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Introduction:
In this work we report on Car-Parrinello[1] simulations of the divalent calcium ion in water, aimed at understanding the structure of the hydration shell and at comparing theoretical results with a series of recent experiments. Our paper shows some of the progress in the investigation of aqueous solutions brought about by the advent of *ab initio* molecular dynamics and highlights the importance of accessing subtle details of ion-water interactions from first-principles.

Calcium plays a vital role in many biological systems, including signal transduction, blood clotting and cell division. In particular, calcium ions are known to interact strongly with proteins as they tend to bind well to both negatively charged (*e.g.* in aspartate and glutamate) and uncharged oxygens (*e.g.* in main-chain carbonyls).[2, 3] The ability of calcium to coordinate multiple ligands (from 6 to 8 oxygen atoms) with an asymmetric coordination shell enables it to cross-link different segments of a protein and induce large conformational changes. The great biochemical importance of the calcium ion has led to a number of studies to determine its hydration shell and its preferred coordination number in water.

Experimental studies have used a variety of techniques, including XRD,[4-6] EXAFS,[7, 8] and neutron diffraction[9, 10] to elucidate the coordination of Ca^{2+} in water. The range of coordination numbers (n_C) inferred by X-ray diffraction studies varies from 6 to 8, and is consistent with that reported in EXAFS experiments (8[7] and 7.2[8]). A wider range of values (6 to 10) was found in early neutron diffraction studies,[9] depending on concentration, while a more recent measurement by Badyal, *et al.* reports a value close to 7.[10]

In addition to experimental measurements, many theoretical studies have been carried out to investigate the solvation of Ca^{2+} in water and have also reported a wide range of coordination numbers. Most of the classical molecular dynamics (MD)[4, 7, 11] and QM/MM simulations[12, 13] report n_C in the range of 8 to 10; in general, n_C appears to be highly sensitive to the choice of the ion-water potential used in the calculations.[11] Even *ab initio* MD simulations have so far obtained conflicting values for n_C. For the structure of the first salvation shell Naor, *et al*. found n_C = 7 to 8 and a Ca^{2+} - oxygen average distance ($r_{Ca\text{-}O}$) of 2.64 Å,[14] while Bakó, *et al*. found n_C = 6 and $r_{Ca\text{-}O}$ = 2.45 Å.[15]

In view of the existing controversies, we have carried out extensive Car-Parrinello[1, 16] simulations of Ca^{2+} solvation in water, using both a rigid and a flexible water model, up to time scales of 40 ps. Our simulations show variations of coordination numbers from 6, 7 and 8 occurring over intervals of ~ 0.3/0.4 exchanges/ps, and yielding average coordination numbers of 6.2 and 7 for flexible and rigid water models, respectively. These results are consistent with those reported in recent EXAFS[8] and neutron diffraction[10] experiments. In addition, our calculations show an asymmetric coordination of Ca^{2+} to oxygen, similar to the case of Mg^{2+}.[17]

Computational Methods

We used simulation cells with 60 water molecules and a Ca^{2+} ion. The electronic structure was described within density functional theory (DFT) with the Perdew-Burke-Ernzerhof (PBE) generalized gradient approximation.[18] Electron-ion interactions were treated with norm conserving non-local pseudopotentials of the Hamann type,[19] with both $3p^6$ and $4s^2$ electrons treated as Ca valence electrons; the Kohn-Sham orbitals and charge density were expanded in plane waves up to a kinetic energy cutoff of 85 and 340 Ry, respectively.

Three *ab initio* molecular dynamics simulations have been carried out, with different starting configurations generated independently using classical potentials (TIP5P[20] for water) and long simulation runs (200 ps). Two of the simulations (simulations A and B) were carried out with flexible water molecules, using a time step of 0.06 fs, and a fictitious mass parameter of 530 a.u. A third simulation (C) was performed by keeping the intermolecular geometry of the water molecules fixed (rigid water model).[21] By eliminating the high frequency ionic motion, a fictitious mass parameter of 1100 a.u. could be used along with a time step of 0.24 fs.[21]

The initial configurations for simulations A and B were chosen so as to have different coordination numbers for the Ca^{2+} ion. In simulation A, a snapshot from the classical molecular dynamics simulation was selected where seven water molecules surrounded the Ca^{2+}. This snapshot was used as a starting configuration for a ~3 ps *ab initio* molecular dynamics with a weakly-coupled velocity-scaling thermostat set to 300 K. The thermostat was then removed and statistics were collected for an additional 10 ps. The average temperature of simulation A was 285.1 K.

In simulation B, a geometry optimization was first performed for the $[Ca(H_2O)_8]^{2+}$ gas phase cluster, at the BLYP/6-311+G** level of theory. A 200 ps classical molecular dynamics simulation was then performed to equilibrate 52 water molecules around the $[Ca(H_2O)_8]^{2+}$ cluster, while holding its geometry rigid. After a short *ab initio* molecular dynamics equilibration (~ 1 ps) at constant temperature, both the thermostat and the distance constraints were removed and statistics were collected for an additional 6 ps at an average temperature of 289.1 K.

