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“Site Binding” of Ca^{2+} Ions to Polyacrylates in Water: A Molecular Dynamics Study of Coiling and Aggregation

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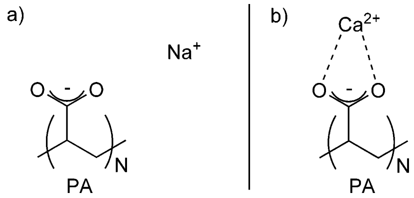
ABSTRACT: The interaction of Ca^{2+} ions with short polyacrylate chains (NaPA) in water is investigated using molecular dynamics simulations, accelerated with the recently developed metadynamics algorithm. The much discussed “site binding” of calcium ions to these industrially relevant polymers is driven by an entropy gain as water molecules are released into the solution. At high NaPA concentrations, increased Ca^{2+}−PA monomer ratios will not result in strong coiling of PA oligomers. This is due to the local rigidity induced by the binding of many Ca^{2+} ions to the polymer. Because the uncoiled state of the crowded chain obstructs formation of high Ca^{2+}−COO^- coordination numbers, interchain interactions will become favorable, and formation of PA aggregates can be expected. On the other hand, at low NaPA concentrations, introduction of Ca^{2+} ions to the solution leads to the formation of very stable coiled configurations, with local crystal-like structures, in which the Ca^{2+} ions cluster together. It is the sharing of carboxylate groups among the metal ions that leads to the formation of these crystal-like conformations, inducing desolvation and precipitation of the chain at threshold Ca^{2+} concentrations.

Introduction

Polyelectrolytes are receiving an increasing amount of attention for their technological applications and biological effects. The simple structure and broad applicability of sodium polyacrylates, the sodium salts of poly(acrylic acid) (NaPA, Scheme 1a), render them the ideal test cases for polyelectrolyte studies. In aqueous solution the sodium ions dissociate and form counterion clouds around the negatively charged polymer chains at a distance of approximately 4−5 Å.[1] The polymers are assumed to have stretched conformations due to intramolecular repulsion among the negative charges on the chain. An amount of intermolecular attraction is present at longer distances, aided by the presence of the counterion clouds, and a degree of ordering can be detected in the solution.[2] In contrast to monovalent ions such as Na^+, a strong coordination of divalent or trivalent metal cations to polyacrylates was observed in solution (site binding)[3] and proposed to be an entropic effect.[4] The strong coordination of Ca^{2+} (Scheme 1b) renders polyacrylates useful as dispersion agents for pigments[5] or incrustation inhibitors in both laundry detergents[6] and seawater desalination.[7] So far, experiment has not been able to provide a conclusive answer on the exact nature of “site binding”. A recent infrared spectroscopy study on the CO stretching modes of the carboxylate groups in the presence of Ca^{2+} ions could distinguish several stable forms of calcium binding but was unable to ascribe definite structural conformations to the spectra.[8] Recently, atomistic simulations were employed to tackle the subject of PA−cation interaction,[1] previously investigated by coarse-grained computations[9−17] and experiment[3,18,19] only. This molecular dynamics (MD) investigation[1] covered the initial stages of Ca^{2+} binding to short PA chains in water. It gave evidence that there are two stable conformations: one in which Ca^{2+} is directly coordinated to one or two carboxylate groups and another which displays indirect coordination through an interposed water molecule. However, the limited time scale sampled in the standard MD simulations may have been insufficient, and not all possible complexes of Ca^{2+} with the polymer molecule may have been found.

Scheme 1. Schematic Picture of Metal Cation Interaction with the Carboxylate Group of One Monomer of a Polyacrylate Chain: (a) Monovalent Na^+ Cations Display Weak Interaction; (b) Divalent Ca^{2+} Ions Bind Strongly



Increase of the calcium cation concentration in solutions of long chains leads to formation of coils,[18] which collapse at a threshold value as the polymer complex precipitates—an undesirable effect in all above-mentioned applications. The threshold Ca^{2+} concentration depends on the concentration of polymer in solution. However, it has been found that in the presence of small concentrations of NaCl (0.1 M), independent of the molar mass of the polymer, an increase of the total number of PA monomeric units by three[18,19] shifts the precipitation concentration of calcium upward with ∼1 additional Ca^{2+} ion. This result changes when higher NaCl concentrations are present. Coarse-grained simulations have shown that indeed higher concentrations of multivalent counterions result in a smaller radius of gyration due to a decreased repulsion between monomers as a result of charge neutralization.[20] Atomistic MD simulations on short oligomers also showed that at high PA and Ca^{2+} concentrations aggregation/precipitation is initiated by long-range interactions. These long-range interactions between individual chains are due to shielding of the negative charges of the COO^- groups by the closely bound Ca^{2+} ions and a related dispersion of the surrounding sodium cloud.[1]

