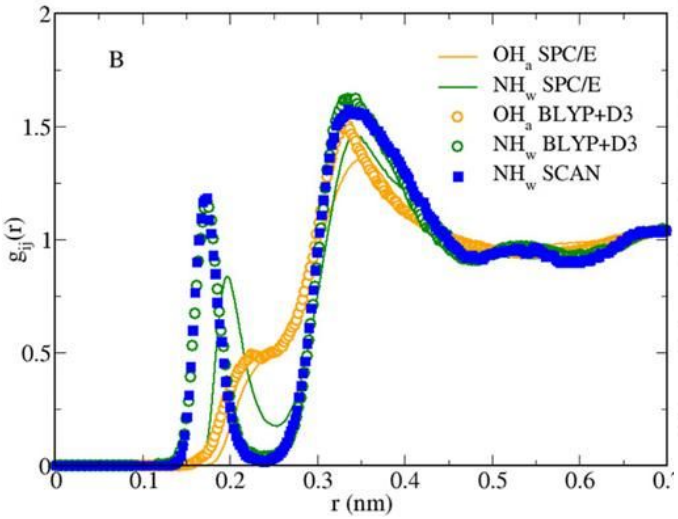


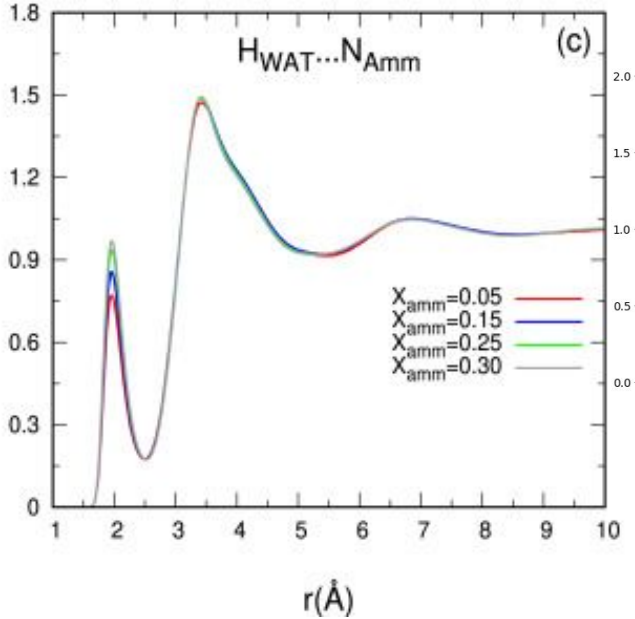
NH3:
MD (lines) and AIMD (symbols) at χ = 0.1 (NH3:H2O). The three different force fields used for water are represented by orange (SPC), black (SPC/E), and green (TIP4P) lines, while ab initio BLYP+D3 and SCAN correlations are indicated as magenta circles and cyan squares, respectively. [16]

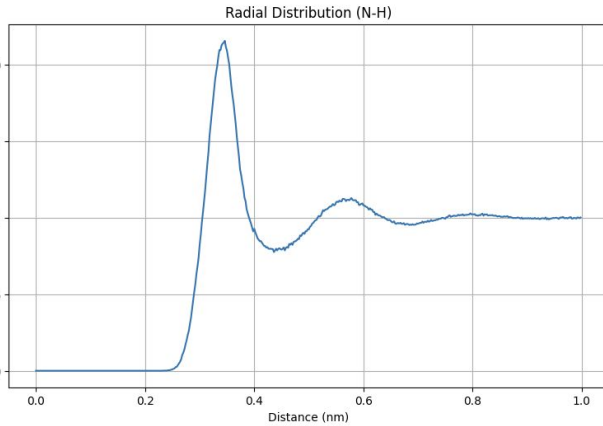
NH3:
MD simulation at χ = 0.05-0.30 [17]

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
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[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
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[9] The osmotic and activity coefficients of aqueous solutions of ammonium chloride and ammonium nitrate at 25° https://doi.org/10.1039/TF9534900027
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[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

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[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