The starting configuration for simulation C was generated by selecting a snapshot ~6 ps into simulation A. All of the intermolecular O-H bond lengths were rescaled to 0.9926 Å and H-O-H angles to 104.6º. A velocity-scaling thermostat was then used to re-equilibrate the system with *ab initio* molecular dynamics at a temperature of 300 K for 2 ps. The thermostat was then removed and statistics were collected for 40 ps at an average temperature of 291.0 K.

Results and Discussion

In Fig. 1, the radial distribution functions (RDFs) $g_{CaO}(r)$ and $g_{CaH}(r)$ obtained in simulations A, B and C are shown. The first peak in $g_{CaO}(r)$ and $g_{CaH}(r)$ are located at 2.43 Å and 3.03 Å, respectively, in the flexible water simulations, and at 2.44 Å and 3.07 Å in the rigid model. Overall the differences between the RDFs obtained in simulations A and

B, and in C are similar to the differences observed in simulations of flexible and rigid water;[21] these differences are rather small, *i.e.* smaller than those reported in recent experimental measurements. For example, neutron diffraction isotopic substitution experiments on a 1 molar solution of $CaCl_2$ in D_2O found the corresponding peaks at 2.46±0.03 Å and 3.07±0.03 Å,[9] and X-ray absorption fine structure (EXAFS) spectroscopy on concentrated $CaCl_2$ solutions obtained Ca-O distances of 2.437±0.010 Å and Ca-H distances of 2.97 Å.[8]

In Fig. 1 we also show the running integration number, $n(r) = \frac{4\pi N}{\Omega} \int_0^r g_{CaX}(r')\, dr'$, where N is the number of oxygen or hydrogen atoms, Ω is the volume of the simulation cell, and X represents oxygen or hydrogen atoms. The value of n(r) at the first minimum of $g_{CaO}(r)$ yields the average number of water molecule in the first solvation shell of the ion, which is 6.2 for simulations A and B, and 7.0 for simulation C. These results are consistent with an average coordination number of 7.2±1.2, as estimated from a recent X-ray absorption fine structure measurement of a 6 molar $CaCl_2$ solution.[8]

Our results on the structure of the first solvation shell around Ca^{2+} are also consistent with those of *ab initio* MD simulations reported by Bako *et al.*,[15] but not with those of Naor, *et al*.[14] Naor, *et al*. report the first peak in $g_{CaO}(r)$ is at a distance of 2.64 to 2.68 Å, depending on the instantaneous value of the ions coordination number, which varied from 7 to 8.[14] The possible reasons for this rather large discrepancy include the smaller system size used by Naor, *et al*. (32 water molecules) and, perhaps more importantly, the use of a valence-only pseudopotential to represent the calcium ion (*i.e.* semicore $3p^6$ states were included in the core). This approximation will most likely lead to large inaccuracies in the description of the cation polarizability. Bako, *et al*. explicitly treated the $3s^2$, $3p^6$ and $4s^2$ electrons of calcium and used a larger simulation cell (54 water molecules) to obtain a first peak in $g_{CaO}(r)$ at 2.45 Å, and a coordination number of six.[15]

An important point to consider regarding the determination of coordination numbers is the dependence on simulation time. In Fig. 2 the variation of the Ca-O distance as a function of time is shown for all water molecules that come within 3.5 Å of Ca^{2+} for the rigid water simulation C (a similar analysis for simulations A and B can be found in the supplemental material). Inspection of Fig. 2 reveals that exchanges of water molecules between the first and second solvation shells occur at a rate of approximately 0.4 exchanges/ps with instantaneous values of the coordination number switching between six, seven and eight. In simulations A and B, a slightly slower rate of 0.3 exchanges/ps is found. However, given the limited simulation times achieved in the flexible water simulations (~10 ps), and the slight differences in simulation temperatures, the difference in observed exchange rates is not likely to be significant.

In order to quantify the orientation of the first solvation shell water molecules, one can compute the so-called water tilt angle, defined as the angle between the molecular dipole moment vector of each molecule and a vector between the ion and the water's oxygen atom (see the inset in Fig. 3). If we assume an intermolecular water geometry with r_{OH}=1

Å and ∠HOH=105° and use the first peak of the RDFs in Fig. 1 as is often done in the analysis of experimental data, we find a tilt angle of 39.7°, as compared to 38° for the neutron diffraction data reported by Hewish, *et al*.[9] However, having direct access to the atomic coordinates in our simulation, the probability distribution of the first solvation shell water tilt angles can be computed directly; this turns out to be 40.1°, in good agreement with the estimate obtained above. In Fig. 3 we show the range of observed water tilt angles, which is rather broad, and spans a range of 0° to 90°. Such a broad distribution is often attributed to simple thermal fluctuations causing a "wagging" motion of the oxygen-hydrogen intramolecular bonds. However, it is interesting to note that the curve displayed in Fig. 3 has a broad shoulder at approximately 50°, and is not well represented by a simple exponentially decaying function. As pointed out by Lightstone, *et al*. in the case of Mg^{2+},[17] it is possible that in addition to thermal fluctuations, the water tilt angle distribution is slightly influenced by the lone-pair electrons on the waters oxygen atom.