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Our study aims at supplying quantitative information about "site binding", going beyond the initial stages of interaction, and it investigates the role of coiling of a single short chain in the process of precipitation. We performed simulations using the metadynamics method for the efficient investigation of rare events.[21−23] We restricted our investigation to a short PA chain of 20 monomeric units at different calcium concentrations. The maximum concentration used (5 Ca^{2+} ions for every 20-mer chain) approximates the precipitation threshold region.[18,19]

Method

The NAMD high-performance parallel molecular dynamics program package was used for the simulations,[24] and the system was described with the CHARMM force field, with standard TIP3P water molecules.[25] In order to accelerate the MD simulations, we implemented the metadynamics algorithm,[21,22] which uses one or more order parameters ($S_i(\mathbf{R})$) to describe the process under investigation. A history-dependent term is added to the potential in the space of $S_i(\mathbf{R})$, in order to encourage the system to leave a free energy minimum and explore a larger region of space. After sufficient sampling, the sum of the individual added potential terms (in the form of Gaussians) provides an estimate of the free energy surface in the space of the chosen reaction coordinates.

An isotactic sodium polyacrylate (PA) chain of 20 monomer units ($M_w = 1200$ D) was placed in a box of 7875 H_2O (TIP3P) molecules with an amount of dissociated $CaCl_2$ units which ranges from one to five. At room temperature and pressure this amounts to a polymer concentration of 7.3 mmol/L. The carboxylate groups are completely deprotonated, which corresponds to a pH of 11. It is known from recent experimental work on polymers of the same length, at a concentration of 8.3 mmol/L and a pH of 10, that these short polymers show Ca^{2+} interaction comparable to that found in long chains.[8] The starting configurations, with Ca^{2+} ions coordinated to only one monomer unit of the stretched polyacrylate, were equilibrated for 500 ps at room temperature and constant volume. The subsequent metadynamics runs lasted from 3 to 10 ns. For the estimation of free energy barriers, runs were terminated when the system escaped a free energy well. The height of the added Gaussians was always 0.5 kcal/mol, and the widths were always chosen at 0.05 units for the dimensionless coordination number order parameters (see below) and at 0.2 Å for all distances. These choices are based on the experience that the optimal Gaussian size is in the order of one-tenth of the well size.[22] Using these parameters in the relation described in ref 22, an upper limit for the free energy error is established at 1 kcal/mol. [The error on the free energy is $\epsilon = c(d)[(SW\sigma)/(\beta D\Delta t)]^{1/2}$, where c is a dimensionless constant depending on the dimension of the metadynamics simulation (0.5 in this case), s is the system size, w and σ are Gaussian height and width, β is the Boltzmann factor, D is the diffusion coefficient, and Δt is the time between the deposition of two successive Gaussians.]

Several order parameters $S_i(\mathbf{R})$ were used in this study. They can be divided into two categories: those describing the mode of binding of Ca^{2+} to the carboxylate groups (1) and those describing coiling of the chain (2). The order parameters are defined below.

(1a) The distance of a Ca^{2+} ion to the nearest carboxylate oxygen in the chain (see Scheme 1) is

$$S_{1a}(\mathbf{R}) = \min(r_{\mathrm{Ca-O(CO)}})$$

(1b) The coordination number of a Ca^{2+} ion to the carboxylate units defined as a sum of switching functions $f(r)$[26] on Ca−O(CO^-) distances ($r_{\mathrm{Ca-O}}$):

$$S_{1b}(\mathbf{R}) = \sum_{i,j\in N} g_{ij},$$
$$g_{ij} = f(r_{\mathrm{Ca-O}_i}) + f(r_{\mathrm{Ca-O}_j}) - f(r_{\mathrm{Ca-O}_i})\, f(r_{\mathrm{Ca-O}_j}) \quad (1)$$

$$f(r_{\mathrm{Ca-O}}) = \frac{1 - \left(\dfrac{r_{\mathrm{Ca-O}}}{r_0}\right)^n}{1 - \left(\dfrac{r_{\mathrm{Ca-O}}}{r_0}\right)^m} \quad (2)$$

where i and j represent the oxygen atoms in the N carboxylate groups. The parameters n, m, and r_0 in eq 2 were optimized, taking care that the derivative of the order parameter does not go to zero too quickly at atom−atom distances that are regularly populated. This has led to values of 8, 16, and 3.5 Å, respectively, for these parameters. For our short chain $S_{1b}(\mathbf{R})$ can in theory be a number between 0 and 20. However, because of the limited space around the Ca^{2+} ion, this number does not exceed five.

