5.3.2. Ion binding

The cation-CB[6] oxygen radial distribution function (RDF) (Fig. 5.4) has a first sharp peak that shows the binding of cations to the oxygens. The position of the first peak corresponds to the size of the cations. Sodium and calcium have similar sizes (0.2586nm and 0.2872nm) and, therefore, their first peaks are at almost the same distance (~0.25nm). Their height, however, differs by a factor of two. There is mainly one sodium cation bound to CB[6], whereas there are two calciums. This is also confirmed by the average number of cations in the shell up to the first minimum after the first peak (Fig. 5.4, lower boxes). There are twice as many calciums (0.121) than sodiums (0.059). Potassium ions are notably bigger (0.3334nm), and the first peak is further (0.27nm). The average number of potassium ions in the first peak is almost the same as that of sodium. This means that there are equal numbers of sodium and potassium bound to CB[6].

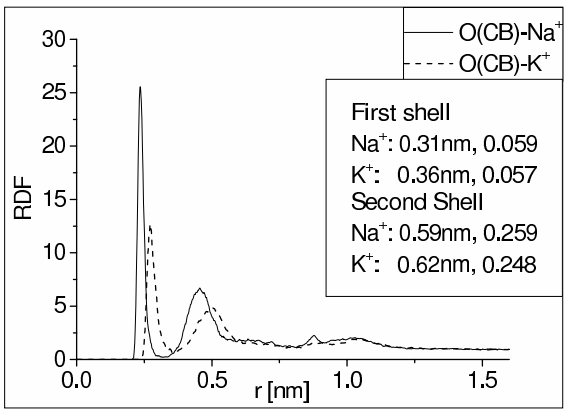

Figure 5.4a.

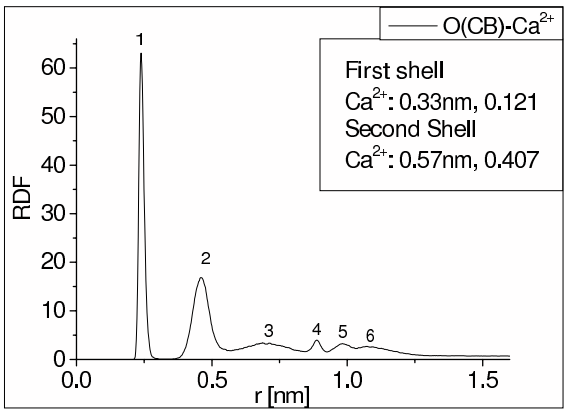

Figure 5.4b.

Figure 5.4. Radial distribution functions of CB[6] oxygen and sodium (a), potassium (b), and calcium atoms (c), respectively. The lower box in the figure indicates the positions of the minima after the first and the second peaks, followed by the number of cations in the first and second shells. The number of cations in the second shell does not include the number of the first.

There are several distinguishable peaks in all RDF functions. They are especially notable in the case of calcium chloride. This is due to the low mobility of these cations around the cucurbituril oxygens (see the "Ion Binding Dynamics" section). To attribute the origins of these peaks a period of 4ns was investigated, during which one calcium cation stayed bound to the same oxygen. Peak 1 is due to cations that immediately bind to one of the CB[6] oxygens. The other peaks correspond to distances between this cation and other CB[6] oxygen atoms. Peak 2 is due to the ortho-oxygens (by analogy with the benzene substitution scheme). The very broad peak 3 is mainly due to the meta-oxygens. The second contributor to peak 3 is the para-oxygen on the opposite side of the same face. It is, however, slightly shifted, has a smaller intensity (there is only one para-position), and is smeared between peak 3 and 4. Peak 3 is invisible for sodium and

potassium chloride solutions, as these ions are much more mobile than calcium. Peak 4 is seen sharply also in the cases of sodium and potassium. It corresponds to the distance to the mirror image of the binding oxygen on the other face. The last two peaks – 5 and 6 – merge into a very broad one in case of sodium and potassium. Peak 5 is due to the "ortho-image" oxygens, and peak 6 to the two "meta-image" oxygens, with a broad contribution from the "para-image" oxygen.