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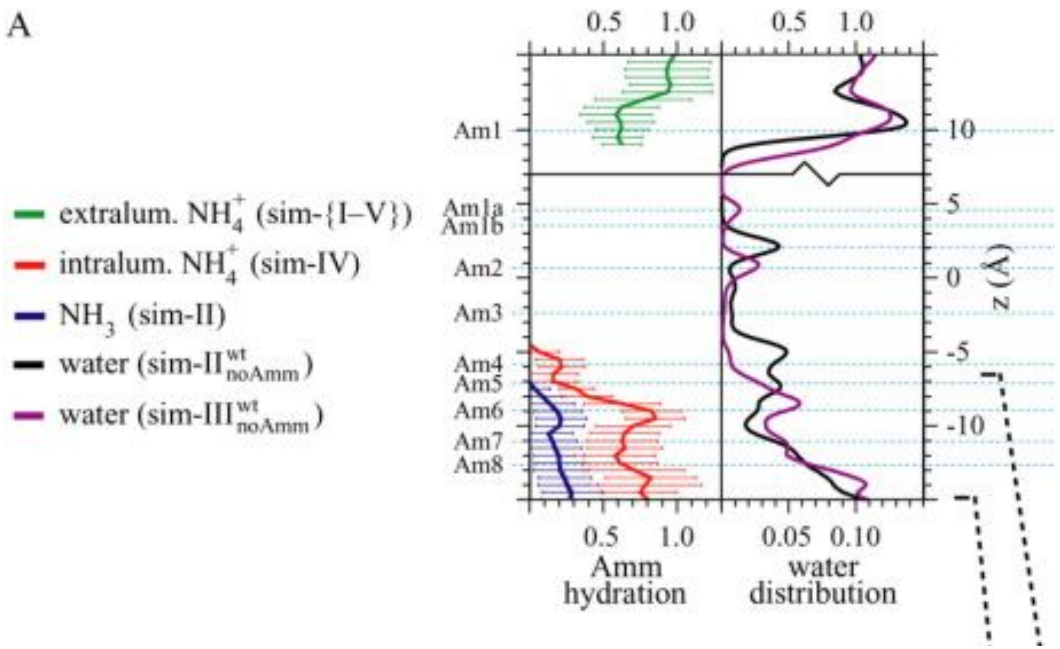
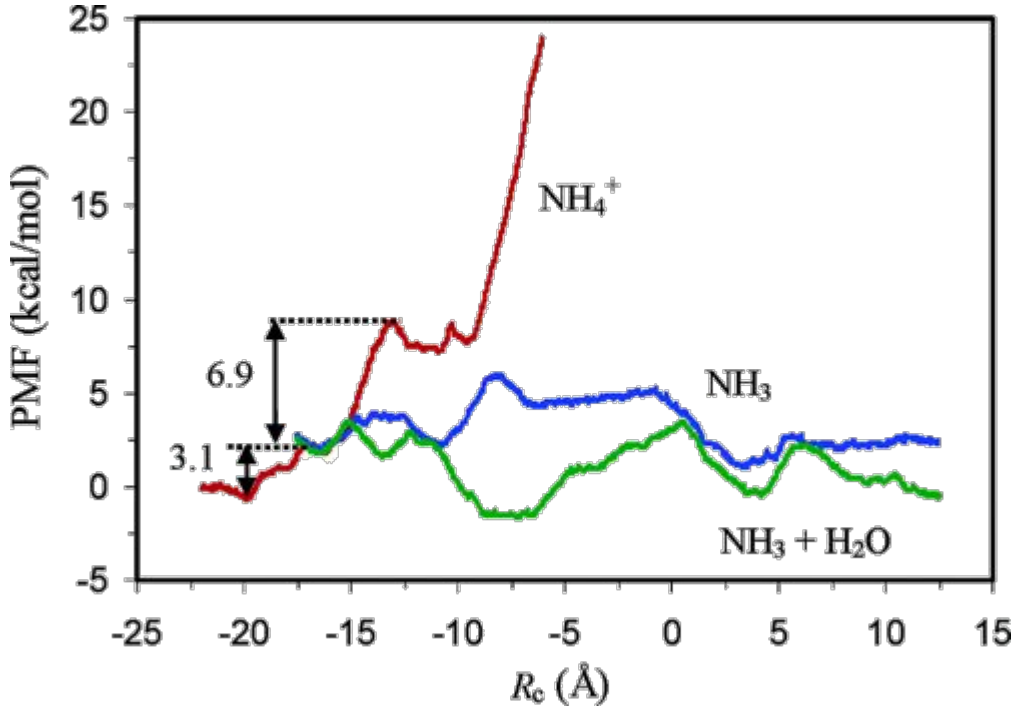
[b]



Research on NH4 conduction in ion channel

[c]



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[f] Experiment