

This item is the archived peer-reviewed author-version of:

Parametrization and molecular dynamics simulations of nitrogen oxyanions and oxyacids for applications in atmospheric and biomolecular sciences

Reference:

Cordeiro Rodrigo M., Yusupov Maksudbek, Razzokov Jamoliddin, Bogaerts Annemie.- Parametrization and molecular dynamics simulations of nitrogen oxyanions and oxyacids for applications in atmospheric and biomolecular sciences
The journal of physical chemistry : B : condensed matter, materials, surfaces, interfaces and biophysical - ISSN 1520-6106 - 124:6(2020), p. 1082-1089
Full text (Publisher's DOI): <https://doi.org/10.1021/ACS.JPCB.9B08172>
To cite this reference: <https://hdl.handle.net/10067/1664880151162165141>

Parametrization and Molecular Dynamics Simulations of Nitrogen Oxyanions and Oxyacids for Applications in Atmospheric and Biomolecular Sciences

Rodrigo Maghdissian Cordeiro, Maksudbek Yusupov, Jamoliddin Razzokov, and Annemie Bogaerts

J. Phys. Chem. B, **Just Accepted Manuscript** • DOI: 10.1021/acs.jpcc.9b08172 • Publication Date (Web): 20 Jan 2020

Downloaded from pubs.acs.org on January 22, 2020

Just Accepted

“Just Accepted” manuscripts have been peer-reviewed and accepted for publication. They are posted online prior to technical editing, formatting for publication and author proofing. The American Chemical Society provides “Just Accepted” as a service to the research community to expedite the dissemination of scientific material as soon as possible after acceptance. “Just Accepted” manuscripts appear in full in PDF format accompanied by an HTML abstract. “Just Accepted” manuscripts have been fully peer reviewed, but should not be considered the official version of record. They are citable by the Digital Object Identifier (DOI®). “Just Accepted” is an optional service offered to authors. Therefore, the “Just Accepted” Web site may not include all articles that will be published in the journal. After a manuscript is technically edited and formatted, it will be removed from the “Just Accepted” Web site and published as an ASAP article. Note that technical editing may introduce minor changes to the manuscript text and/or graphics which could affect content, and all legal disclaimers and ethical guidelines that apply to the journal pertain. ACS cannot be held responsible for errors or consequences arising from the use of information contained in these “Just Accepted” manuscripts.

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Parametrization and Molecular Dynamics Simulations of Nitrogen Oxyanions and Oxyacids for Applications in Atmospheric and Biomolecular Sciences

Rodrigo M. Cordeiro^{†}, Maksudbek Yusupov[§], Jamoliddin Razzokov[§] and*

Annemie Bogaerts[§]

[†] Centro de Ciências Naturais e Humanas, Universidade Federal do ABC, Avenida dos Estados 5001, CEP 09210-580, Santo André (SP), Brazil

[§] Research Group PLASMANT, Department of Chemistry, University of Antwerp, Universiteitsplein 1, B-2610 Antwerp, Belgium

* Corresponding author. Tel.: +55 11 49960173. *E-mail address:*

rodrigo.cordeiro@ufabc.edu.br

ABSTRACT

Nitrogen oxyanions and oxyacids are important agents in atmospheric chemistry and medical biology. Although their chemical behavior in solution is relatively well understood, they may behave very differently at the water/air interface of atmospheric aerosols or at the membrane/water interface of cells. Here, we developed a fully classical model for molecular dynamics simulations of NO_3^- , NO_2^- , HNO_3 and HNO_2 in the framework of the GROMOS 53A6 and 54A7 force field versions. The model successfully accounted for the poorly structured solvation shell and ion pairing tendency of NO_3^- . Accurate pure-liquid properties and hydration free energies were obtained for the oxyacids. Simulations at the water/air interface showed a local enrichment of HNO_3 and depletion of NO_3^- . The effect was discussed in the lights of earlier spectroscopic data and *ab initio* calculations suggesting that HNO_3 behaves as a weaker acid at the surface of water. Our model will hopefully allow for efficient and accurate simulations of nitrogen oxyanions and oxyacids in solution and at microheterogeneous interface environments.

1. INTRODUCTION

Nitrate (NO_3^-) and nitrite (NO_2^-) are common nitrogen oxyanions that constitute the basic forms of nitric (HNO_3) and nitrous (HNO_2) acid. These species exist as natural or anthropogenic constituents of atmospheric aerosols and play an important role in climate, pollution and public health issues.¹ In the food industry, they are largely employed as preservatives, with concerns being raised about their potential carcinogenic side-effects.² Under controlled conditions, however, they may turn out to be very useful in medical applications. For instance, photodynamic therapy³ and plasma-based cancer treatments⁴ rely on the delivery of reactive oxygen and nitrogen species (RONS) to tumoral tissue, culminating in localized cell death.

Whether in the atmosphere or in the organism, chemical and physical processes are influenced by interfaces. The water/air interface of atmospheric aerosols and the membrane/water interface of cells are environments where chemical reactions take place, including those involving nitrogen oxyanions and oxyacids. To understand these processes, it is helpful to have molecular models and computer simulation tools that are efficient and accurate, especially at microheterogeneous interface environments. However, even the description of bulk-phase solvation can be challenging. Neutron diffraction measurements^{5,6} and *ab initio* calculations⁷⁻¹⁰ have consistently revealed a poorly structured hydration shell around NO_3^- , while classical molecular-mechanics models tended to overestimate ion-solvent¹⁰ and even ion-ion¹¹ interactions. It has been noted that the rigid structure of typical water models and the use of atomic point charges may produce coordination shells that are artificially well-structured.⁶ This issue becomes critical in the case of NO_3^- and NO_2^- due to charge delocalization, from which one would rather expect smoother charge distributions and

1
2
3 stronger polarizability. In principle, these effects could be incorporated into a classical model
4
5 by distributing the ionic charge into additional virtual sites or by adding a polarization term to
6
7 the force field. However, each of these improvements has its drawbacks with regards to
8
9 computational efficiency and stability.¹²
10

11
12 To our knowledge, there is no molecular-mechanical model in the literature for
13
14 nitrogen oxyanions that also comprises their conjugated acid forms. With a pK_a of -1.38,¹³
15
16 HNO_3 is one of the strongest inorganic acids, found in water almost exclusively in the ionized
17
18 form. However, spectroscopic measurements¹⁴ and *ab initio* calculations¹⁵⁻¹⁸ have shown that
19
20 the molecular form of HNO_3 is stabilized at the water/air interface, meaning that HNO_3
21
22 behaves as a weaker acid in this region. It is true that fully classical models do not incorporate
23
24 the electronic degrees of freedom that are necessary to explicitly describe
25
26 protonation/deprotonation events. However, local changes in the acid ionization constant (K_a)
27
28 are closely related to the partitioning of the involved species between the aqueous bulk and
29
30 the interface region, as conceptually demonstrated by the thermodynamic cycle in Figure 1a.
31
32 Assuming that the pH does not change from the bulk to the interface, an interface-induced
33
34 drop in K_a should translate into the interfacial enrichment of HNO_3 and depletion of NO_3^- . In
35
36 principle, a successful molecular mechanical model should capture this tendency at least on
37
38 the qualitative level.
39
40
41
42
43

44
45 With that in mind, we present the systematical development of a GROMOS-type¹⁹
46
47 molecular-mechanical model for NO_3^- , NO_2^- , HNO_3 and HNO_2 . We validated the model by
48
49 showing that it successfully accounted for solvation properties and ion-pairing tendencies of
50
51 these species. Most importantly, the model captured experimentally supported interfacial
52
53 phenomena, such as the enrichment of HNO_3 at the water surface¹⁴ and the surface-induced
54
55 ion-pairing of $NaNO_2$.²⁰ Many well-established force field families are framed within the
56
57 rules of simplicity (i.e. functional form with as few terms as possible), versatility (i.e.
58
59 modularity and transferability of molecular building blocks) and efficiency (i.e. computational
60

1
2
3 speed). Our molecular model was developed with the same philosophy and thus represents a
4
5 useful tool for large-scale simulations of various kinds of interfacial environments in
6
7 chemistry and biology.
8
9

10 11 12 **2. COMPUTATIONAL METHODS** 13

14 15 16 17 **2.1. General Setup and Parametrization Philosophy** 18 19 20

21 Molecular dynamics (MD) simulations²¹ were performed with GROMACS 5.0.4.^{22,23}
22
23 Newton's equations of motion were solved with the following setup: time step of 2 fs; bond
24
25 length constraints; periodic boundary conditions; particle mesh Ewald (PME) electrostatics
26
27 with a real-space cutoff of 0.9 nm; double-range truncation of Lennard-Jones interactions at
28
29 0.9 and 1.4 nm; and long-range dispersion corrections of energy and pressure. Interatomic
30
31 interactions were based on the framework of the GROMOS 53A6 force field and the SPC
32
33 water model.¹⁹ The parametrization of nitrogen oxyanions and oxyacids followed a trial-and-
34
35 error approach, in which force field parameters were iteratively adjusted to match reference
36
37 data from more fundamental *ab initio* calculations and experiments. Force field and molecular
38
39 topology files are available as Supporting Information. Force field data are also summarized
40
41 in Table S1.
42
43
44
45
46
47
48

49 **2.2. Parametrization of Nitrogen Oxyanions** 50 51 52

53 The molecular geometries of NO_3^- and NO_2^- were taken from earlier molten salt
54
55 parametrizations.^{24,25} Lennard-Jones interactions were selected from the existing GROMOS
56
57 database and partial atomic charges were adjusted for a correct description of hydration
58
59 structure and ion pairing in solution. Various systems were simulated, ranging from the
60

1
2
3 infinitely dilute regime (i.e. a single ion pair in a $3 \times 3 \times 3$ nm³ water box), up to a concentration
4
5 of ~ 4.5 mol/L. Equilibration took place at the isothermal-isobaric (NPT) ensemble at 1 bar
6
7 and 298 K for 5 ns, followed by data acquisition for 25 ns. Radial and spatial distribution
8
9 functions (RDF and SDF, respectively) were computed to show the distribution of hydration
10
11 waters and Na⁺ counterions around NO₃⁻ and NO₂⁻. The positions of the minima after the first
12
13 RDF peaks were used as distance cut-offs for the determination of hydration numbers and
14
15 ionic pairs. Diffusion coefficients were calculated from the mean square displacement of the
16
17 anions.
18
19
20
21
22

23 **2.3. Parametrization of Nitrogen Oxyacids**

24
25
26
27
28 We relied on earlier *ab initio* calculations and spectroscopic data to describe the
29
30 internal structure and conformational equilibrium of nitrogen oxyacids.²⁶⁻³¹ The HNO₃ model
31
32 was assembled based on small adaptations to the Lennard-Jones parameters previously
33
34 developed for small and electrically neutral RONS.^{32,33} Atom-centered partial charges were
35
36 initially estimated from electronic structure calculations using Gaussian 09.³⁴ B3LYP density
37
38 functional calculations were performed with the 6-311++G(3df,3pd) basis set, followed by
39
40 CHelpG fitting of the electrostatic potential. Partial charges were then iteratively scaled up in
41
42 order to account for polarization effects at the condensed phase, and provide an optimized
43
44 description of pure-liquid and hydration properties. Pure HNO₃ was equilibrated for 5 ns and
45
46 sampled for the same duration for computation of its density and heat of vaporization.^{19,32} The
47
48 hydration free energy at infinite dilution (ΔG_{hyd}) of HNO₃ was calculated via the
49
50 thermodynamic integration (TI) method.²¹ A single HNO₃ molecule was placed in a $3 \times 3 \times 3$
51
52 nm³ water box and TI was performed at 1 bar and 298 K. Each TI calculation was partitioned
53
54 into 72 individual simulation runs describing distinct solute-solvent coupling states, which
55
56 were combined to yield ΔG_{hyd} (c.f. eq S1). At each intermediate state, the system was
57
58
59
60

1
2
3 equilibrated for 600 ps and sampled for 5 ns. Further details are provided as Supporting
4
5 Information.