In order to examine if a similar lone-pair effect occurs around Ca^{2+}, a localized orbital analysis was performed using maximally localized Wannier functions (MLWFs).[22, 23] The MLWFs are localized orbitals similar to Boys orbitals often used in quantum chemistry.[24] Within the pseudopotential approximation used here, each water molecule has eight valence electrons and four doubly occupied MLWFs. Two of the MLWFs correspond to the OH covalent bonds, and the remaining two to the lone-pair orbitals on the oxygen atom. In Fig. 4, the radial distribution functions between oxygen and the four nearest MLWF centroids are shown for the flexible water simulation A and the rigid water simulation C. The solid line is the distribution collected for the first solvation shell water molecules, and the dashed line is for the remaining "bulk" water molecules. We see that the covalent bond distributions are very similar in the first shell and in bulk water. However, the distribution for the oxygen lone-pair MLWFs for the first shell water molecules clearly exhibits a bimodal character (with two peaks centered at 0.305 Å and 0.342 Å in simulation A), while the bulk water molecules distribution consists of a single peak. The splitting of the lone-pair distribution is similar to the case of Mg^{2+}, where the first shell water molecules were found to asymmetrically coordinate the cation through a single lone-pair orbital.[17]

We have also analyzed the probability distribution of the water dipole moments[17, 25] for both the first solvation shell and the water molecules outside of the first solvation shell, which we refer to as "bulk" water. In simulation A, the bulk water dipole moment distribution is peaked at 3.19 D and has a rather long tail extending to moments of up to 4.5 D. In simulation C, the bulk water distribution is peaked at 3.12 D and extends over a smaller range than in the flexible water simulation, which is consistent with previous simulations of pure water.[21] The dipole moment distributions for the first solvation shell water molecules are increased relative to the bulk by ~0.2 D in both simulations A and C. A larger shift of ~0.4 D has been observed in previous first principle simulations of Ca^{2+} in flexible water.[15]

The first solvation shell water molecules are primarily oriented so that the oxygen atoms coordinate to the Ca^{2+} and the hydrogen atoms point away; therefore, the hydrogen atoms

from this shell should be available to form hydrogen bonds, although the first solvation shell oxygen atoms will be limited in their ability to participate in hydrogen bonding. In order to quantify this effect, we have adopted a set of geometric criteria to identify hydrogen bonds in our simulations. Two water molecules are hydrogen bonded when their oxygen atoms are separated by at most 3.3 Å, and there is a hydrogen atom located between them so that the corresponding O-H-O angle is at least 145°. Each hydrogen bonded water molecule can be further classified as a hydrogen bond acceptor or donor based on the relative location of the shared hydrogen atom (the water molecule with the shorter O-H distance is a hydrogen bond donor). In Fig. 5, the average number of hydrogen bond acceptors and donors is shown as a function of the distance from the Ca^{2+} ion. Also shown in Fig. 5 is the oxygen-oxygen radial distribution function for reference. As expected, within the first solvation shell, the number of hydrogen bond donors immediately attains its bulk value, while the number of hydrogen bond acceptors slowly rises to its bulk value near the onset of the second solvation shell at 3.7 Å. Interestingly, we have not found any evidence of an increase in hydrogen bonding outside of the first solvation shell due to the presence of the cation. This is consistent with previous first principle simulations[17, 26] and recent measurements[27, 28] of cations such as Na^{+} and Mg^{2+}, which also find that hydrogen bonding is not significantly altered outside of the first solvation shell.

Conclusions

In summary, we have performed a series of first-principle simulations of Ca^{2+} in water in order to examine the structural and dynamical properties of the solvated ion. In addition to the standard approach where the intramolecular geometry of the water molecules is allowed to fluctuate, we have investigated the use of a rigid water approximation. By suppressing high-frequency motions, this approximation enables a three to four-fold increase in the molecular time step that would normally be used in a Car-Parrinello simulation of an aqueous system.[21]

Our simulations indicate that the first peak in the calcium-oxygen radial distribution function is located at 2.43 Å. This first-solvation shell distance is in good agreement with recent experimental measurements,[6, 8, 10] and with a previous first-principle simulation[15] of Ca^{2+} with 54 water molecules where semi-core states on the calcium ion were explicitly treated (as was done in this work). It appears that the use of a valence only pseudopotential for calcium, in combination with small 32 water simulation cells[14] leads to a poor description of the first solvation shell around Ca^{2+}, which results in significantly larger first-solvation shell distances than those found here.

As reported by Lightstone, *et al.*,[17] divalent cations such as Mg^{2+} prefer to coordinate with six water molecules in the first solvation shell, and, for the time scales that can be routinely accessed with *ab initio* MD simulations (~ 10 ps), no exchange events between the first and second solvation shells are found. In contrast, the solvation shell around Ca^{2+} is found to be rather flexible and allows for coordination numbers that range from six to eight water molecules, with a strong preference for seven-fold coordination. In order to capture this variability in a quantitative fashion, rather long (~40 ps) simulations

are required. The rigid water approximation used here appears to be an effective approach for accessing these long time scales in *ab initio* simulations of aqueous solutions.