(1c) The coordination number of a Ca^{2+} ion to the oxygen atoms of the chain. $S_{1c}(\mathbf{R})$ is the sum of switching functions $f(r_{\mathrm{Ca-O}})$ (eq 2, with n, m, and r_0 at 8, 16, and 3.5 Å, respectively) for all the oxygen atoms on the polymer chain. In principle, this can be a number between 0 and 40 for the current 20-mers, but in practice it does not exceed 6. We added this order parameter to obtain more detailed information about the mode of calcium binding.

(1d) The chelation number of a Ca^{2+} ion to the carboxylate groups of the chain, where chelation is defined as simultaneous coordination of one Ca^{2+} to both oxygen atoms in a monomer (Scheme 1b, eq 3). This number cannot be greater than 1 per monomer, so in the 20-monomer chain the theoretical maximum would be 20. The actual maximum is 3.

$$S_{1d}(\mathbf{R}) = \sum_{i,j\in N} f(r_{\mathrm{Ca-O}_i})\, f(r_{\mathrm{Ca-O}_j}) \quad (3)$$

where i is one oxygen atom and j the other in the N carboxylate groups. The parameters n, m, and r_0 in $f(r_{\mathrm{Ca-O}})$ are 8, 16, and 3.5 Å, respectively.

(2a) The maximum contact order of all Ca^{2+} ions to all carboxylate units of the chain. The contact order for this system is a dimensionless quantity, defined as the maximum distance along the chain between two monomers coordinated to one Ca^{2+} atom.

$$S_{2a}(\mathbf{R}) = \max(g_{ij}^{Ca_m} \times g_{kl}^{Ca_m} \times \mathrm{dist})$$

where g_{ij} is defined in eq 1. The parameters n, m, and r_0 in $f(r_{\mathrm{Ca-O}})$ are 6, 12, and 3.5 Å, respectively.

(2b) The radius of gyration of the chain, which is defined as the mass-weighted rmsd of all the N atoms of the chain to the center of mass (eq 4).

$$S_{2b}(\mathbf{R}) = \frac{1}{M_{\mathrm{tot}}}\sqrt{\sum_{i\in N} m_i(\mathbf{r}_i - \mathbf{r}_{\mathrm{cm}})^2} \quad (4)$$

Results and Discussion

Binding of Ca^{2+}. To obtain information on the site specific binding of Ca^{2+} to PA, a metadynamics run in a two-dimensional space of order parameters was performed using the distance of a Ca^{2+} ion to the PA chain ($S_{1a}(\mathbf{R})$) and the number

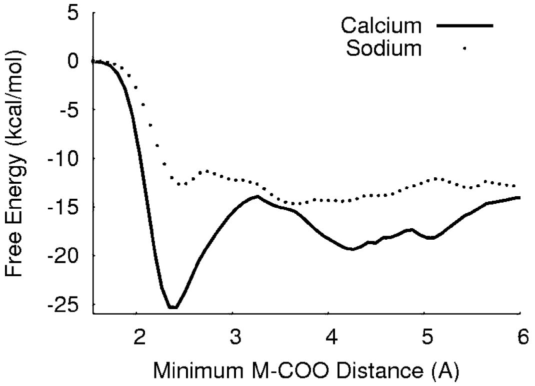

Figure 1. Free energy of metal ion binding to PA as a function of $S_{1a}(\mathbf{R})$, obtained by extracting the maximum values along $S_{1b}(\mathbf{R})$ after a 2-dimensional metadynamics run. The solid line represents the binding of Ca^{2+} and the dotted line that of Na^{+}.

of carboxylate groups to which it is coordinated ($S_{1b}(\mathbf{R})$). Only situations where the distance is smaller than 8 Å were considered. The free energy as a function of the distance is depicted in Figure 1 and reveals a 6 kcal/mol free energy gain for Ca^{2+} coordination to a single carboxylate group, with a barrier for detachment of 11 kcal/mol. In a second run, where the same order parameters are used, the Ca^{2+} ion is replaced by a Na^{+} ion, and the free energies are compared. The free energy describing sodium coordination has, overall, shallower minima than that of calcium, with a barrier for detachment (at 2.5 Å) of 1 kcal/mol. The deepest well is at about 3.5 Å, which means that indirect coordination, involving a water molecule between a carboxylate group and Na^{+}, is the preferred situation. The binding behavior of sodium is totally different from that of the larger calcium ion, for which desolvation is preferred.