Neither positive nor negative ions do ever get inside the CB[6] cavity or even below the plane defined by the carbonyl oxygens. A set of control simulations, with a cation initially placed in the cavity and the solution equilibrated around the complex, show that the ions are ejected within a few picoseconds. This is also evident in the radial distribution functions between the center of mass of CB[6] and the ions (Fig. 5.5). The smallest distance from the center of mass of CB[6], at which cations were registered, is about 0.43nm. Anions do not even get closer than 0.65nm. The peak in the cation RDFs corresponds to the cation being bound by one CB[6] oxygen. The RDF of potassium has a small shoulder before the peak. This effect clearly depends on the size of cations, as sodium does not have the shoulder. It corresponds to two populated positions. K^+ can be coordinated by one or two CB[6] oxygens (see the "Ion Binding Dynamics" section). Another interesting observation is that sodium and potassium cations get closer to the center of mass than calcium ions. Calcium ions are doubly charged. They bind only to one oxygen and stay there for a very long time (see the "Ion Binding Dynamics" section). Sodium and potassium ions are more mobile so they can move easier around one or two oxygens they are bound to and also jump to the second nearest neighbour. Due to the geometrical reasoning they get closer to the C_6 symmetry axis and, therefore, get closer to the CB[6] center of mass.

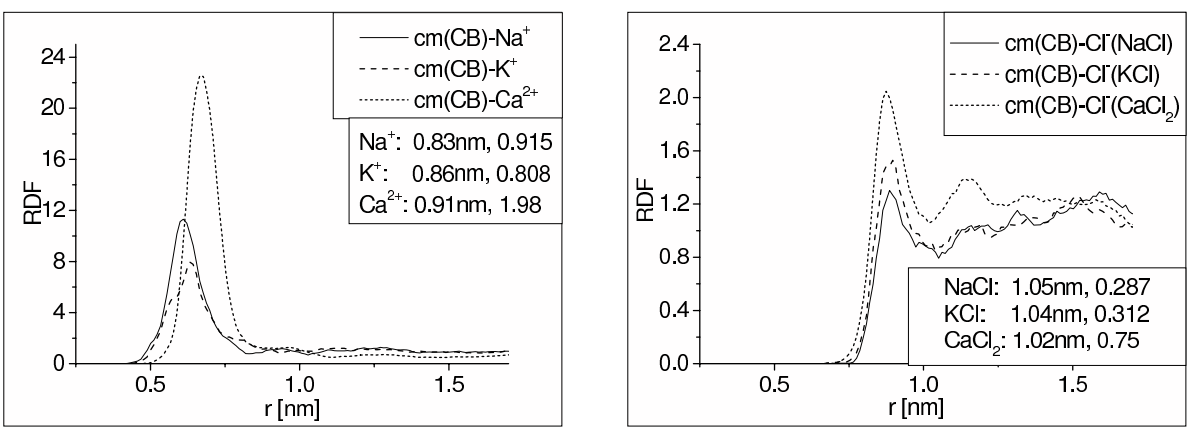

Figure 5.5a. **Figure 5.5b.**

Figure 5.5. Radial distribution functions between the center of mass of cucurbituril (cm(CB)) and positive (a) and negative (b) ions. The lower box in the figure indicates the positions of the first minima after the first peaks and the number of ions up to this distance.

The RDF for the chloride ions has also a sharp peak (Fig. 5.5b). This is due to the association of anions to a cation that is bound to the CB[6] molecule. A more detailed

analysis of the chloride positions revealed that the anions are located outside the CB[6] cage and closer to the CB[6] symmetry plane. This position has the advantage that the chloride is attracted not only by the cation but also by partially positive carbons.

Table 5.6. The time fractions of free CB[6], single-, and double-cation-CB[6] complexes and corresponding free energies.[55]

#	system	r_{bound} [nm]	no complex	single-cation		double-cation	
				fraction	ΔG [kJ/mol]	fraction	ΔG [kJ/mol]
2	Water, CB, Na^+, Cl^-	0.31	46%	48%	-0.1	6%	5.1
3	Water, CB, K^+, Cl^-	0.36	61%	33%	1.5	6%	5.9
4	Water, CB, Ca^{2+}, Cl^-	0.33	3%	55%	-7.6	42%	-6.9