Although the first solvation shell around Ca^{2+} is not as rigid as Mg^{2+}, we have found a similar tendency for the molecules belonging to the first solvation shell to preferentially coordinate the Ca^{2+} with a single lone-pair orbital on the water's oxygen. This subtle interaction leads to a notable effect on the tilt angle distribution and highlights the importance of including a realistic description of the solvation shell via a first-principles based approach. Finally, we note that although the presence of the cation has a strong effect on the dipole moments of the neighboring water molecules, the hydrogen bonding does not appear to be noticeably modified outside of the first solvation shell.

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Figures:

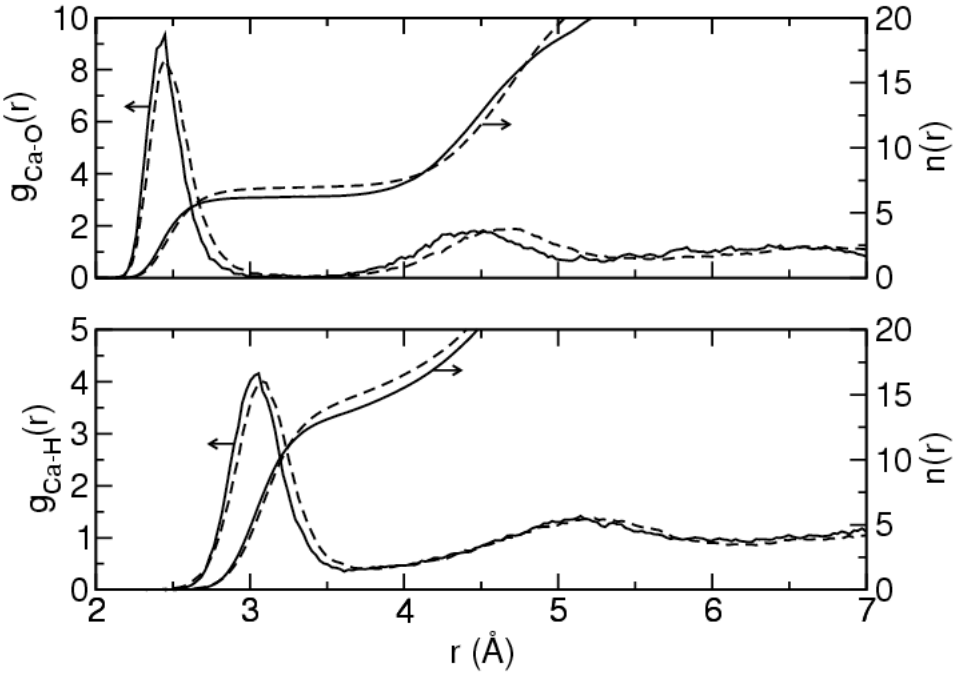

Fig. 1. The calcium-oxygen (top panel) and the calcium-hydrogen (bottom panel) radial distribution functions and running integration numbers. The solid line corresponds to data averaged over the flexible water simulations A and B and the dashed line to the rigid water simulation C.