The combination of order parameters for calcium−oxygen coordination ($S_{1c}(\mathbf{R})$) and calcium−carboxylate chelation ($S_{1d}(\mathbf{R})$) reveals more information about the mode of Ca^{2+} binding. Two simulations were performed to investigate the interaction of one calcium ion with two adjacent and two nonadjacent carboxylate groups, which leave the chain stretched and coiled, respectively. The resulting free energy surfaces (Figure 2) provide information about the stretched and the coiled conformations. The depths of the free energy minima cannot be compared from one simulation to another, since disconnected regions of the configuration space are investigated. The coordinated carboxylate groups were randomly chosen from previous MD trajectories. Figure 2a shows the free energy surface (FES) obtained from a metadynamics simulation where only two adjacent PA monomers were included in the definition of the coordination/chelation order parameters. This form of binding does not require any coiling of the chain, which indeed remains stretched throughout the simulation. In Figure 2 the number of coordinated oxygen atoms is depicted on the *x*-axis, while on the *y*-axis the double coordination of one monomer (which in this case cannot exceed 2) is displayed. The deepest free energy minimum corresponds to a conformation with three of the four oxygen atoms bound to the calcium ion (barrier; 3.4 kcal/mol). Barrier heights for bond formation and breaking when only one monomer is involved (2−3 cal/mol) are significantly lower than those for coordination to, or dissociation from, a second unit (6−8 kcal/mol). The most striking feature of the free energy surface for adjacent monomers (Figure 2a) is the absence of the free energy minimum for coordination of all four oxygen atoms. The results for the bent chain, where PA monomers 2 and 7 bind the calcium ion, are depicted in Figure 2b where coordination of all four oxygen atoms is the deepest minimum (Figure 2b, barrier; 5.0 kcal/mol). For nonadjacent monomers this four-coordinated conformation is preferred over the two- and three-coordinated bent conformations (barriers; 3.3 and 1.2 kcal/mol, respectively). Typical geometries for the four-coordinated states of adjacent and nonadjacent monomers (Figure 2) differ in the orientation of the two-coordinated carboxylate groups with respect to each other. We performed standard MD simulations starting from these two conformations and found indeed that the simulations starting from the stretched geometry (Figure 2a) immediately left the four-coordinated state, confirming that it is not a minimum on the free energy surface. On the contrary, in the trajectory starting from the bent geometry (Figure 2b), the four-coordinated state is preserved for the full length of the simulation (140 ps). From purely energetic considerations the four-coordinated configuration should be favorable also in the stretched geometry in Figure 2a, and its instability is related to an entropic effect. Because of geometrical restrictions, when a Ca^{2+} ion binds to two adjacent carboxylate groups, it displays a large solvent accessible surface, and its solvation shell still includes more water molecules (∼5) than the configuration in Figure 2b, where the PA chain hinders the accessibility of water to the calcium ion. Therefore, the number of degrees of freedom of the solvent in the former situation is reduced, resulting in a negative entropic contribution. This conclusion is in agreement with earlier findings that the binding of Ca^{2+} to PA is driven by entropy.[4]