6
7 Parametrization of HNO₂ followed a similar route. However, additional considerations
8
9 were needed because of the existence of two stable conformational states, *cis*- and *trans*-
10 HNO₂. These states contribute together to the experimentally measured ΔG_{hyd} of HNO₂, but
11
12 are separated by a large energy barrier.²⁹⁻³¹ A complete exploration of the conformational
13
14 space would require prohibitively long TI simulations. Enhanced sampling methods such as
15
16 metadynamics have been successful in dealing with similar situations.³⁵ Here, however, we
17
18 chose to pursue a simpler, yet thermodynamically equivalent approach. First, we assembled
19
20 one set of force field parameters to describe both *cis*- and *trans*-HNO₂ (Table S1). CHelpG
21
22 charges obtained for each conformer were averaged out and employed as starting values for
23
24 the iterative charge optimization. We did not employ any particular optimization algorithm.
25
26 Instead, charges were gradually scaled up by successive trials aiming at a ΔG_{hyd} value within
27
28 ~ 1 kJ/mol of reference data. Next, we set up a thermodynamic cycle to relate the
29
30 conformational equilibria of HNO₂ in the gas and aqueous phases, as depicted in Figure 1b.
31
32 We considered the weighted contributions of both conformers to the overall Henry's law
33
34 constant of HNO₂ (eqs S2 to S4), resulting in the following expression for the overall
35
36 hydration free energy (ΔG) of HNO₂:
37
38
39
40
41
42
43
44
45
46
47

$$\Delta G = \Delta G_2 - RT \ln \frac{1 + \exp(-\Delta G_4 / RT)}{1 + \exp(-\Delta G_1 / RT)}, \quad (1)$$

48
49
50
51
52
53 where R is the ideal gas constant, T is the temperature and $\Delta G_4 = \Delta G_1 - \Delta G_2 + \Delta G_3$ is
54
55 calculated according to the thermodynamic cycle in Figure 1b. The ΔG_1 term was derived
56
57 directly from the torsional potential employed in the topological description of HNO₂. Finally,
58
59 ΔG_2 and ΔG_3 were determined by TI. Given that isomerization was extremely unlikely within
60

1
2
3 5 ns simulation windows, TI could be performed for each conformer separately. In less than
4
5 1% of the individual TI windows, isomerization occurred and simulations had to be reinitiated
6
7 to ensure sampling of only the desired conformational state.
8
9

10 11 12 **2.4. Simulations at the Water/Air Interface** 13 14 15

16
17 A water slab with a $5.6 \times 5.6 \text{ nm}^2$ surface area and a thickness of $\sim 5.6 \text{ nm}$ was
18 assembled with 5500 molecules. In total, 20 units of each of the following species were added
19 together: NO_3^- , NO_2^- , HNO_3 , HNO_2 (initially *trans*) and HNO_2 (initially *cis*). Individual
20 concentrations were equivalent to $\sim 0.2 \text{ mol/L}$. A total of 40 Na^+ counterions were added to
21 keep electroneutrality. Equilibration was run at 310 K for 100 ns to allow enough time for
22 HNO_2 isomerization, followed by 50 ns of sampling to determine the distribution and spatial
23 configurations of the different species as function of position across the water/air interface. A
24 shorter simulation was performed with only ions, but at a 10-fold higher concentration. In this
25 case, equilibration was performed for 30 ns, followed by sampling for 35 ns. The tendency for
26 ion pairing was quantified as function of the distance to the water/air interface.
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41

42 **3. RESULTS AND DISCUSSION** 43 44 45

46 **3.1. Hydration Structure of Nitrogen Oxyanions** 47 48 49 50

51 It is well known that NO_3^- has a poorly structured hydration shell.⁵⁻¹⁰ Therefore, the
52 NO_3^- model was assembled with the relatively large atom types “NR” and “OM”, whose
53 Lennard-Jones interactions are described by large repulsive terms. In the GROMOS force
54 field, Lennard-Jones interactions are defined in terms of atom types, with “OM” being the
55 standard atom of choice for the description of anionic carboxylate groups. Atom-centered
56
57
58
59
60

1
2
3 point charges of $+0.65e$ and $-0.55e$ were considered for nitrogen and oxygen, respectively. As
4
5 depicted in Figure 2, the hydration structure of our NO_3^- model was in reasonable agreement
6
7 with *ab initio* MD data and showed a significant improvement over earlier fully classical MD
8
9 models.¹⁰ The ion-water RDFs exhibited little structuring, suggesting that water molecules
10
11 were only weakly H-bonded to NO_3^- . SDFs revealed that coordinating waters were preferably
12
13 located at the equatorial O—N—O bisector regions, in agreement with *ab initio* data.⁸ We
14
15 speculate that the spatially anisotropic hydration structure of NO_3^- might play a role in its
16
17 interactions and reactivity, in the sense that the out-of-plane regions of NO_3^- are less hydrated
18
19 and therefore free to interact with other molecules.
20
21
22

23
24 The NO_2^- model was assembled with the same atom types as NO_3^- , but with partial
25
26 charges of $+0.4e$ and $-0.7e$ for nitrogen and oxygen, respectively. It is also shown in Figure 2
27
28 that NO_2^- had a more structured hydration shell than NO_3^- . H-bonds were established mainly
29
30 between its oxygen atoms and water, with fewer solvent molecules coordinated to the
31
32 nitrogen atom. This is in qualitative agreement with *ab initio* quantum mechanical charge
33
34 field molecular dynamics results,³⁶ which were taken as reference for NO_2^- parametrization.
35
36 We emphasize that the partial charges of the ions were empirically adjusted by trial-and-error
37
38 and that their values played a critical role in the hydration structure of NO_2^- . Point charges
39
40 directly derived from electronic structure calculations in vacuum (B3LYP/6-
41
42 311++G(3df,3pd)/CHelpG) were not as effective in reproducing the preference of water for
43
44 the oxygen sites of NO_2^- (Figure S1). Continuum solvent quantum mechanical models or
45
46 empirical corrections need to be employed to account for solvent-induced polarization. Our
47
48 empirical charge set implicitly incorporates solvent-induced polarization effects that are
49
50 necessary for the proper description of NO_2^- hydration. As a side note, CHelpG charges
51
52 performed worse in NO_2^- than in NO_3^- , where H-bonding appeared to be less important.
53
54 However, even in the case of NO_3^- , we opted to employ an empirical charge set with lower
55
56 absolute values than the CHelpG charges. Our empirical charge set emphasized charge
57
58
59
60

1
2
3 delocalization in NO_3^- and led to less structured coordination shells. The importance of this
4
5 result lies in the fact that models based on point-charges and rigid solvent tend to produce
6
7 excessively structured hydration shells.⁶
8
9

10 The properties obtained for NO_3^- and NO_2^- solutions are summarized in Table 1 and
11 compared to reference experimental data. A total of 7-8 coordinating waters were found
12 around both NO_3^- and NO_2^- , irrespective of concentration. These values were consistently
13 higher than the experimental data of Kameda et al.,^{5,37} but we note that the hydration numbers
14 reported for NO_3^- vary widely in the literature.³⁸ Our results closely agreed with the number
15 of 8 coordinating waters found in recent *ab initio* MD simulations.^{9,10} The diffusion
16 coefficients from simulations were also consistently higher than experimental reference data,
17 but in the same order of magnitude. Within uncertainty, diffusion coefficients were practically
18 the same for NO_3^- and NO_2^- , much in line with experimental data. Even though NO_3^- is bigger
19 than NO_2^- , the latter has a larger hydrodynamic radius, i.e. it drags a larger number of water
20 molecules as it diffuses. This effect, which is also corroborated by the RDFs in Figure 2, has
21 been used as an explanation for the fact that aqueous solutions of NO_2^- tend to be more
22 viscous than analogous NO_3^- solutions over a large concentration and temperature range.³⁹
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41

42 **3.2. Ion Pairing in Aqueous Solution**

43
44
45
46

47 Nitrates and nitrites are characterized by very high aqueous solubilities that may well
48 exceed 10 mol in 1 L of water.⁴⁰ Using our newly developed model for NO_3^- and NO_2^- , we
49 were able to simulate NaNO_3 and NaNO_2 aqueous solutions that remained stable at
50 concentrations as high as ~ 4.5 mol/L. As summarized in Table 1, the densities of concentrated
51 solutions agreed very well with experimental reference data. Figure 3 shows a panorama of
52 ionic interactions in concentrated solutions of NaNO_3 and NaNO_2 . In both cases, the
53 trajectories revealed a rapid sequence of ion pairing and separation events. Na^+ ions paired
54
55
56
57
58
59
60

1
2
3 mostly with only one anion, forming electrically neutral pairs. Less often, however, larger
4
5 ionic clusters were formed. Ion pairs and larger clusters were short-lived, with lifetimes that
6
7 did not exceed a few hundreds of picoseconds. The formation of ion pairs was reflected on the
8
9 ion-ion RDFs by means of the first peak at distances below 0.4 nm. This peak was higher for
10
11 NO_2^- than for NO_3^- , which indicates a larger tendency for ion pairing in NO_2^- . Simulations
12
13 performed using a different set of CHelpG partial charges led to similar results (Figure S2).
14
15

16
17 The formation of ion pairs in aqueous solution is an important phenomenon that
18
19 reflects the quality and balance of ionic interactions in the force field. Our results are in
20
21 discrepancy with earlier semi-empirical quantum mechanical/molecular mechanical
22
23 simulations, which indicated the existence of both stronger and longer-lived ion pairing in
24
25 NaNO_3 and NaNO_2 aqueous solutions.⁴¹ Ion-ion RDFs obtained from recent MD simulations
26
27 of alkali nitrates also showed higher peaks.¹¹ In that investigation, however, crystallization
28
29 was witnessed at concentrations well below the solubility limit. As shown in Figure 3c, the
30
31 lower propensity for ion pairing in our model appears to be well aligned with experimental
32
33 measurements.⁴² In the case of NaNO_3 , ionization was almost complete at dilute solutions, but
34
35 decreased to a ratio of ~80% at 4.4 mol/L, which is still within its solubility limit. Beyond 4.4
36
37 mol/L, the ion-pairing in the simulations was stronger as compared to the experimental data.
38
39 Larger aggregates were formed, which might indicate the onset of nucleation. Further force
40
41 field improvements could be achieved by considering not only solution, but also solid-state
42
43 properties of NaNO_3 . However, the “near-precipitation” thermodynamic state is beyond the
44
45 scope of this work, since a concentration of 4.4 mol/L already represents an excessively large
46
47 ionic strength for most biomolecular simulations. The ionization degree of NaNO_2 was
48
49 comparably lower than of NaNO_3 at similar concentrations. Currently, there is no reference
50
51 experimental data on ionic interactions of NaNO_2 . It would be interesting to test the
52
53 predictions of our model as experimental data on NaNO_2 ion pairing become available.
54
55
56
57
58
59
60

1
2
3 Although our force field was developed based on GROMOS 53A6, it can be extended
4
5 to later versions. The 54A7 version has been developed for an improved description of protein
6
7 secondary structure.⁴³ All atom types, which define the Lennard-Jones interactions, were
8
9 merely imported from the earlier 53A6 version. Combination of our model oxyanions with
10
11 GROMOS 54A7 would seem straightforward, as the interactions with water and protein
12
13 residues remain unaffected. However, Na⁺ interactions have been reparametrized in
14
15 GROMOS 54A7. If our oxyanion models are simply included in GROMOS 54A7 with no
16
17 further changes, the description of ionic pairing improves for concentrations up to 1 mol/L. A
18
19 slightly poorer description of ion pairing is obtained at the highest ionic strength (Figure S2),
20
21 which is well beyond the conditions employed in most protein simulations.
22
23
24
25
26
27

28 **3.3. Structure, Pure-Liquid Properties and Hydration Energies of Nitrogen Oxyacids**

29
30
31
32

33 The HNO₃ model was consistent with its well-known planar structure. Two
34
35 symmetrically equivalent configurations of HNO₃ were possible as a result of the flipping of
36
37 the O—N—O—H dihedral angle. They were equally stable, but separated by a large energy
38
39 barrier of 32.8 kJ/mol.²⁷ The model was assembled with the atom types “NQ” and “OQ” at
40
41 the —NO₂ fragment and “OP” and “H” at the —OH fragment.^{32,33} The “OQ-OP” interaction
42
43 was made more repulsive in order to improve the pure-liquid properties of the HNO₃ model.
44
45 We emphasize that GROMOS interactions are individually defined for each pair type¹⁹ and
46
47 that changes in the “OQ-OP” interaction bear no influence on the preceding parametrization
48
49 work performed for RONS.^{32,33,44,45} The partial charges were then optimized, resulting in a
50
51 HNO₃ model that yielded pure-liquid density and heat of vaporization values within ±8% of
52
53 reference experimental data^{40,46} (c.f. Table 1). Solvation properties were in even closer
54
55 agreement, with ±1% differences in ΔG_{hyd} between simulations and experiments.^{47,48} It should
56
57
58
59
60 be realized that we employed PME electrostatics and long-range dispersion corrections in our

1
2
3 simulation setup, which although not standard in GROMOS, may be preferred in particular
4 situations, for instance in membrane simulations. Using exactly the same force field
5 parameters, we repeated the calculations for HNO₃ employing the standard reaction field
6 electrostatics without dispersion correction and found a variation of less than 3% in the
7 properties of HNO₃ (data not shown).
8
9
10
11
12
13