The complexation behaviour of CB[6] towards the different ions depends strongly on their charges and sizes (Table 5.6). There is a marked difference between single-valent and double-valent ions. For both Na^+ and K^+ solutions, there are significant fractions of time, when no cation is attached to the CB[6], whereas for the Ca^{2+} solution, there is nearly always at least one Ca^{2+} bound to CB[6]. Also, for Na^+ and K^+, the single-cation complexes outnumber those, where there are two cations bound (nearly always to opposite faces of CB[6]). In contrast, there are similar fractions of single- and double-ion complexes with Ca^{2+}. The influence of the size is less pronounced, but it is clear that the smaller Na^+ shows larger complexation propensity than the bigger K^+. The populations of Table 5.6 can be Boltzmann inverted to yield relative free energies (potentials of mean force) for the different complexation states (the amount of three-fold and higher complexation is insignificant). For K^+, the single-ion complex is 1.5 kJ/mol higher in energy than free CB[6] and double-ion complex 5.9 kJ/mol. For Na^+, the binding of the first ion has a negative free energy (-0.1 kJ/mol) and the binding of the second has a positive free energy (5.1 kJ/mol). For Ca^{2+}, both the single-ion complex (-7.6 kJ/mol) and double-cation complex (-6.9 kJ/mol) are more stable than the free CB[6]. These energies, being potentials of mean force, are characteristic of the conditions in the simulations, especially of the concentrations of CB[6] and salt. Therefore, they cannot be quantitatively compared with experimental binding free energies obtained for other compositions. However, they give the same order as those of Buschmann *et al.*[20] derived from concentration measurements and of Zhao *et al.*[19] for CB[5] soluble derivative from titration calorimetry.

5.3.3. Diffusion and reorientation dynamics

The self-diffusion coefficient of water $2.62 \cdot 10^{-5}$ cm^2/s (Table 5.5) is close to the value in pure liquid water, $2.27 \cdot 10^{-5}$ cm^2/s[56]. The CB[6] molecule's mobility is highest in pure water. Its mobility is reduced by at least a factor of 2 if salt is added. It also depends on the size and charge of the cations. The diffusion coefficient of CB[6] in potassium chloride solution is higher than in NaCl. Potassium has a larger radius σ. The lowest

mobility of cucurbituril is found in the $CaCl_2$ solution, which is the only double-charged cation. These findings can be explained by the differences in ion binding. Cations bind to the negatively charged CB[6] oxygens and also reduce the water mobility in their environment (solvation shell). This produces a "particle" bigger than CB[6] itself. The longer lifetime of this complex reduces its diffusion. The lifetime, in turn, depends on the interaction strength between the cations and water or CB[6] oxygens. The smaller size (Na^+) or stronger charge (Ca^{2+}) of a cation increases the electrostatic interactions between them and the negative oxygens and, therefore, extends the life of the complex of CB[6] and the hydrated ion.

The rotational correlation functions $C_1(t) = \langle \cos(\varphi(t)) \rangle$ and $C_2(t) = \frac{1}{2}\langle 3\cos^2(\varphi(t)) - 1 \rangle$ of the vector along the C_6 axis of CB[6] have been also calculated in order to estimate rotational correlation times (Fig. 5.6, Table 5.5). The angle $\varphi(t)$ is the angle between the vector at $t = 0$ and the time t. Averaging was performed over all time origins. The statistical basis is small, as only one cucurbituril molecule is present in each system. It is, however, evident that the behaviour of the correlation functions (≤500ps) reflects the mobility of CB[6] (Table 5.5): Smaller diffusion coefficients correspond to longer relaxation times. An exception is the potassium chloride solution, where the CB[6] molecule reorients faster than in pure water. Nevertheless, a more detailed look reveals that during the first 190ps the correlation function drops slightly faster in pure water. The phenomenon of the fast decay in potassium chloride solution might still be due to the lack of statistical data. The inset in the Fig. 5.6 shows the short-time rotational relaxation to be exponential within the limits of statistics. This is indicative of Debye rotational diffusion.