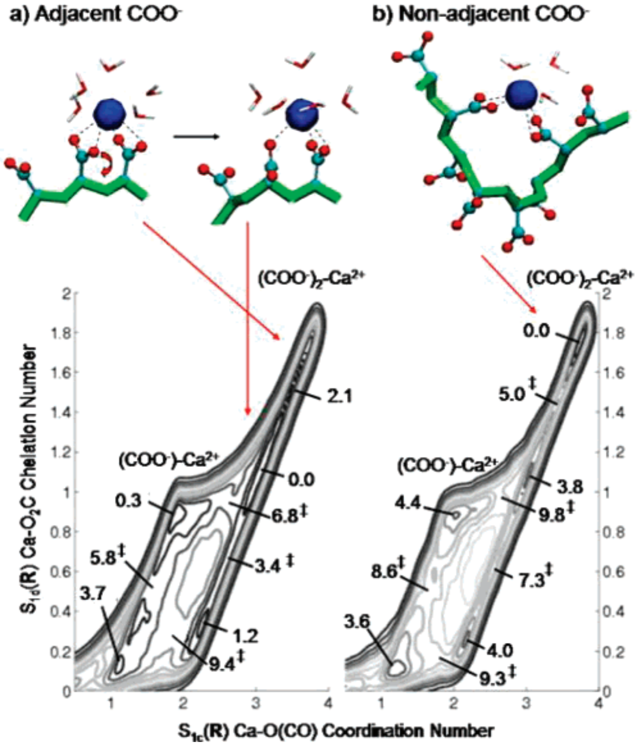

Figure 2. Snapshots and contour plots of the free energy surface (FES) for Ca^{2+}−PA monomer coordination. Blue spheres represent calcium ions. Along the *x*-axis the number of Ca^{2+}−oxygen bonds is plotted, and the number of Ca^{2+}−carboxylate double bonds is plotted along the *y*-axis. (a) Ca^{2+} coordination to the first two adjacent PA monomers (stretched chain); (b) Ca^{2+} coordination to nonadjacent PA monomers 2 and 8 (bent chain). The values of the free energies of the wells and of the barriers (‡), with respect to the deepest well are reported. For details, see text.

Coiling of the Chain. Above we have demonstrated a preference for desolvation of Ca^{2+}, which is the primary reason why strongly coordinated Ca−PA complexes are formed. In this section we address the link between coiling and precipitation

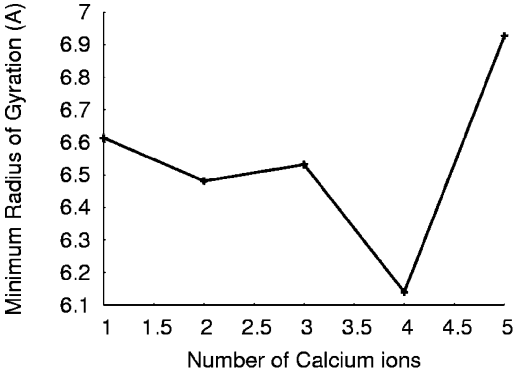

Figure 3. Minimum radius of gyration achieved for metadynamics simulations exploring the radius of gyration space, after 9 ns, at various Ca^{2+} concentrations.

as suggested by experiments.[18] To this aim we exploit order parameters related to the extent of coiling of a PA chain, such as the radius of gyration, and we investigate the behavior of the PA chain at different Ca^{2+} concentrations, ranging from 1 to 5 calcium ions per chain of 20 monomers. Metadynamics runs with the radius of gyration as the single reaction coordinate ($S_{2b}(\mathbf{R})$) produced qualitative information on possible coiled states, by allowing the system to visit a wide range of compact and stretched conformations. During the full length of these runs, the calcium ions stay firmly attached to the chain, indicating that binding is strong and that detachment of Ca^{2+} from the chain is unlikely at these calcium concentrations. In all simulations the initial configuration was a rather stretched chain with a radius of gyration of about 9 Å. After ~9 ns the minimum radius of gyration, as reported in Figure 3, reaches similar values for all calcium concentrations ($S_{2b}(\mathbf{R}) = 7-6$ Å). The series of 1-, 2-, 3-, or 4-coordinated Ca^{2+} ions displays a modest decrease in the minimum radius of gyration. However, when five Ca^{2+} ions are coordinated, the chain remains relatively stretched within the simulation time ($S_{2b}(\mathbf{R}) = 7$ Å). This result suggests that for these short PA chains high calcium concentrations do not necessarily lead to strongly coiled conformations. An examination of the trajectories showed that the short chain becomes more rigid at high Ca^{2+} concentrations. This local rigidity can be attributed to a decrease in freedom of the torsional angles between adjacent monomers coordinated to the same calcium ion. Previous studies have shown that initial inefficient coordination indeed occurs to adjacent monomers,[1] causing the above-mentioned local rigidity. However, we do not state that higher calcium concentrations prevent coiling altogether, but simply that stable conformations with very high contact order, which can be stable from a thermodynamic point of view, are kinetically difficult to achieve. These results also suggest that at high NaPA concentrations interchain interactions would precede the possible occurrence of coiling of a single chain. Indeed, previous simulations have shown that at high NaPA concentration shielding by the calcium ions helps chains to approach one another close enough to bind.[1]