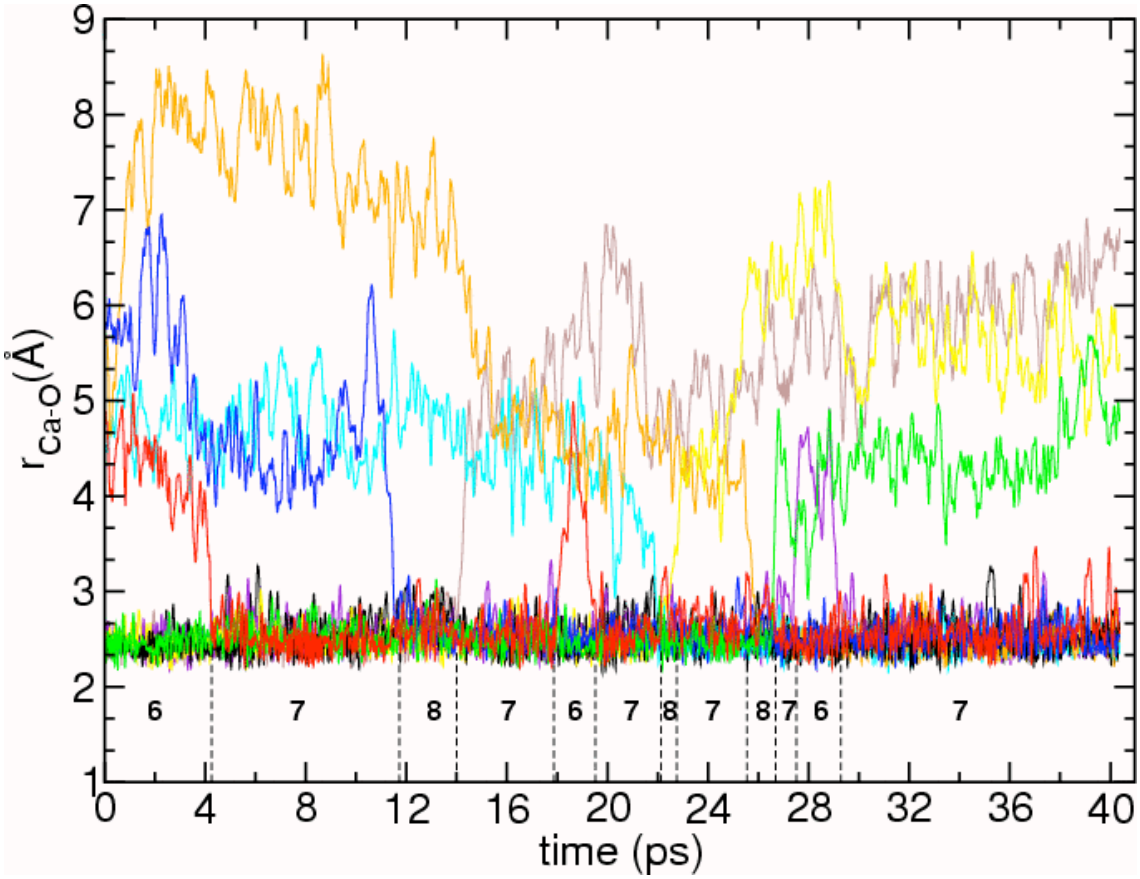

Fig. 2. The calcium-oxygen distance as a function of simulation time for the water molecules that come within 3.5 Å of the calcium at any time during the rigid water simulation C. The solid black lines represent water molecules that remain in the first solvation shell for the entire simulation, and the solid colored lines represent water molecules that make exchanges between the first and second solvation shells. The horizontal dashed lines denote an exchange event and the numbers listed between these lines correspond to the number of water molecules in the first solvation shell.

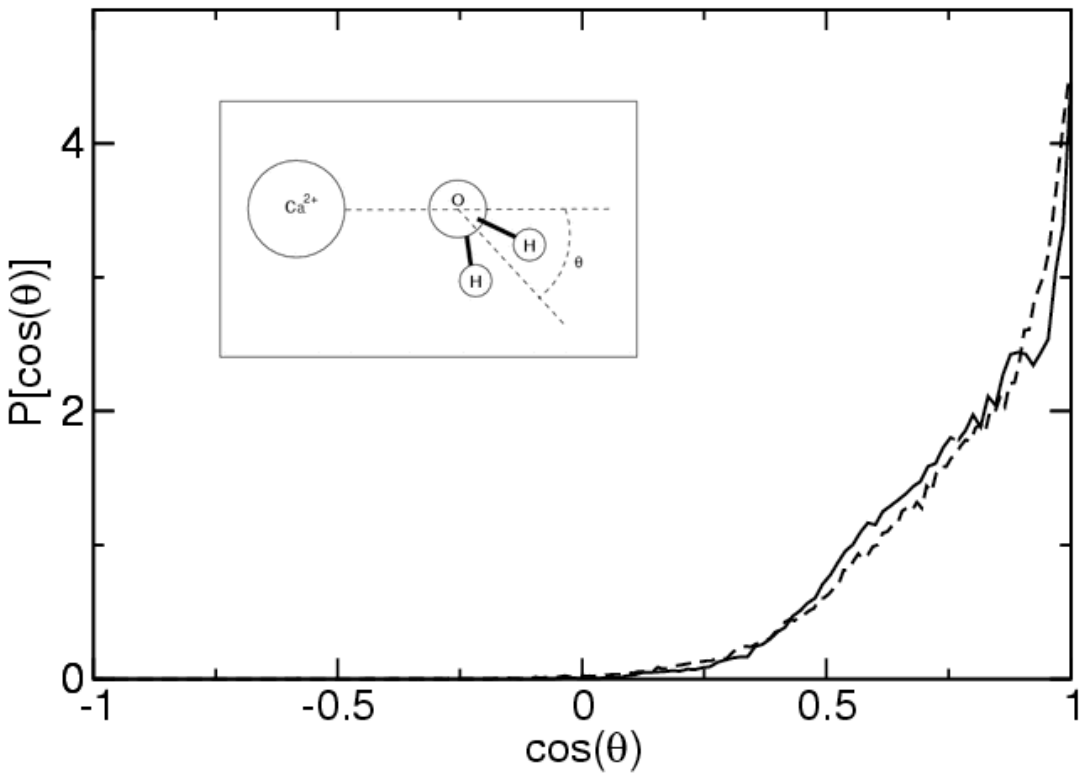

Fig. 3. Water tilt angle distribution within the first solvation shell around Ca^{2+}. The solid line corresponds to the distribution collected over the flexible water simulations A and B and the dashed line to the rigid water simulation C.