14 The HNO₂ model successfully accounted for its gas-phase conformational behavior.
15 *Trans*-HNO₂ had the lowest energy and was separated from *cis*-HNO₂ by a small energy
16 difference of 1.56 kJ/mol (corresponding to ΔG_1) and a large isomerization barrier of 39
17 kJ/mol.^{30,31} In aqueous solution, HNO₂ was mostly hydrated around its —OH fragment, as
18 shown in Figure 4a. Configurations around the energy minima were thoroughly explored
19 within short 5 ns simulations, but full isomerization events were rare (Figure 4b). TI
20 simulations were well-converged for individual conformers (Figure S3). As shown in Table 1,
21 the aqueous environment increased the stability of *trans*- over *cis*-HNO₂, with a free energy
22 difference $\Delta G_4 = 8.4$ kJ/mol between the hydrated conformers. We explain this result by
23 considering that the *trans* conformation leads to a larger molecular dipole moment. Following
24 eq 1, the weighted average between both conformers led to an overall ΔG_{hyd} value in close
25 agreement with experimental data for HNO₂.
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44

45 **3.4. Nitrogen Oxyanions and Oxyacids at the Water/Air Interface**

46
47
48
49 Figure 5 shows the distributions of NO₃⁻, NO₂⁻, HNO₃ and HNO₂ across the water/air
50 interface. The density of water molecules decreased smoothly from the bulk aqueous to the
51 vapor phase, giving rise to a ~1-nm-thick interfacial region. The NO₃⁻ and NO₂⁻ ions remained
52 excluded from this region, in agreement with earlier MD simulations performed with a
53 polarizable force field.^{49,50} On the other hand, the electrically neutral, acidic forms of HNO₃
54 and HNO₂ accumulated at the interface, reaching local concentrations many times larger than
55
56
57
58
59
60

1
2
3 in the bulk aqueous phase. We did not draw a distinction between *cis*- and *trans*-HNO₂
4 because simulations were long enough to allow for a significant number of isomerization
5 events. Indeed, the *cis/trans* ratio evolved from 1:1 at the beginning of the simulation to 1:24
6 at equilibrium, in consistency with the ΔG_4 value (Figure S4). In the case of HNO₃, both
7 parallel and perpendicular orientations of the molecular plane were possible with respect to
8 the surface, but the proportion of parallel arrangements was somewhat larger than expected
9 for a completely random distribution.

10
11 The fact that HNO₃ accumulated at the interface, while its conjugated base NO₃⁻ was
12 excluded from it, ultimately translates into HNO₃ being a weaker acid at the interface than in
13 the bulk (c.f. Figure 1a). This conclusion follows directly from the definition of a position-
14 dependent pK_a shift, as:

$$\Delta pK_a(z) = \Delta \text{pH}(z) - \log \frac{C_b(z)/C_b^\infty}{C_a(z)/C_a^\infty}, \quad (2)$$

15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37 where z designates the position along the water/air interface and C the position-dependent
38 concentrations of the acidic (a) and basic (b) forms at equilibrium (see also eqs S5 and S6). In
39 classical simulations, the base/acid ratio in the bulk (C_b^∞/C_a^∞) is arbitrarily defined based on
40 the initial number of molecules placed at the aqueous phase. However, note that eq 2 allows
41 expressing ΔpK_a not as a function of absolute concentrations, but rather of ratios between
42 local and bulk concentrations. With the distributions in Figure 5b and the rather crude
43 assumption of no spatial pH variation, eq 2 predicts a pK_a increase that can exceed one unit at
44 the interface (Figure S5). However, given the qualitative nature of our analysis, this figure is
45 probably best taken as a higher-bound estimate of ΔpK_a . In fact, theoretical calculations have
46 suggested that the auto-ionization of water may be slightly favored near the interface.⁵¹ That
47 would have the effect of enhancing the local concentration of H₃O⁺ ions, which would in turn
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3 lead to a lower ΔpK_a according to eq 2. The interfacial stabilization of HNO_3 in its molecular
4 form is also supported by experimental data. X-ray photoelectron spectroscopy has revealed a
5
6
7
8 $\sim 20\%$ decrease in HNO_3 ionization at the solution interface.¹⁴ This value is likely to be
9
10 underestimated because one cannot easily distinguish between contributions of the top and
11
12 subsurface layers. Indeed, our simulations suggest that the effect is confined to an interface
13
14 layer narrower than 1 nm. That might explain why no change in HNO_3 ionization has been
15
16 detected in a different investigation using glancing-angle Raman spectroscopy, with an
17
18 estimated probing depth of 50-100 nm.⁵²
19
20

21
22 Another interesting spectroscopic observation is that NO_2^- ions are able to populate the
23
24 water/air interface in the form of ion pairs.²⁰ Figure 6 shows the variations of the ionic pairing
25
26 tendencies of NaNO_3 and NaNO_2 across the water/air interface, as recorded during
27
28 simulations performed with ~ 2 mol/L of each salt. As seen earlier, ions were for the most part
29
30 excluded from the interface. However, for the few ions that reached the surface, ion pairing
31
32 was favored. The degree of ionization dropped at the outermost interface layers, where the
33
34 hydration level was less than 10% as in the bulk. Any experimental technique designed to
35
36 probe nitrogen oxyanions at the interface is likely to produce a response signal with a
37
38 significant contribution from ion pairs. Interfacial properties, such as surface tension, are also
39
40 likely to be affected by the increased prevalence of ion pairs relative to dissociated ions at the
41
42 surface.
43
44
45
46
47
48

49 **3.5. Applications in Atmospheric and Biomolecular Sciences**

50
51
52
53 Nitrogen oxyanions and oxyacids are well-known components of atmospheric
54
55 aerosols.¹ Chemical speciation within aqueous aerosol particles may be largely influenced by
56
57 the interface due to their large surface-to-volume ratios. Although nitrogen oxyanions and
58
59 oxyacids were not explicitly interconvertible in our simple molecular-mechanical formalism,
60

1
2
3 the model was still successful in reproducing the larger surface activity of the protonated
4 species as compared to their anionic counterparts. That implies a surface-induced stabilization
5 of the molecular forms of HNO_3 and HNO_2 over NO_3^- and NO_2^- , respectively. The
6
7 implications for atmospheric chemistry follow from the fact that interfacial reactions are
8 likely to occur in a more acidic environment than expected from the bulk pH. It is true that *ab*
9
10 *initio* MD simulations will continue to be the preferred method for studying the dynamics of
11
12 chemical reactions. However, the time scales that can be achieved are still severely limited by
13
14 current computational resources. A fully classical model of nitrogen oxyanions and oxyacids
15
16 allows for a statistically more complete analysis of phenomena such as molecular diffusion,
17
18 partitioning and reorientation. A reliable and well-validated classical model can be used to
19
20 generate interaction and hydration configurations of molecules at the air/water interface, later
21
22 to be employed as starting points for more detailed *ab initio* calculations of chemical
23
24 reactions.
25
26
27
28
29
30
31
32

33 The advantage of higher efficiency becomes more evident in the case of biomolecular
34
35 simulations. Proteins, membranes and other biological structures are often too large for a full
36
37 quantum mechanical treatment. As an example of biological application, we can consider the
38
39 interaction between cell membranes and plasma (i.e., ionized gas) species. Plasma-based skin
40
41 treatments generate large quantities of NO_3^- and NO_2^- , which have been found to permeate all
42
43 skin layers very effectively, including the *stratum corneum*.⁵³ To reconcile this observation
44
45 with the low ionic permeability of phospholipid membranes, we speculate that nitrogen
46
47 oxyanions may reside at the membrane surface and traverse its hydrophobic interior in their
48
49 conjugated acid form. Further studies are underway to investigate this issue. We also point out
50
51 that NO_3^- and NO_2^- are potential targets of enzymatic action.⁵⁴ Studies of enzyme-anion
52
53 binding may profit from a well-balanced description of ionic interactions.
54
55
56
57
58
59
60

4. CONCLUSIONS

1
2
3
4
5 We developed a fully classical model for molecular dynamics simulations of NO_3^- ,
6 NO_2^- , HNO_3 and HNO_2 in the framework of the GROMOS 53A6 and 54A7 force field
7 versions. The model successfully accounted for: *i*) the poorly structured solvation shell of
8 NO_3^- and the anisotropic water distribution around NO_2^- ; *ii*) a well-balanced ion-pairing
9 tendency in NaNO_3 solutions; *iii*) accurate pure-liquid properties and hydration free energies
10 of HNO_3 and HNO_2 ; *iv*) the stabilization of the molecular form of HNO_3 at the water/air
11 interface; and *v*) the increased ion-pairing tendency of NaNO_2 at the water/air interface.
12 Atmospheric and biological chemistry often takes place at interfaces. Our work resulted in a
13 simple, yet accurate tool for simulations of nitrogen oxyanions and oxyacids at
14 microheterogeneous interface environments.
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29

30 SUPPORTING INFORMATION

31
32
33
34
35 The thermodynamic integration method (eq S1). Conformer contribution to hydration free
36 energy (eqs S2 to S4). Force field parameters for nitrogen oxyanions and oxyacids (Table S1).
37 Effect of charge on nitrogen oxyanion hydration (Figure S1). Effect of force field on ionic
38 interactions (Figure S2). Convergence of thermodynamic integration (Figure S3).
39 Convergence of conformer distribution (Figure S4). Position-dependent $\text{p}K_a$ shift (eq S5, eq
40 S6 and Figure S5). Force field and molecular topology files for NO_3^- , NO_2^- , HNO_3 and HNO_2 .
41
42
43
44
45
46
47
48
49

50 ACKNOWLEDGEMENTS

51
52
53
54
55 We thank Universidade Federal do ABC for providing the computational resources needed for
56 completion of this work.
57
58
59
60

REFERENCES

- (1) Pöschl, U. Atmospheric Aerosols: Composition, Transformation, Climate and Health Effects. *Angew. Chemie Int. Ed.* **2005**, *44*, 7520–7540.
- (2) Mensinga, T. T.; Speijers, G. J. A.; Meulenbelt, J. Health Implications of Exposure to Environmental Nitrogenous Compounds. *Toxicol. Rev.* **2003**, *22*, 41–51.
- (3) Brown, S. B.; Brown, E. A.; Walker, I. The Present and Future Role of Photodynamic Therapy in Cancer Treatment. *Lancet Oncol.* **2004**, *5*, 497–508.
- (4) Keidar, M. Plasma for Cancer Treatment. *Plasma Sources Sci. Technol.* **2015**, *24*, 033001.
- (5) Kameda, Y.; Saitoh, H.; Uemura, O. The Hydration Structure of NO₃⁻ in Concentrated Aqueous Sodium Nitrate Solutions. *Bull. Chem. Soc. Jpn.* **1993**, *66*, 1919–1923.
- (6) Wang, H.-W.; Vlcek, L.; Neufeind, J. C.; Page, K.; Irle, S.; Simonson, J. M.; Stack, A. G. Decoding Oxyanion Aqueous Solvation Structure: A Potassium Nitrate Example at Saturation. *J. Phys. Chem. B* **2018**, *122*, 7584–7589.
- (7) Tongraar, A.; Tangkawanwanit, P.; Rode, B. M. A Combined QM/MM Molecular Dynamics Simulations Study of Nitrate Anion (NO₃⁻) in Aqueous Solution. *J. Phys. Chem. A* **2006**, *110*, 12918–12926.
- (8) Yadav, S.; Choudhary, A.; Chandra, A. A First-Principles Molecular Dynamics Study of the Solvation Shell Structure, Vibrational Spectra, Polarity, and Dynamics around a Nitrate Ion in Aqueous Solution. *J. Phys. Chem. B* **2017**, *121*, 9032–9044.
- (9) Vchirawongkwin, V.; Kritayakornupong, C.; Tongraar, A.; Rode, B. M. Symmetry Breaking and Hydration Structure of Carbonate and Nitrate in Aqueous Solutions: A Study by Ab Initio Quantum Mechanical Charge Field Molecular Dynamics. *J. Phys. Chem. B* **2011**, *115*, 12527–12536.
- (10) Thøgersen, J.; Réhault, J.; Odellius, M.; Ogden, T.; Jena, N. K.; Jensen, S. J. K.; Keiding, S. R.; Helbing, J. Hydration Dynamics of Aqueous Nitrate. *J. Phys. Chem. B* **2013**, *117*, 3376–3388.
- (11) Xie, W. J.; Zhang, Z.; Gao, Y. Q. Ion Pairing in Alkali Nitrate Electrolyte Solutions. *J. Phys. Chem. B* **2016**, *120*, 2343–2351.
- (12) Salvador, P.; Curtis, J. E.; Tobias, D. J.; Jungwirth, P. Polarizability of the Nitrate Anion and Its Solvation at the Air/Water Interface. *Phys. Chem. Chem. Phys.* **2003**, *5*, 3752–3757.
- (13) *Lange's Handbook of Chemistry, 15th ed.*; Dean, J. A., Ed.; McGraw-Hill.
- (14) Lewis, T.; Winter, B.; Stern, A. C.; Baer, M. D.; Mundy, C. J.; Tobias, D. J.; Hemminger, J. C. Does Nitric Acid Dissociate at the Aqueous Solution Surface? *J. Phys. Chem. C* **2011**, *115*, 21183–21190.
- (15) Shamay, E. S.; Buch, V.; Parrinello, M.; Richmond, G. L. At the Water's Edge: Nitric Acid as a Weak Acid. *J. Am. Chem. Soc.* **2007**, *129*, 12910–12911.
- (16) Ardura, D.; Donaldson, D. J. Where Does Acid Hydrolysis Take Place? *Phys. Chem. Chem. Phys.* **2009**, *11*, 857–863.
- (17) Wang, S.; Bianco, R.; Hynes, J. T. Depth-Dependent Dissociation of Nitric Acid at an Aqueous Surface: Car-Parrinello Molecular Dynamics. *J. Phys. Chem. A* **2009**, *113*, 1295–1307.