On the other hand, previously reported light scattering experiments on very long chains at low polymer concentrations, which showed increased coiling up to the threshold calcium concentration for precipitation of the complex,[18,19] suggest that on long time scales stable coiled conformations can be achieved. Of course, for very long chains the above-mentioned local rigidity would not prevent long-range bending of the polymer, and interactions between distant parts of the polymer would be more likely to occur. But to find such coiled conformations for our short polymers and obtain estimates of the free energy barriers, additional order parameters have been employed in subsequent metadynamics simulations, in order to probe the way in which calcium binds.

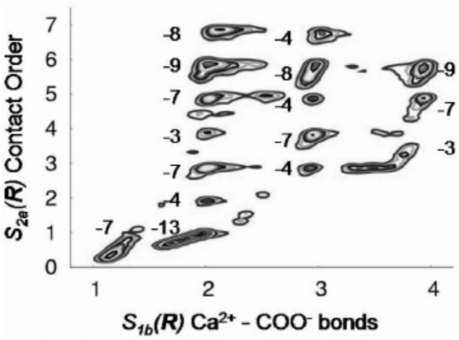

Figure 4. FES from a single metadynamics run for the system with one calcium ion. The number of calcium−carboxylate bonds and the contact order were used as order parameters. Free energies (contours) are in kcal/mol.

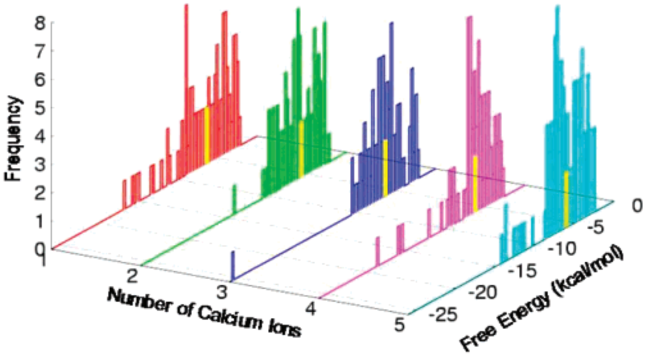

Figure 5. Histogram of barrier heights for all free energy minima as a function of calcium concentration. The yellow lines represent the average free energies.

The contact order ($S_{2a}(\mathbf{R})$) represents an alternative description of the state of coiling of a PA chain. When used as an order parameter, it influences the Ca−COO interactions as well as coiling, allowing a larger range of conformations to be explored. For the systems with 1−5 calcium ions bound to the chain, we performed a number of metadynamics runs with the contact order in combination with other order parameters, such as coordination number ($S_{1b}(\mathbf{R})$) and radius of gyration ($S_{2b}(\mathbf{R})$). An example of a free energy surface as a function of coordination number and contact order from a single metadynamics run is provided in Figure 4. The figure indicates that with a single-coordinated calcium ion the chain prefers a low contact order, corresponding to a stretched state. Overall, we found a large number of minima, separated by barriers of about 8 kcal/mol. However, a limited number of very deep minima, corresponding to coiled conformations, was also found at nearly all concentrations investigated (Figure 5), thus supporting the experimental finding of particularly stable coiled states.[19] The average free energy values as a function of calcium concentration did not show a clear trend.

Figure 6a,b depicts several probability-weighted averages as a function of the number of calcium ions bound. We obtained these values somewhat arbitrarily by selecting the deepest point of every minimum and using the exponential of the well depth as a weighting factor for all the properties in those points. The average contact order (Figure 6a) increases with the number of calcium ions, until a plateau is reached when three calcium ions are bound. This trend is mirrored by the behavior of the radius of gyration, which indeed decreases to a plateau for the same calcium concentrations. Indeed, one would expect that at higher Ca^{2+} concentrations a shielding of the charges on the chain