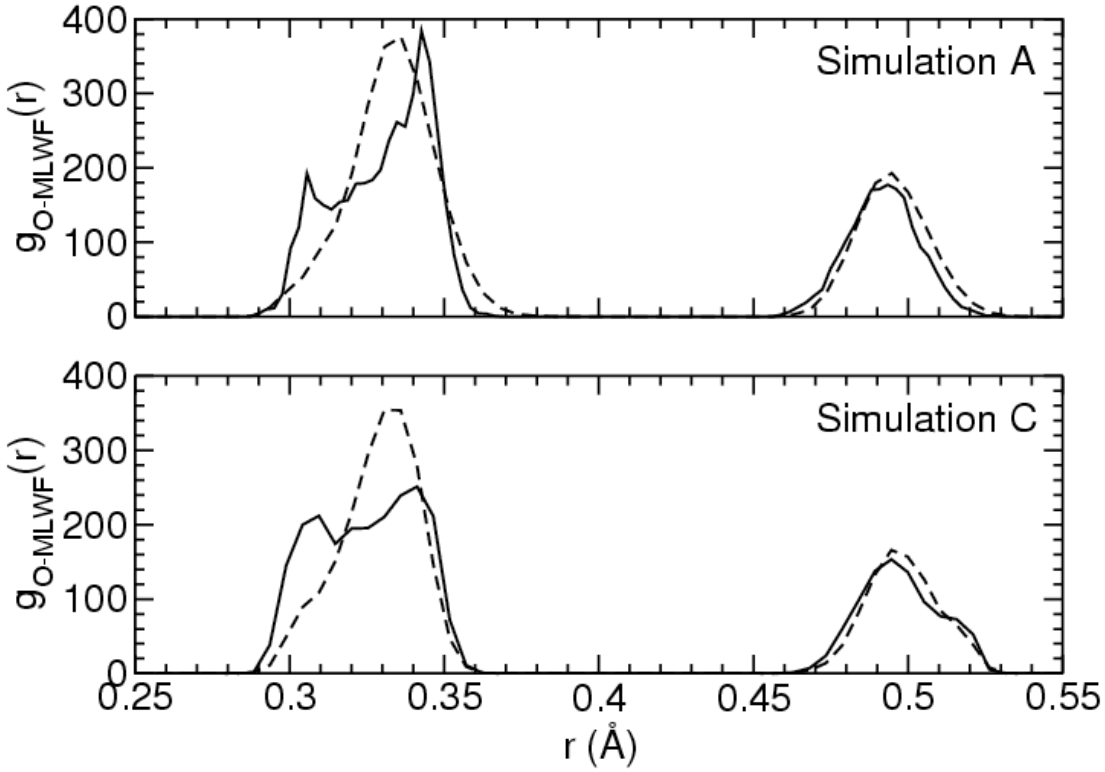

Fig. 4. The oxygen-MLWF center radial distribution functions averaged over the flexible water simulation A (top panel) and the rigid water simulation C (bottom panel). The solid lines correspond to oxygen atoms within the first solvation shell around calcium and the dashed lines to oxygen atoms outside of the first solvation shell.

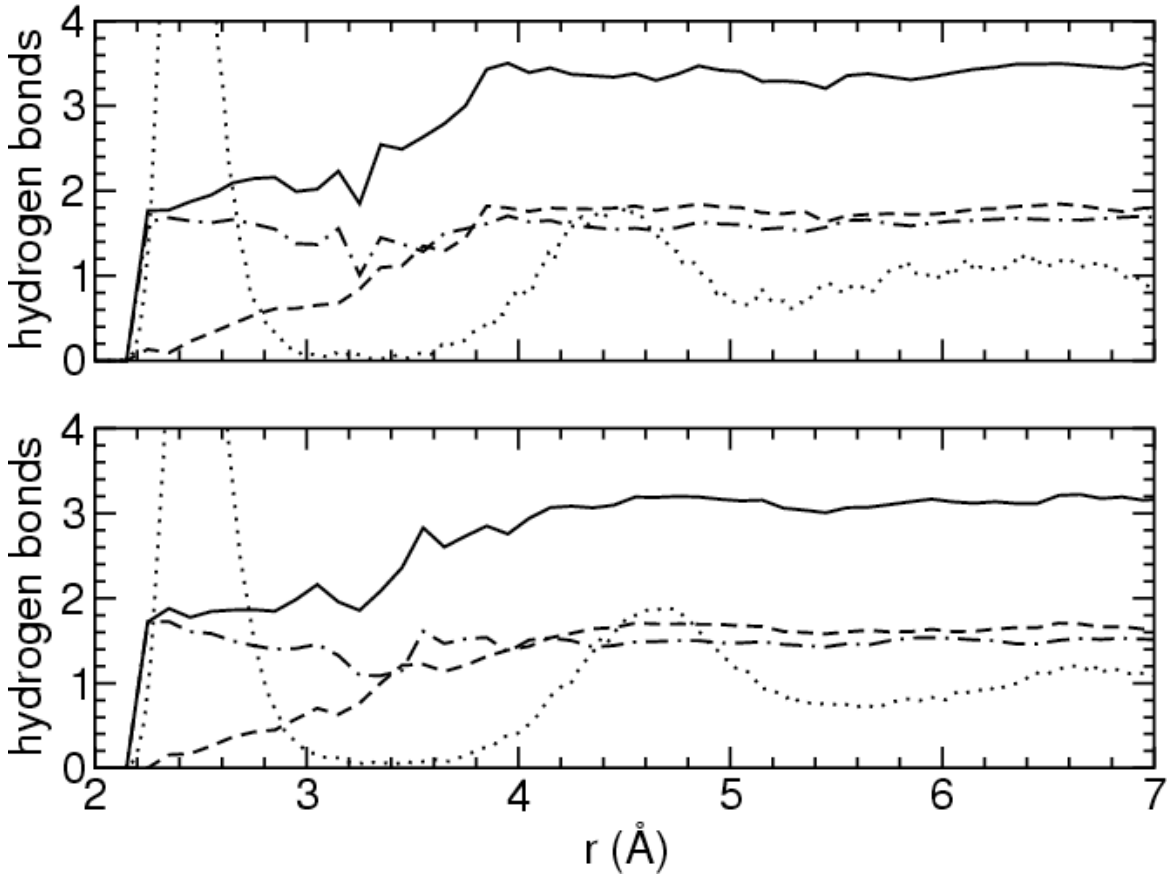

Fig. 5. The average number of hydrogen bonds per water as a function of the distance from the calcium ion in the flexible water simulations A and B (top panel) and the rigid water simulation C (bottom panel). The solid line corresponds to the total number of hydrogen bonds per water, and the dashed (dashed-dotted) line to the number of hydrogen bond acceptors (donors) per water. The corresponding calcium-oxygen radial distribution functions are shown with a dotted line for reference.