- 1
2
3 (18) Baer, M. D.; Tobias, D. J.; Mundy, C. J. Investigation of Interfacial and Bulk
4 Dissociation of HBr, HCl, and HNO₃ Using Density Functional Theory-Based
5 Molecular Dynamics Simulations. *J. Phys. Chem. C* **2014**, *118*, 29412–29420.
- 6
7 (19) Oostenbrink, C.; Villa, A.; Mark, A. E.; Van Gunsteren, W. F. A Biomolecular Force
8 Field Based on the Free Enthalpy of Hydration and Solvation: The GROMOS Force-
9 Field Parameter Sets 53A5 and 53A6. *J. Comput. Chem.* **2004**, *25*, 1656–1676.
- 10
11 (20) Otten, D. E.; Onorato, R.; Michaels, R.; Goodknight, J.; Saykally, R. J. Strong Surface
12 Adsorption of Aqueous Sodium Nitrite as an Ion Pair. *Chem. Phys. Lett.* **2012**, *519–*
13 *520*, 45–48.
- 14
15 (21) Frenkel, D.; Smit, B. *Understanding Molecular Simulation: From Algorithms to*
16 *Applications*; Academic Press: San Diego, 2001.
- 17
18 (22) van Der Spoel, D.; Lindahl, E.; Hess, B.; Groenhof, G.; Mark, A. E.; Berendsen, H. J.
19 C. GROMACS: Fast, Flexible, and Free. *J. Comput. Chem.* **2005**, *26*, 1701–1718.
- 20
21 (23) Hess, B.; Kutzner, C.; van Der Spoel, D.; Lindahl, E. GROMACS 4: Algorithms for
22 Highly Efficient, Load-balanced, and Scalable Molecular Simulation. *J. Chem. Theory*
23 *Comput.* **2008**, *4*, 435–447.
- 24
25 (24) Jayaraman, S.; Thompson, A. P.; von Lilienfeld, O. A.; Maginn, E. J. Molecular
26 Simulation of the Thermal and Transport Properties of Three Alkali Nitrate Salts. *Ind.*
27 *Eng. Chem. Res.* **2010**, *49*, 559–571.
- 28
29 (25) Ohkubo, T.; Ohnishi, R.; Sarou-Kanian, V.; Bessada, C.; Iwadate, Y. Molecular
30 Dynamics Simulations of the Thermal and Transport Properties of Molten NaNO₂–
31 NaNO₃ Systems. *Electrochemistry* **2018**, *86*, 104–108.
- 32
33 (26) McGraw, G. E.; Bernitt, D. L.; Hisatsune, I. C. Vibrational Spectra of Isotopic Nitric
34 Acids. *J. Chem. Phys.* **1965**, *42*, 237–244.
- 35
36 (27) Perrin, A. Recent Progress in the Analysis of HNO₃ Spectra. *Spectrochim. Acta Part*
37 *A Mol. Biomol. Spectrosc.* **1998**, *54*, 375–393.
- 38
39 (28) Murto, J.; Räsänen, M.; Aspiala, A.; Lotta, T. Ab Initio Calculations on HONO:
40 Energies, Geometries and Force Fields on Different Levels of Theory. *J. Mol. Struct.*
41 *THEOCHEM* **1985**, *122*, 213–224.
- 42
43 (29) McGraw, G. E.; Bernitt, D. L.; Hisatsune, I. C. Infrared Spectra of Isotopic Nitrous
44 Acids. *J. Chem. Phys.* **1966**, *45*, 1392–1399.
- 45
46 (30) Varma, R.; Curl, R. F. Study of the Dinitrogen Trioxide-Water-Nitrous Acid
47 Equilibrium by Intensity Measurements in Microwave Spectroscopy. *J. Phys. Chem.*
48 **1976**, *80*, 402–409.
- 49
50 (31) Shirk, A. E.; Shirk, J. S. Isomerization of HONO in Solid Nitrogen by Selective
51 Vibrational Excitation. *Chem. Phys. Lett.* **1983**, *97*, 549–552.
- 52
53 (32) Cordeiro, R. M. Reactive Oxygen Species at Phospholipid Bilayers: Distribution,
54 Mobility and Permeation. *Biochim. Biophys. Acta, Biomembr.* **2014**, *1838*, 438–444.
- 55
56 (33) Cordeiro, R. M. Reactive Oxygen and Nitrogen Species at Phospholipid Bilayers:
57 Peroxynitrous Acid and Its Homolysis Products. *J. Phys. Chem. B* **2018**, *122*, 8211–
58 8219.
- 59
60 (34) Frisch, M. J. *et al.*, Gaussian 09, Gaussian Inc., Wallingford, CT, 2009.
- (35) Jämbeck, J. P. M.; Lyubartsev, A. P. Exploring the Free Energy Landscape of Solutes
Embedded in Lipid Bilayers. *J. Phys. Chem. Lett.* **2013**, *4*, 1781–1787.

- 1
2
3 (36) Vchirawongkwin, S.; Kritayakornupong, C.; Tongraar, A.; Vchirawongkwin, V.
4 Hydration Properties Determining the Reactivity of Nitrite in Aqueous Solution. *Dalt.*
5 *Trans.* **2014**, *43*, 12164–12174.
6
7 (37) Kameda, Y.; Arakawa, H.; Hangai, K.; Uemura, O. The Structure around the Nitrite
8 Ion in Concentrated Aqueous Solutions. *Bull. Chem. Soc. Jpn.* **1992**, *65*, 2154–2156.
9
10 (38) Ohtaki, H.; Radnai, T. Structure and Dynamics of Hydrated Ions. *Chem. Rev.* **1993**,
11 *93*, 1157–1204.
12
13 (39) Reynolds, J. G.; Mauss, B. M.; Daniel, R. C. The Relative Viscosity of NaNO₃ and
14 NaNO₂ Aqueous Solutions. *J. Mol. Liq.* **2018**, *264*, 110–114.
15
16 (40) *CRC Handbook of Chemistry and Physics*, 84th ed.; Lide, D. R., Ed.; CRC Press, 2004.
17
18 (41) Smith, J. W.; Lam, R. K.; Shih, O.; Rizzuto, A. M.; Prendergast, D.; Saykally, R. J.
19 Properties of Aqueous Nitrate and Nitrite from X-Ray Absorption Spectroscopy. *J.*
20 *Chem. Phys.* **2015**, *143*, 084503.
21
22 (42) Riddell, J. D.; Lockwood, D. J.; Irish, D. E. Ion Pair Formation in NaNO₃/D₂O
23 Solutions: Raman and Infrared Spectra, Partial Molal Volumes, Conductance, and
24 Viscosity. *Can. J. Chem.* **1972**, *50*, 2951–2962.
25
26 (43) Schmid, N.; Eichenberger, A. P.; Choutko, A.; Riniker, S.; Winger, M.; Mark, A. E.;
27 van Gunsteren, W. F. Definition and Testing of the GROMOS Force-Field Versions
28 54A7 and 54B7. *Eur. Biophys. J.* **2011**, *40*, 843–856.
29
30 (44) Cordeiro, R. M. Molecular Dynamics Simulations of the Transport of Reactive
31 Oxygen Species by Mammalian and Plant Aquaporins. *Biochim. Biophys. Acta, Gen.*
32 *Subj.* **2015**, *1850*, 1786–1794.
33
34 (45) Razzokov, J.; Yusupov, M.; Cordeiro, R. M.; Bogaerts, A. Atomic Scale
35 Understanding of the Permeation of Plasma Species across Native and Oxidized
36 Membranes. *J. Phys. D. Appl. Phys.* **2018**, *51*, 365203.
37
38 (46) *Perry's Chemical Engineers' Handbook*, 7th ed.; Perry, R. H., Green, D. W., Maloney,
39 J. O.; McGraw-Hill.
40
41 (47) Schwartz, S. E.; White, W. H. Solubility Equilibria of the Nitrogen Oxides and
42 Oxyacids in Dilute Aqueous Solution. In: *Advances in Environmental Science and*
43 *Engineering*; Pfafflin, J. R., Ziegler, E. N., Eds; Gordon and Breach Science
44 Publishers: New York, 1981; Vol. 4, pp 1–45.
45
46 (48) Sander, R. Compilation of Henry's Law Constants (version 4.0) for Water as Solvent.
47 *Atmos. Chem. Phys.* **2015**, *15*, 4399–4981.
48
49 (49) Minofar, B.; Vácha, R.; Wahab, A.; Mahiuddin, S.; Kunz, W.; Jungwirth, P.
50 Propensity for the Air/Water Interface and Ion Pairing in Magnesium Acetate vs
51 Magnesium Nitrate Solutions: Molecular Dynamics Simulations and Surface Tension
52 Measurements. *J. Phys. Chem. B* **2006**, *110*, 15939–15944.
53
54 (50) Thomas, J. L.; Roeselová, M.; Dang, L. X.; Tobias, D. J. Molecular Dynamics
55 Simulations of the Solution–Air Interface of Aqueous Sodium Nitrate. *J. Phys. Chem.*
56 *A* **2007**, *111*, 3091–3098.
57
58 (51) Hub, J. S.; Wolf, M. G.; Caleman, C.; van Maaren, P. J.; Groenhof, G.; van der Spoel,
59 D. Thermodynamics of Hydronium and Hydroxide Surface Solvation. *Chem. Sci.*
60 **2014**, *5*, 1745–1749.
(52) Wren, S. N.; Donaldson, D. J. Glancing-Angle Raman Study of Nitrate and Nitric
Acid at the Air–aqueous Interface. *Chem. Phys. Lett.* **2012**, *522*, 1–10.

- 1
2
3 (53) Duan, J.; Gan, L.; Nie, L.; Sun, F.; Lu, X.; He, G. On the Penetration of Reactive
4 Oxygen and Nitrogen Species Generated by a Plasma Jet into and through Mice Skin
5 with/without Stratum Corneum. *Phys. Plasmas* **2019**, *26*, 043504.
6
7 (54) Lundberg, J. O.; Weitzberg, E.; Gladwin, M. T. The Nitrate–nitrite–nitric Oxide
8 Pathway in Physiology and Therapeutics. *Nat. Rev. Drug Discov.* **2008**, *7*, 156–167.
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Table 1. Properties of nitrogen oxyanions and oxyacids.^a

Compound	concentration ^b	ρ (kg/m ³)	ΔH_{vap} (kJ/mol)	ΔG_{hyd} (kJ/mol)	n_{hyd}	D (10 ⁻⁹ m ² /s)	refs.
NO ₃ ⁻	dil				7.5	3.0 [1.902]	40
	1 mol/L				7.5		
	4.4 mol/L	1199 [1206]			7.4 [5.0]		5,39
NO ₂ ⁻	dil				7.1	2.7 [1.912]	40
	4.7 mol/L	1219 [1209]			6.7 [3.7]		37,39
HNO ₃	pure	1390 [1504]	41.0 [39.1]				40,46
	dil			-37.8 [-38]			47,48
<i>trans</i> -HNO ₂	dil			-18.0			
<i>cis</i> -HNO ₂	dil			-11.2			
HNO ₂	dil			-17.1 ^c [-17.6]			47,48

^a Density (ρ), heat of vaporization (ΔH_{vap}), hydration free energy (ΔG_{hyd}), hydration number (n_{hyd}) and diffusion coefficient (D). Simulation results are presented along with reference experimental data within brackets. Uncertainties in the last digits. ^b The entry *dil* stays for “infinitely dilute”. ^c Weighted average between conformers, according to eq 1.