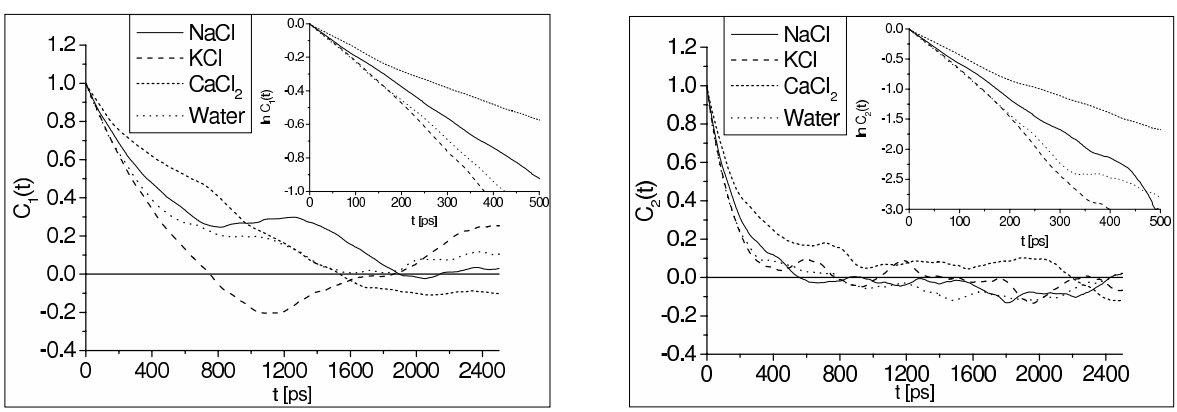

Figure 5.6a. **Figure 5.6b.**

Figure 5.6. Correlation orientation functions of the vector along the C_6 symmetry axis of the cucurbituril molecule $C_1(t) = \langle \cos(\varphi(t)) \rangle$ (a) and $C_2(t) = \frac{1}{2}\langle 3\cos^2(\varphi(t)) - 1 \rangle$ (b) in pure water and in salt solutions.

5.3.4. Ion binding dynamics

The motion of cations among the CB[6] oxygen atoms was investigated (Fig. 5.7) by a neighbourhood analysis (which neighbouring atoms are within a certain radius of the target atom). The "bound" radii of Table 5.6 were used. As examples, we consider in the following the cations, which were bound to CB[6] for the longest time. The sodium ion (Fig. 5.7a) hops relatively freely between the CB[6] oxygens of one face. Jumps occur between nearest or second nearest neighbours. At any time, the sodium ion is bound mainly to only one of the oxygens (the resolution does not quite show this). Only 12% of the time is a bound Na^+ coordinated by two oxygens simultaneously, which are always nearest neighbours. The residence time of a sodium at one CB[6] oxygen can last up to approximately 350ps. It is evident that during its total residence time of about 4.5ns, the sodium hops between all six oxygens of one face.

The potassium ion is bigger and more weakly bound than the sodium. Therefore, it stays around any one oxygen atom for noticeably shorter periods (up to around 150ps) (Fig. 5.7b). It jumps in the same way as sodium: from one oxygen to an ortho or meta position. However, sometimes but very rarely (just 2 events were found) it hops to the para oxygen of the same face. In the particular case (Fig.5.7b), K^+ attaches to one side of CB[6] and then diffuses away and later attaches to the other side. A potassium ion also can be shared by two (40%) and sometimes even by three (1%) of the oxygens. Multiple coordination was also found by Heo *et al.*[13]: from aqueous solutions of CB[6] and KCl in the presence of tetrahydrofuran (THF), a one-dimensional polymer-like crystal of alternating CB[6] and $K_2(OH)_2$ units is formed. X-ray crystallography shows that each potassium atom is coordinated by four carbonyl oxygens (two oxygens from each of two CB[6] molecules) and two hydroxide oxygens.

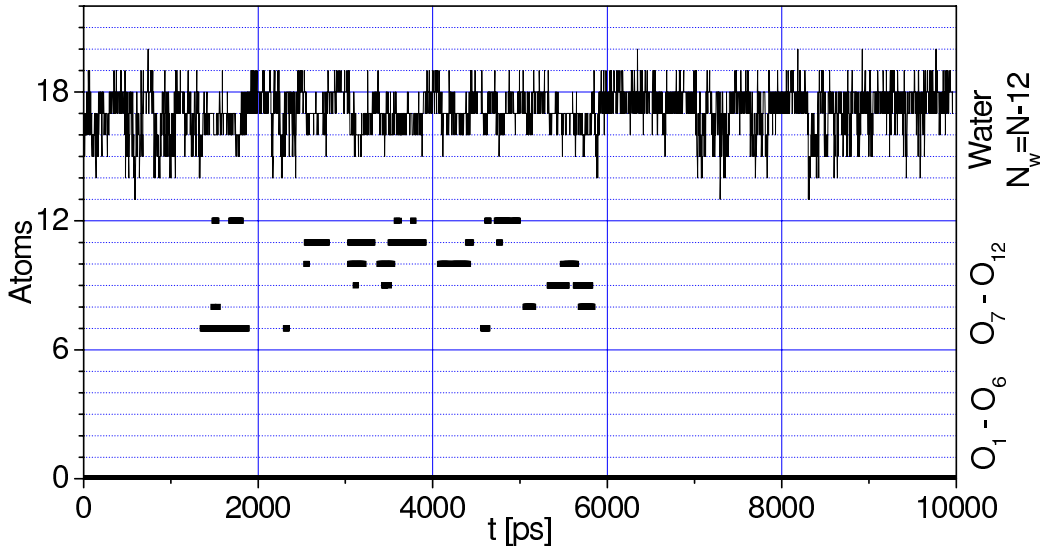

Figure 5.7a.