Supplemental Material:

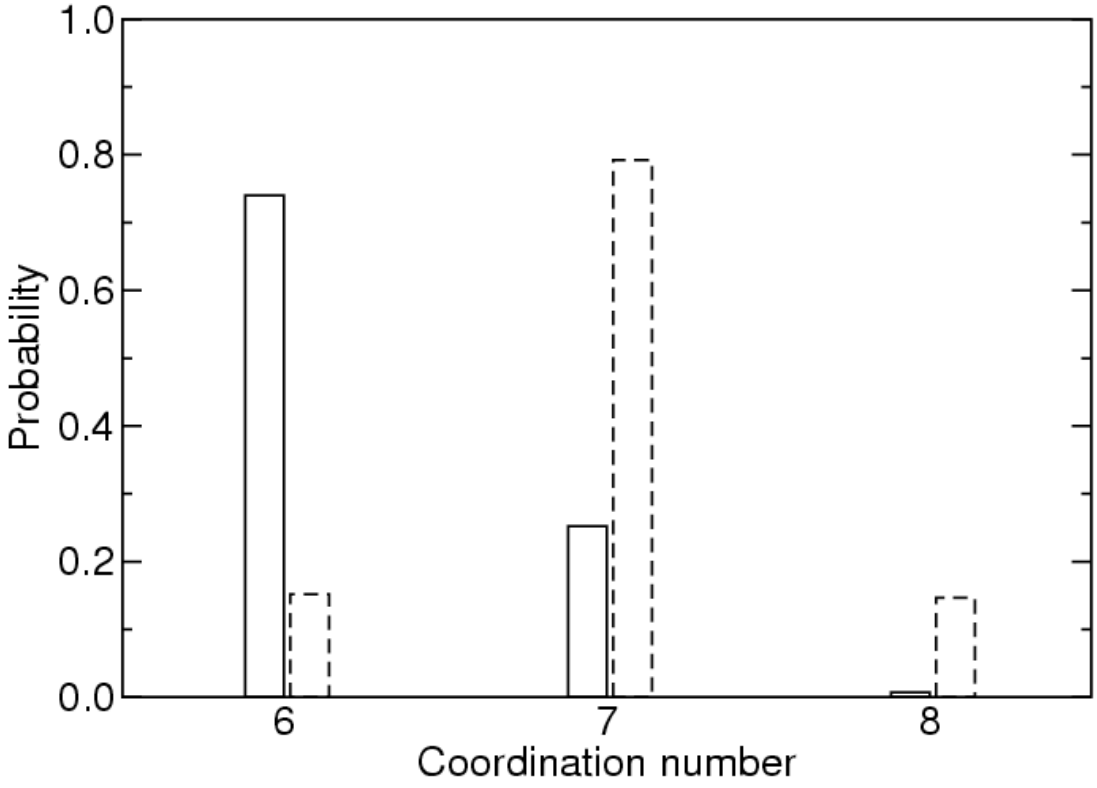

Fig. 6. The probability distribution of calcium-oxygen 1st solvation shell coordination numbers. The solid line corresponds to the flexible water simulations A and B and the dashed line to the rigid water simulation C.