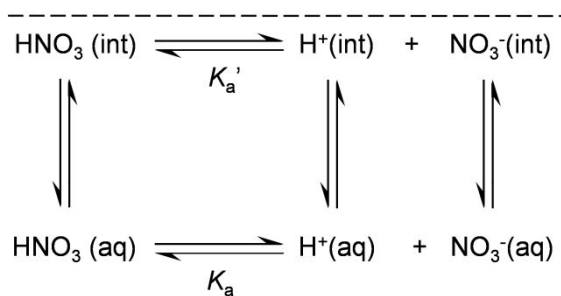
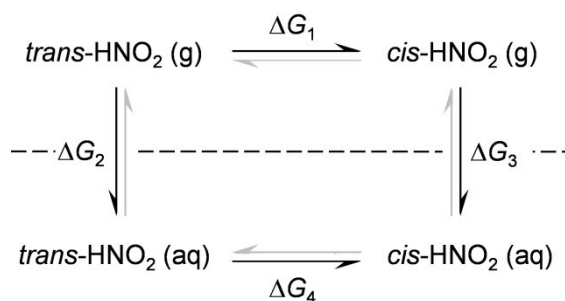
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
a)**b)**

Figure 1. (a) Thermodynamic cycle relating local changes in the ionization constant (K_a) of HNO_3 with the partitioning of the involved species between the aqueous bulk (aq) and the water/air interface (int , dashed line). (b) Thermodynamic cycle relating the hydration of HNO_2 conformers and isomerization at the gas (g) and aqueous phases. Free energy variations ΔG_1 refer to processes occurring in the direction of the darker arrows.

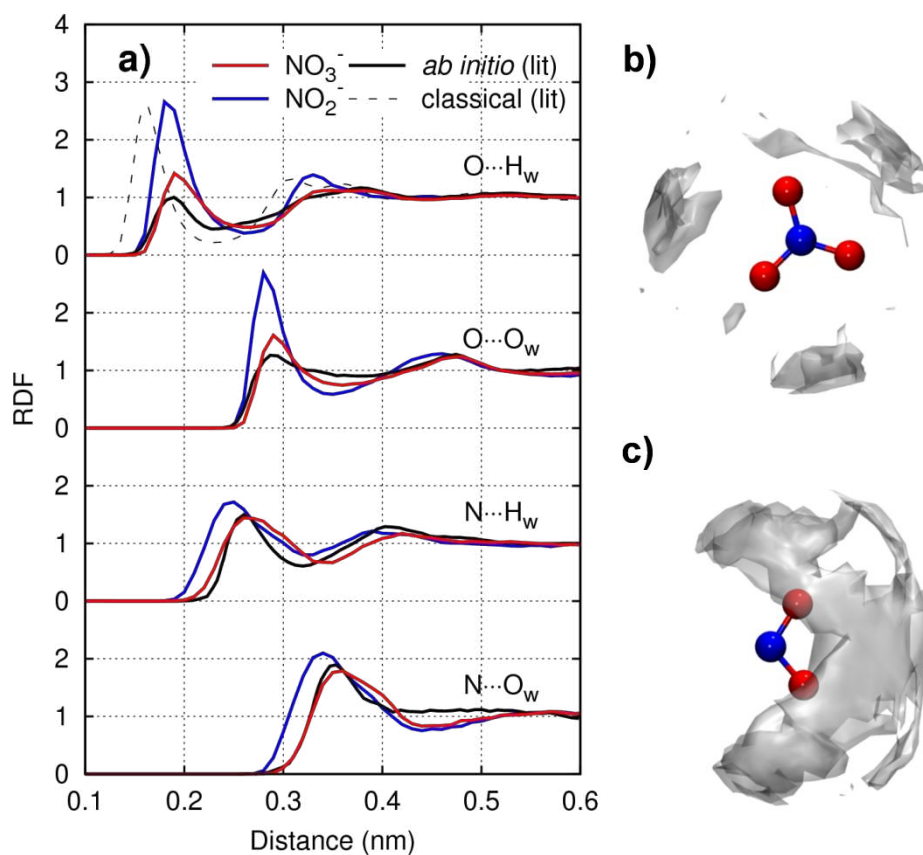


Figure 2. Hydration structure of nitrogen oxyanions at infinite dilution. (a) Ion-water radial distribution functions for NO₃⁻ (red) and NO₂⁻ (blue), as obtained from our molecular dynamics simulations. Results are compared to *ab initio* (black) and classical (dashed) simulations of NO₃⁻ from the literature (*lit*).¹⁰ Three-dimensional spatial distribution of hydrating waters around (b) NO₃⁻ and (c) NO₂⁻. The grey surfaces enclose regions where the local water density was at least 2.5 times higher than in the bulk.

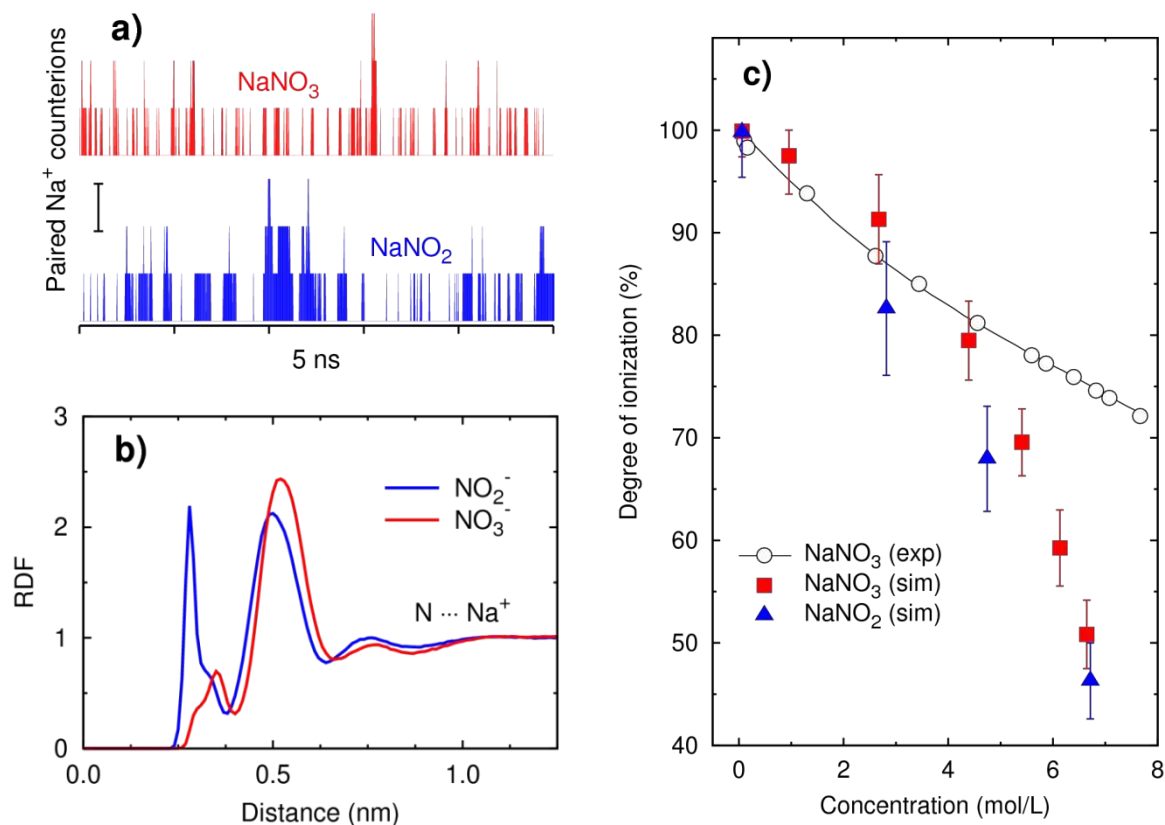


Figure 3. Ion pairing in aqueous solutions of nitrogen oxyanions. (a) 5-ns trajectory excerpts for selected NO₃⁻ and NO₂⁻ anions, showing the temporal fluctuations in the number of paired Na⁺ counterions. The vertical bar indicates the unity scale of the ordinate (i.e. one ion pair). (b) Ion-ion radial distribution functions at the high-concentration regime. (c) Degrees of ionization at several concentrations, as compared to experimental data from the literature for NaNO₃.⁴²

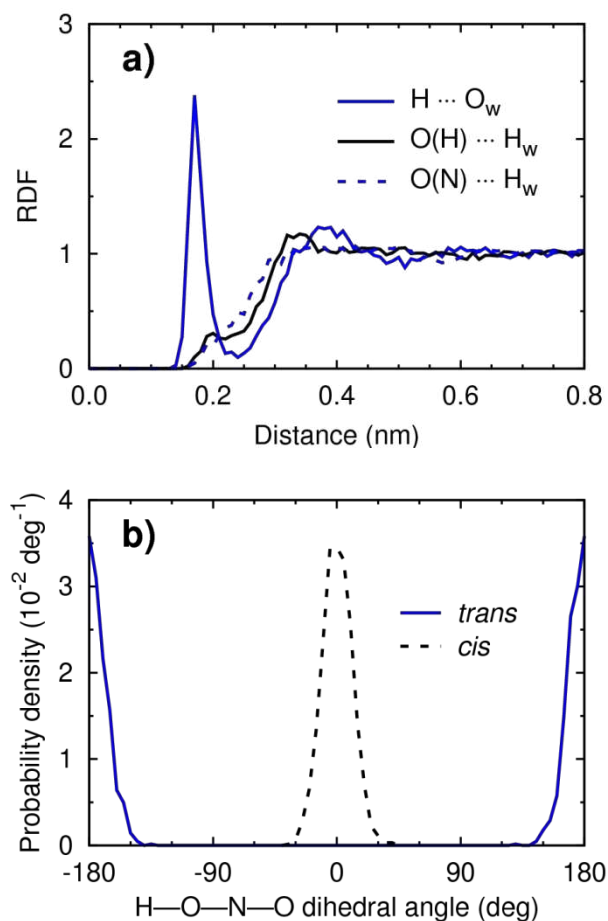


Figure 4. Hydration structure and conformational behavior of HNO₂. (a) Radial distribution functions of hydrating waters around *trans*-HNO₂. (b) Sampling of the conformational space by *cis*- and *trans*-HNO₂ during 5 ns simulations in aqueous solution.

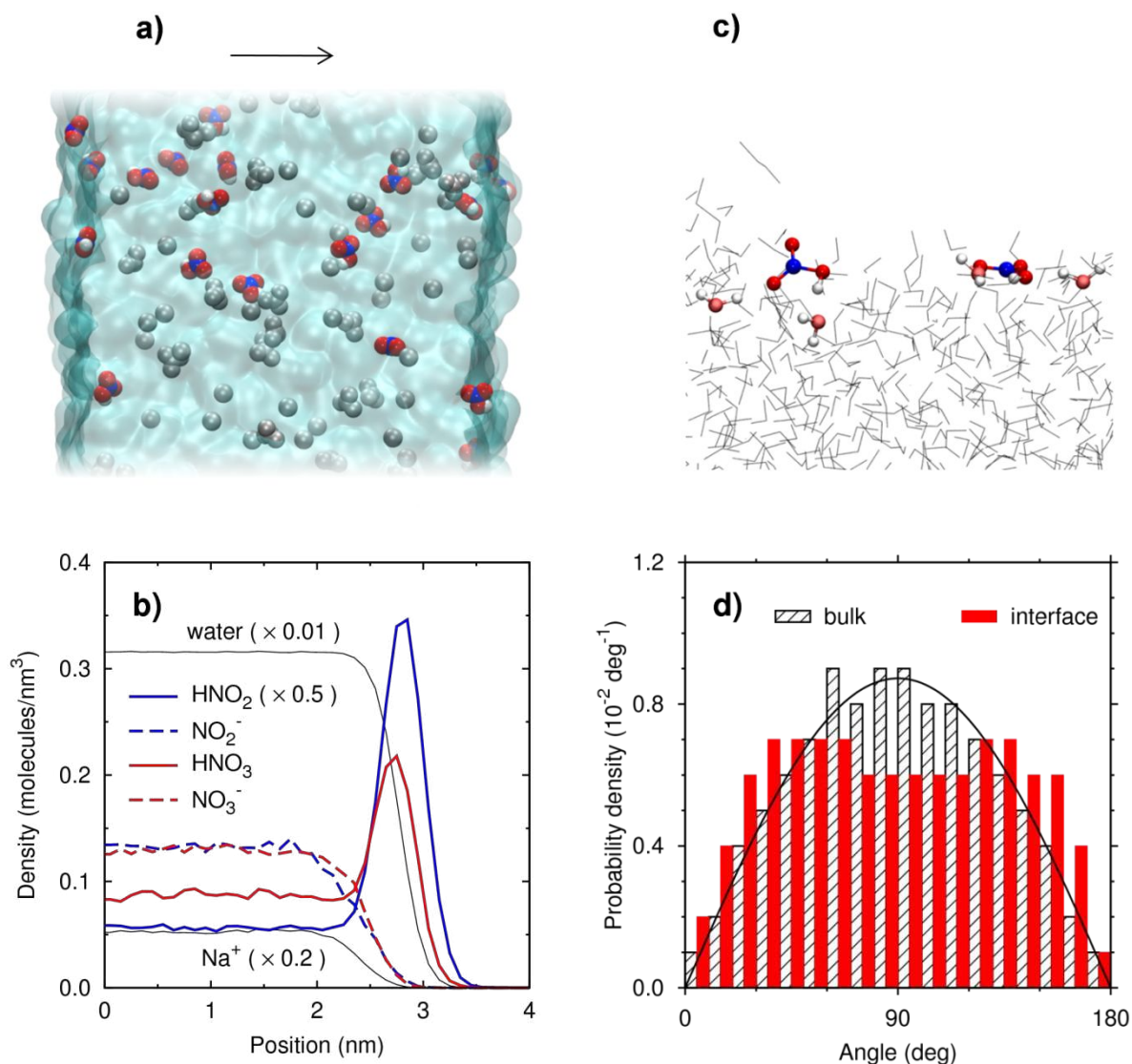


Figure 5. Interfacial behavior of nitrogen oxyanions and oxyacids. (a) Image of the equilibrated water slab (blue region), with NO_3^- and Na^+ represented as grey van der Waals spheres and HNO_3 highlighted in color (white H, red O, blue N). The arrow points to the surface normal direction. (b) Local concentrations as function of the distance from the slab center. Some distributions were scaled by the factors within brackets for better visualization. (c) Detailed image of two interfacial HNO_3 molecules with H-bonded hydration waters. (d) Local distributions of the relative angle between the normal vectors of the HNO_3 molecular plane and the interface plane. The black line represents a theoretical random distribution.

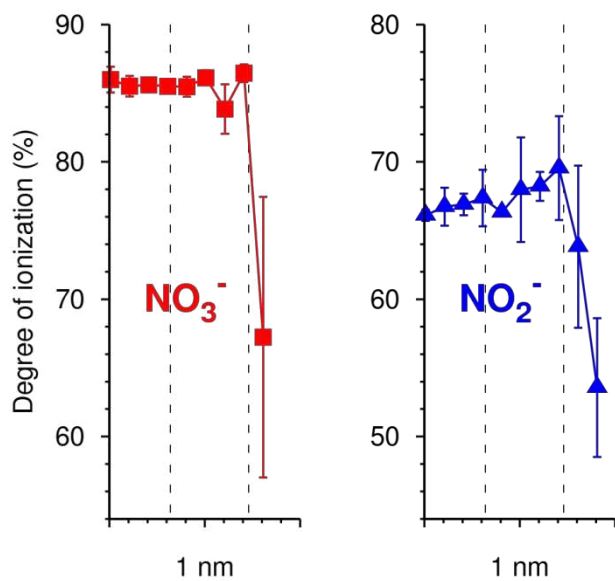
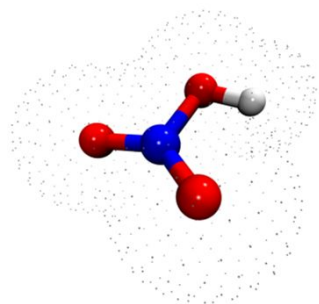


Figure 6. Ion pairing of nitrogen oxyanions within a 1-nm-thick region at the water/air interface of a concentrated solution. Vertical dashed lines indicate the region where the water density drops from 90% to 10% of its bulk value. Error bars were estimated based on the variation of the results among both surfaces of the water slab.

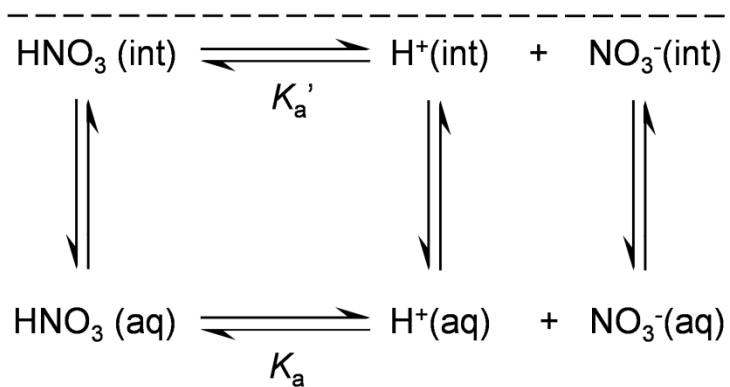
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

TOC GRAPHIC

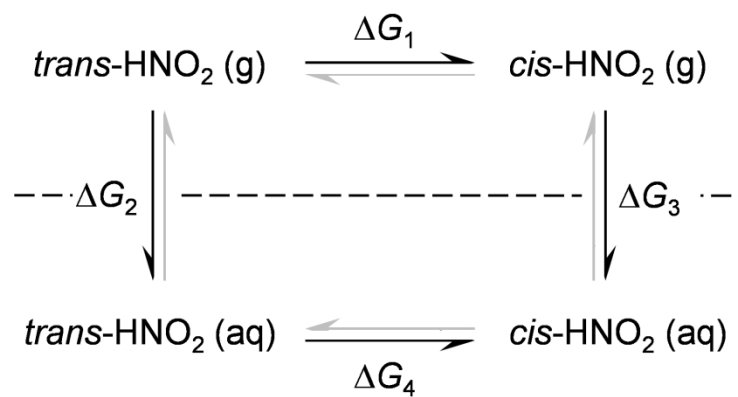


1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

a)

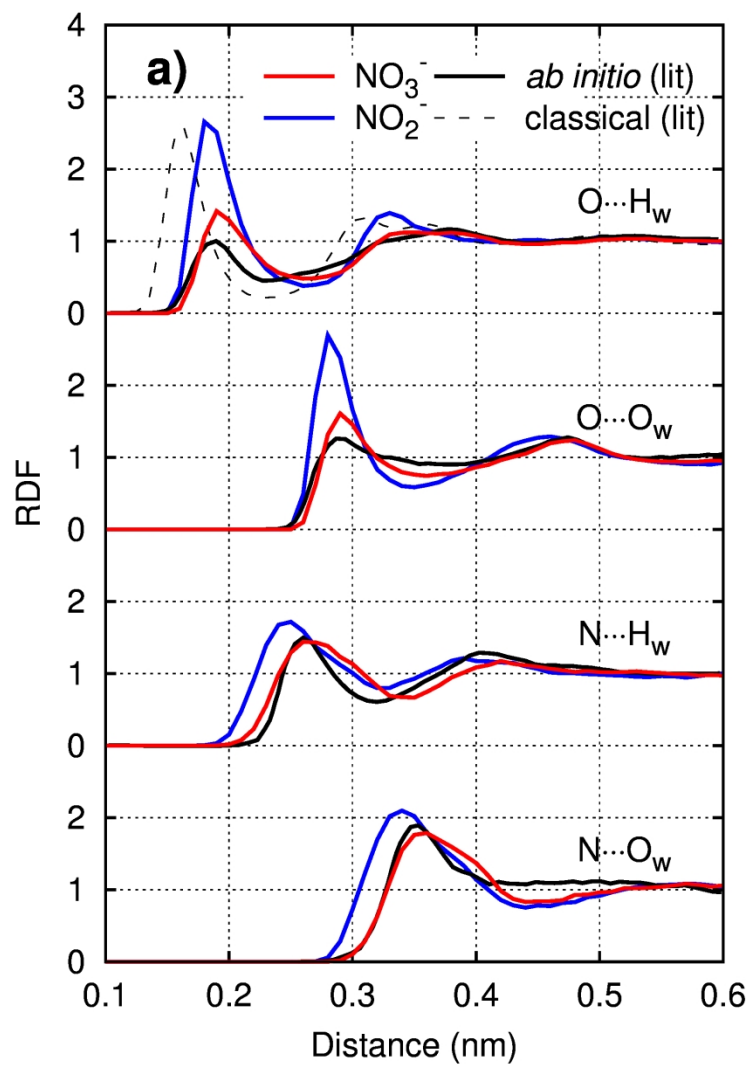


b)



Figure_1

83x120mm (600 x 600 DPI)

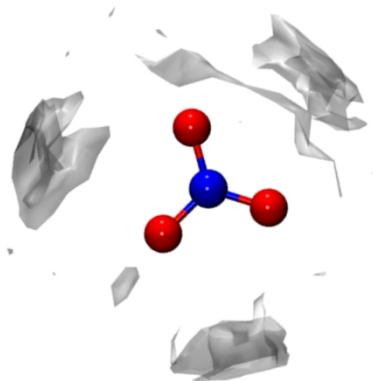


Figure_2a

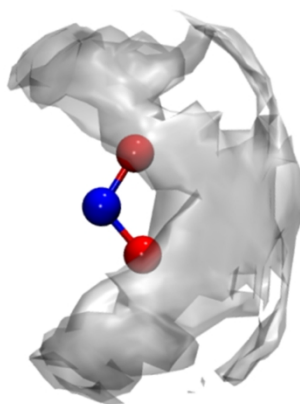
83x127mm (600 x 600 DPI)

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

b)

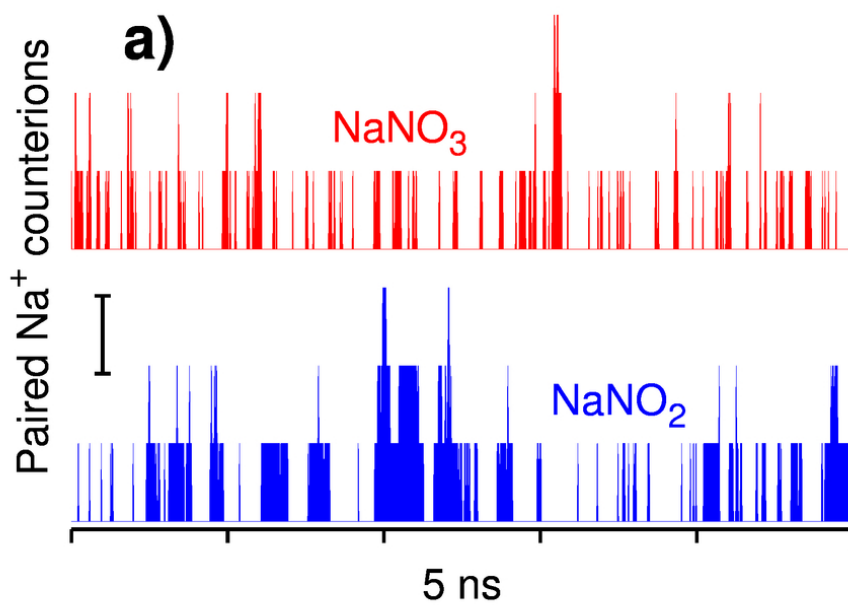


c)



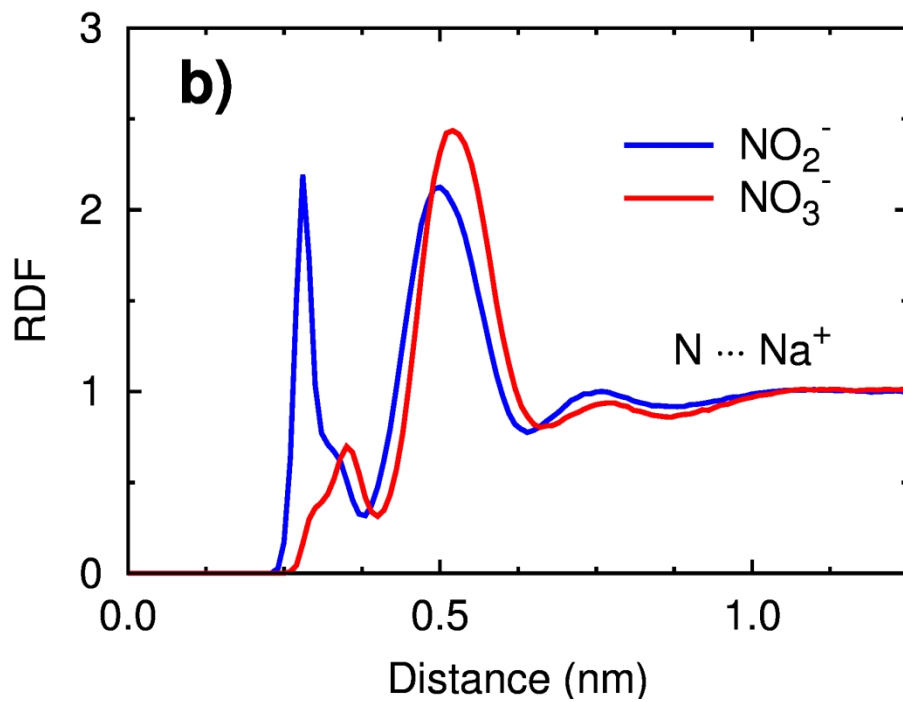
Figure_2bc

49x127mm (600 x 600 DPI)