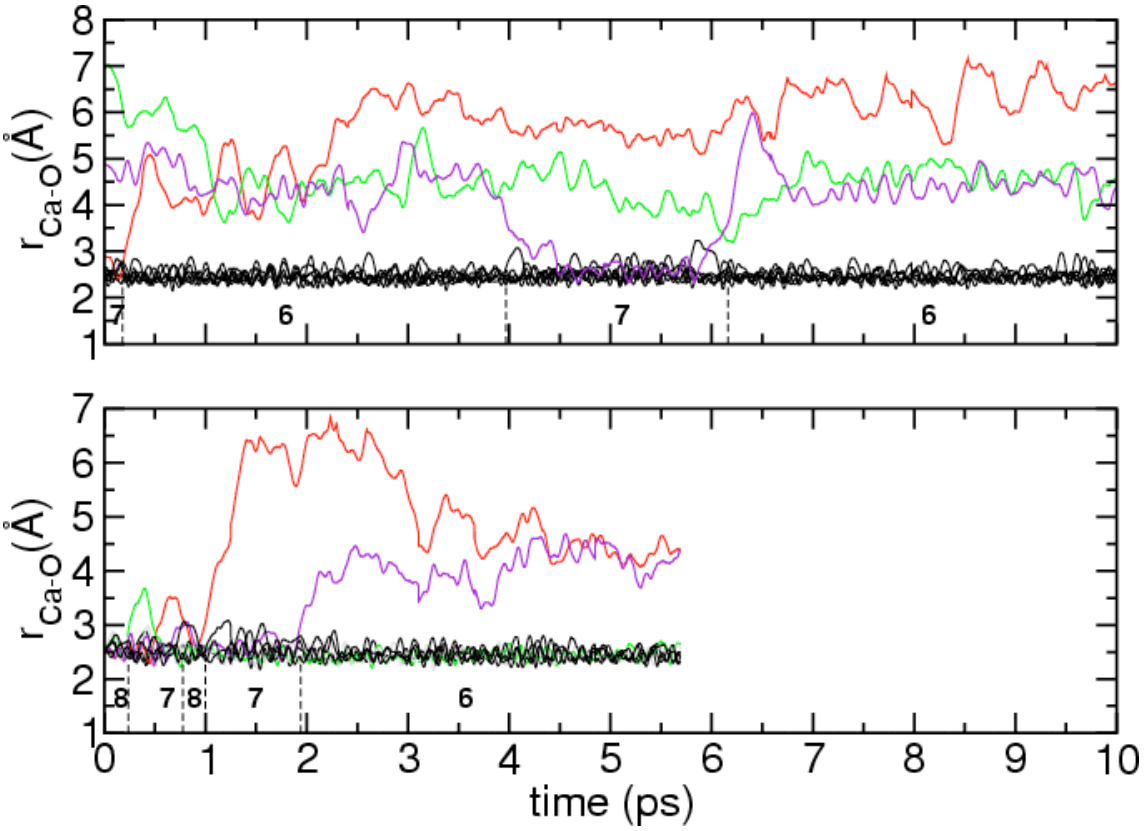

Fig. 7. The calcium-oxygen distance as a function of simulation time for the water molecules that come within 3.5 Å of the calcium at any time during the flexible water simulations A (top panel) and B (bottom panel). The black lines represent water molecules that remain in the first solvation shell for the entire simulation, and the colored lines represent water molecules that make exchanges between the first and second solvation shells. The horizontal dashed lines denote an exchange event and the numbers listed between these lines correspond to the number of water molecules in the first solvation shell.

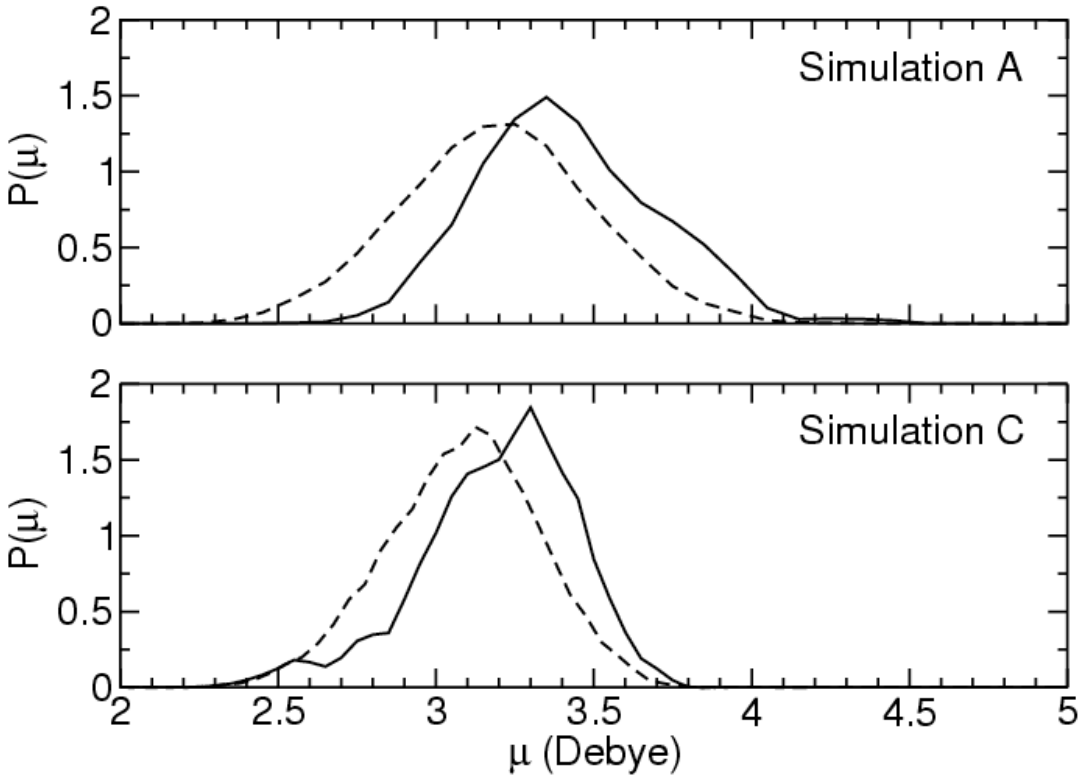

Fig. 8. The probability distribution of water dipole moments averaged over the flexible water simulation A (top panel) and the rigid water simulation C (bottom panel). The solid line corresponds to the dipole moment distribution of water molecules within the first solvation shell around calcium and the dashed line to the water molecules outside of the first solvation shell.