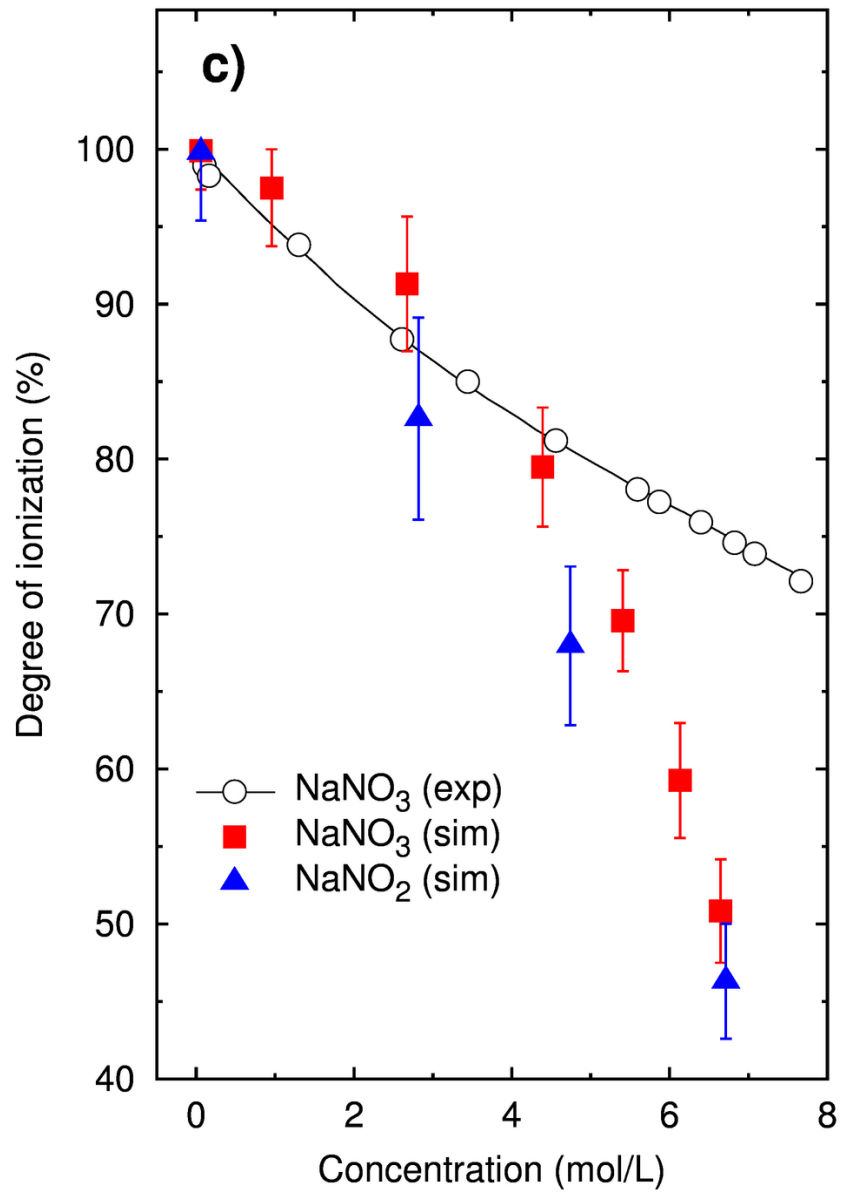
Figure_3a_revised

83x58mm (300 x 300 DPI)



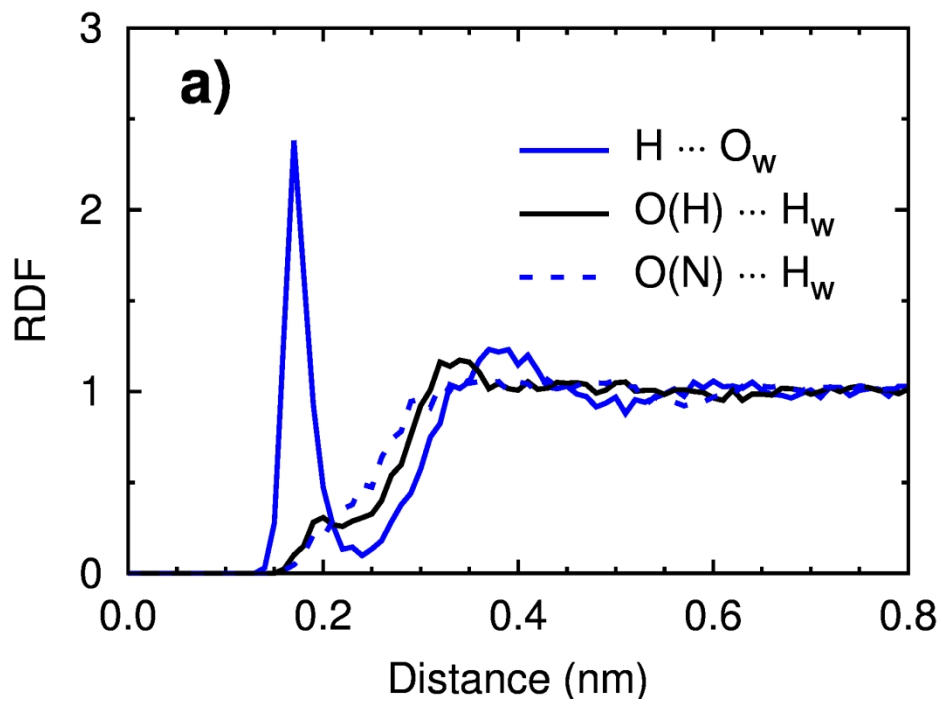
Figure_3b

83x58mm (600 x 600 DPI)



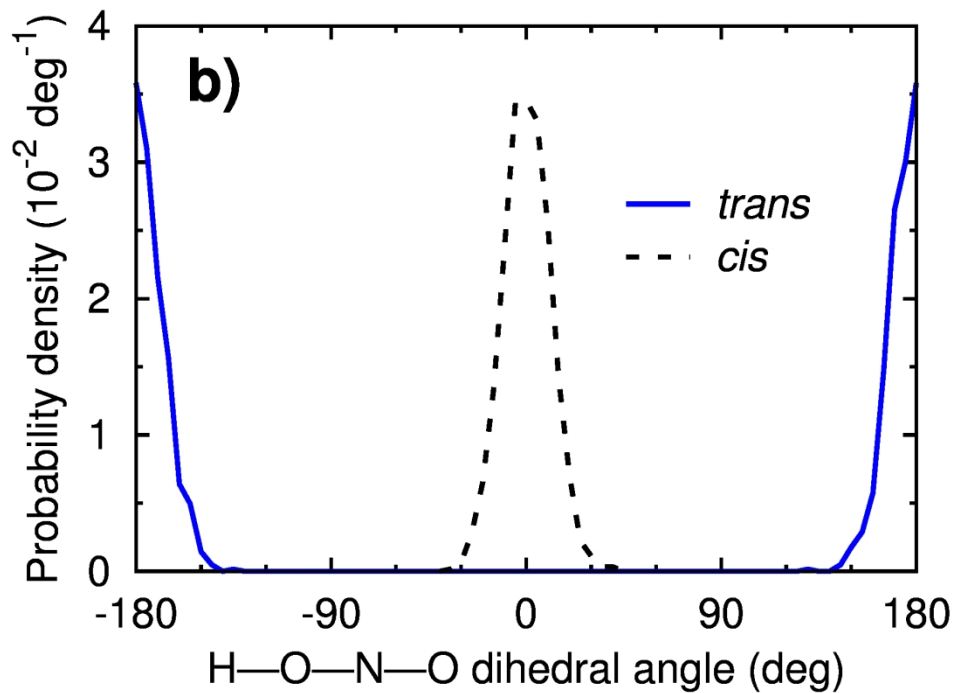
Figure_3c_revised

83x116mm (300 x 300 DPI)



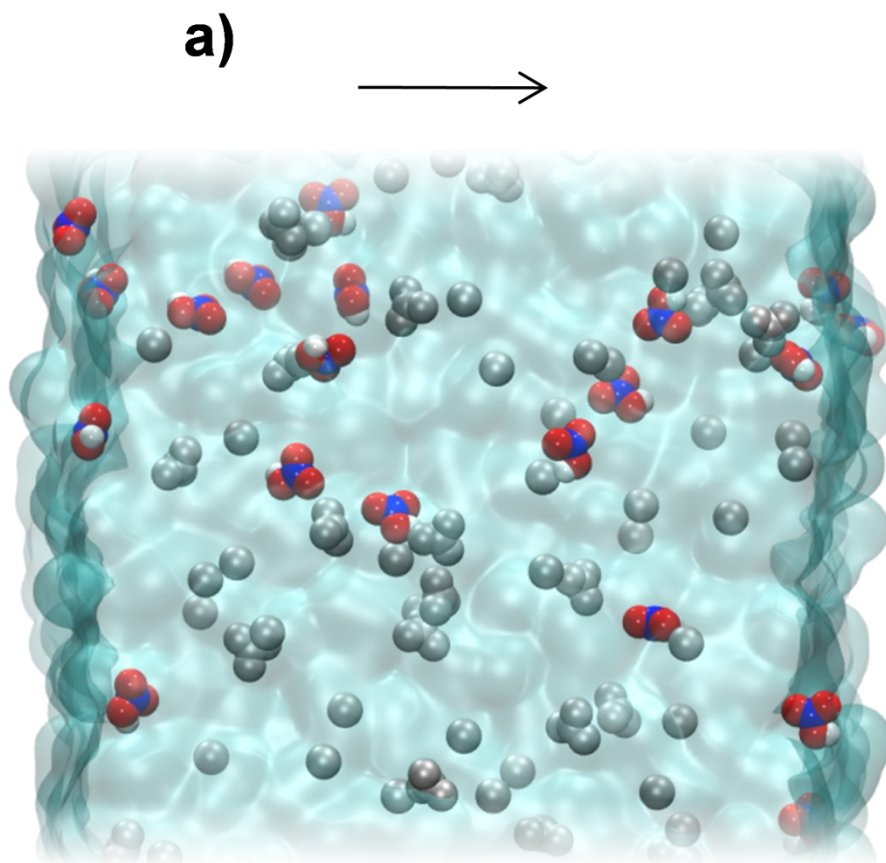
Figure_4a

83x58mm (600 x 600 DPI)



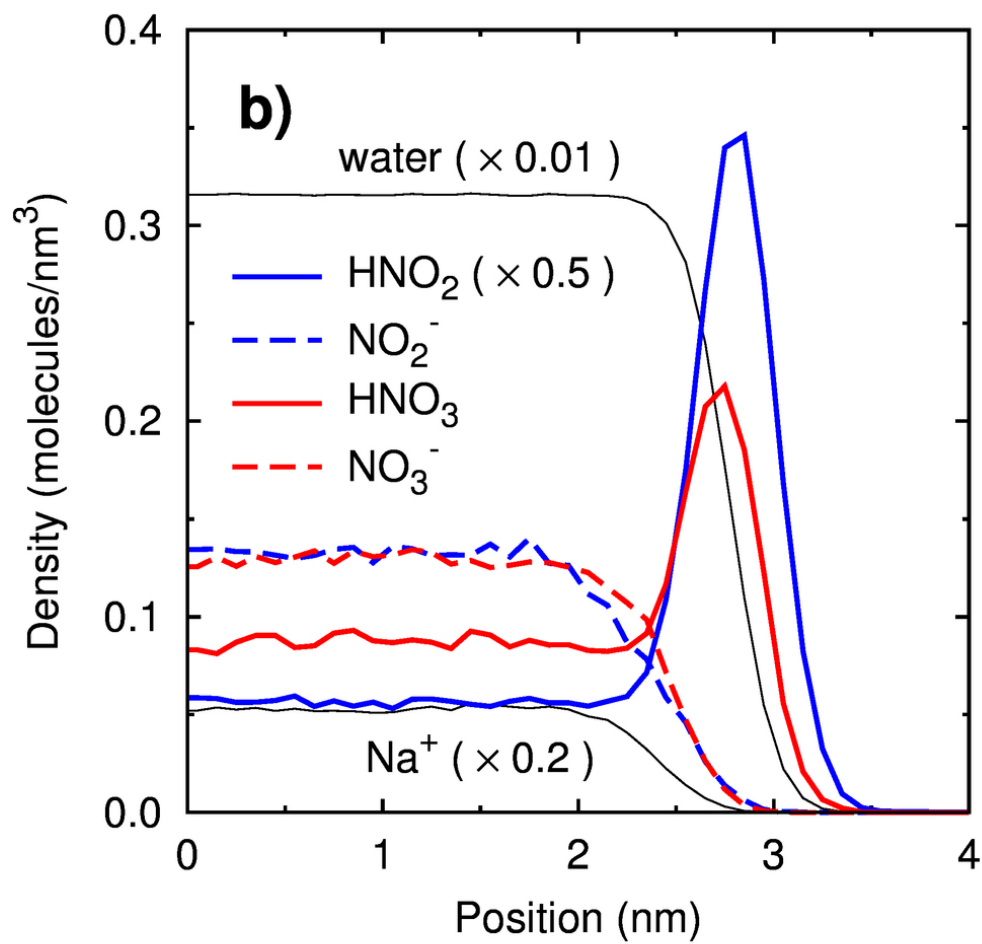
Figure_4b

83x58mm (600 x 600 DPI)



Figure_5a

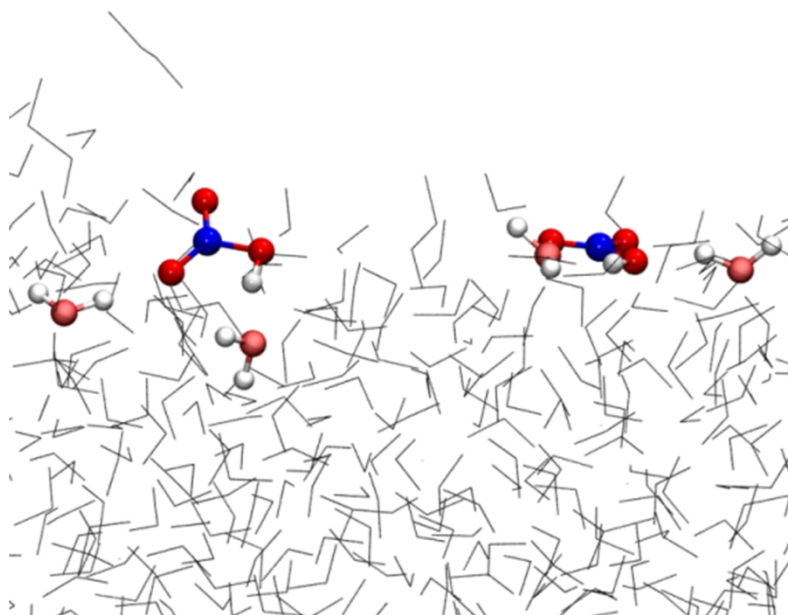
83x83mm (600 x 600 DPI)



Figure_5b_revised

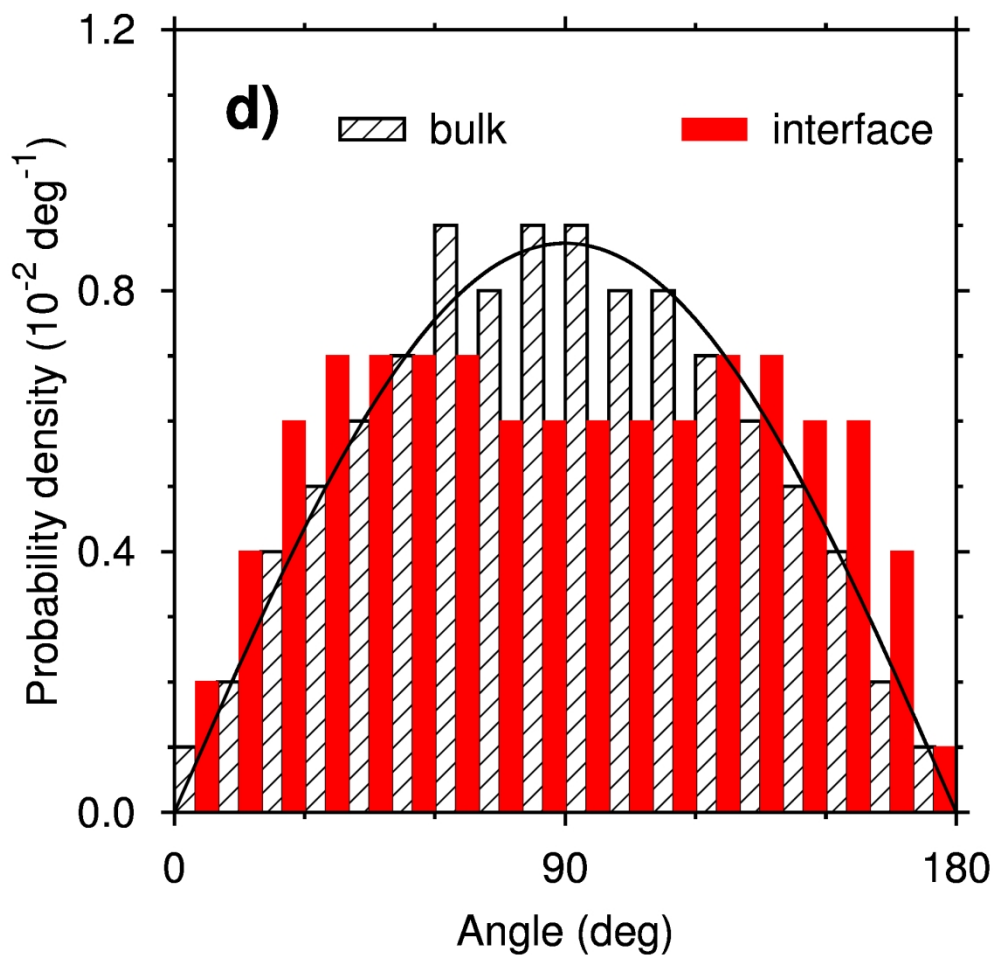
83x83mm (300 x 300 DPI)

1
2
3
4
5
6
7
8
9
10 **c)**
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60



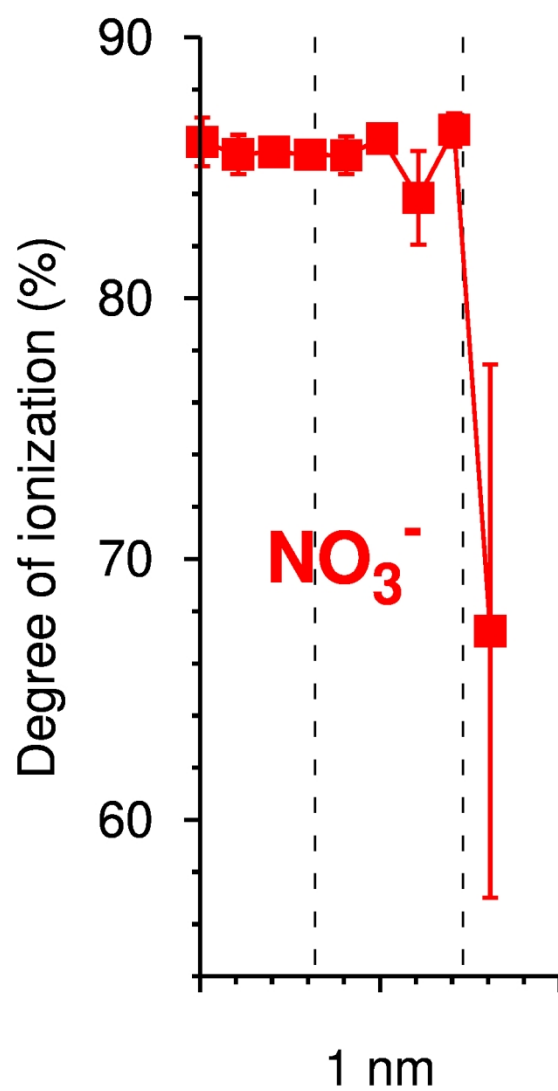
Figure_5c

83x83mm (600 x 600 DPI)



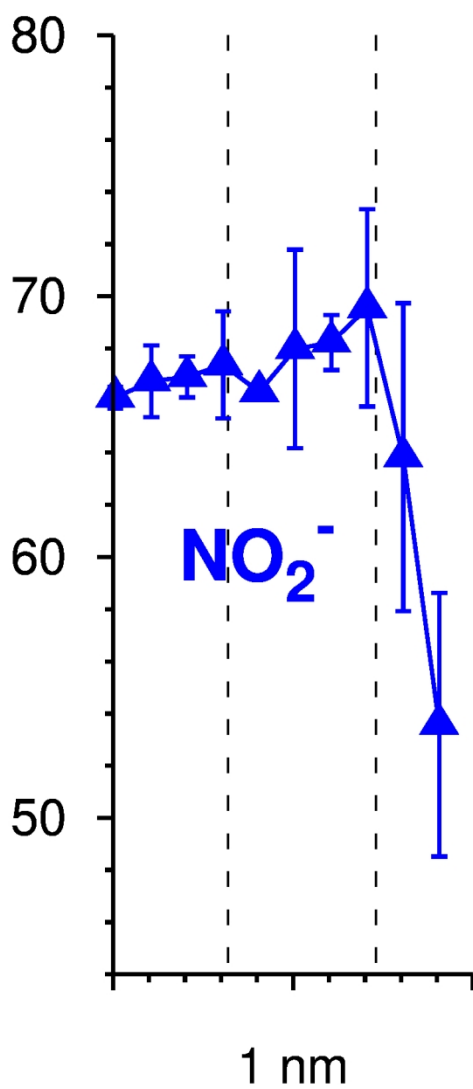
Figure_5d

83x83mm (600 x 600 DPI)



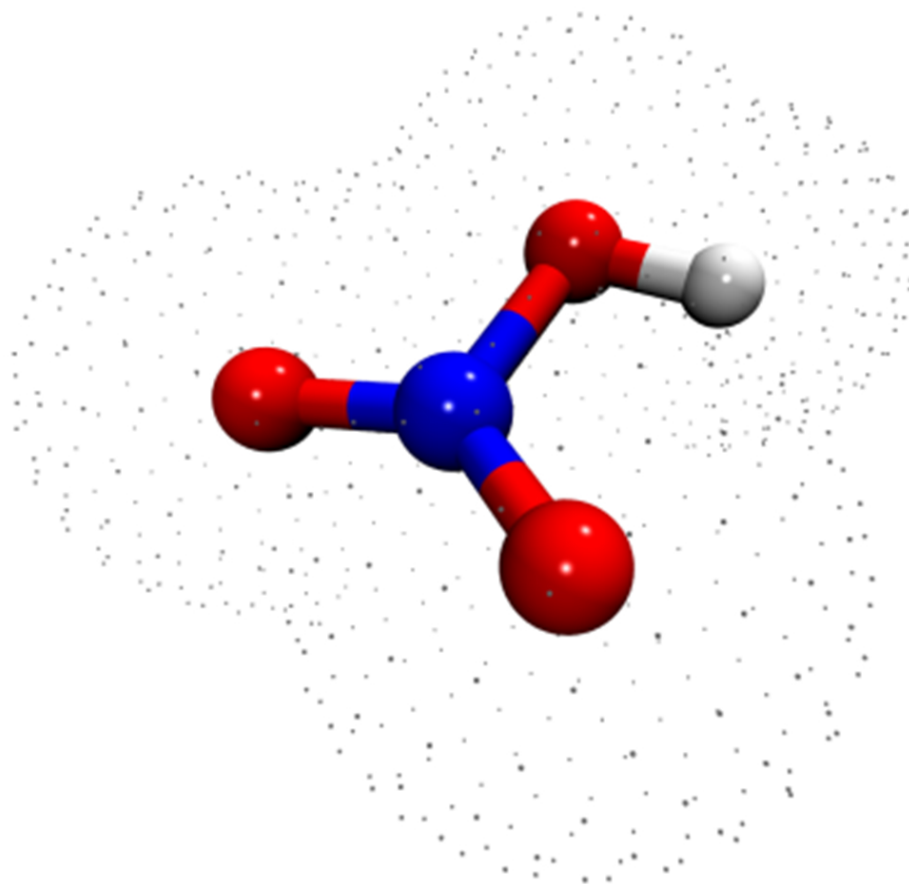
Figure_6a

41x83mm (600 x 600 DPI)



Figure_6b

41x83mm (600 x 600 DPI)



Graphical_abstract

44x44mm (600 x 600 DPI)