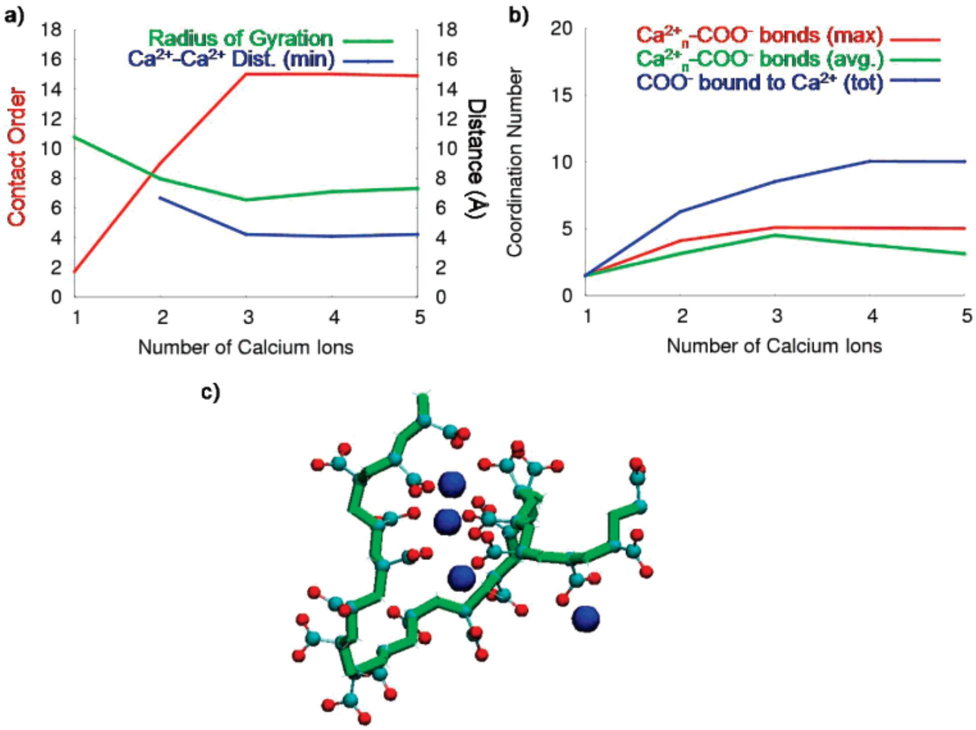

Figure 6. (a, b) Probability-weighted averages for several properties as a function of Ca^{2+} concentration. (c) Snapshot of the conformation of the chain in a very deep minimum (18 kcal/mol). The blue dots represent the Ca^{2+} ions. The shortest Ca−Ca distances amount to 4.16 and 4.09 Å.

would reduce the electrostatic repulsion between the negatively charged monomers, resulting in increased coiling. While the chain becomes more compact at higher calcium concentrations, the minimum distance between the bound calcium ions decreases until it reaches 4 Å. Figure 6b shows that the maximum and the average number of monomers coordinated to one calcium ion increase with Ca^{2+} concentration. If the average number of bonds of one calcium ion is compared to the total number of bound monomers, it is evident that many of the coordinated monomers are shared between calcium ions. In fact, the analysis of the stable conformations extracted from the metadynamics trajectories shows that often the carboxylate groups binding to calcium ions contribute only one oxygen per Ca^{2+}, leaving the other oxygen available for additional coordination. This result is related to the behavior of adjacent monomers, discussed in the previous section. A representative snapshot of a very stable conformation is shown in Figure 6c. In this type of conformation the $Ca^{2+}-Ca^{2+}$ distances are of the order of 4 Å, and many of the oxygen atoms are shared between calcium ions. This clustering of calcium ions in one region of the chain is in agreement with the experimental findings of pearl necklace conformations, and it provides a local arrangement reminiscent of the crystal structure of $CaCO_3$ minerals, namely calcite, which indeed has very similar Ca−Ca and Ca−O distances.[27] The deepest minima at calcium ion numbers of 3, 4, and 5 all involve similarly clustered regions of 3 calcium ions. Minima involving bigger clusters of calcium ions might also exist, but we were unable to locate them in the finite simulation time. In view of these results, we suggest that the clustering enhances the stability of coiled conformations and gives the Ca−PA complex its tendency to desolvate and precipitate at high Ca^{2+} concentrations.

At low PA concentrations the polymer chain can attain a stable coiled conformation, with local clustering of the calcium ions in a crystal-like fashion, in certain regions of the chain. These crystal-like conformations will eventually lead to desolvation of the complexes, and precipitation would then be the result of hydrophobic interactions between the coiled complexes. The unwanted coiling can be prevented by using stiffer chains. In addition, we suggest the introduction of more flexible side groups. In this manner each calcium ion could be fully coordinated and shielded by two neighboring carboxylate groups, making sharing of the monomers, and related coiling/cross-linking, unnecessary.

Conclusion

We have performed extensive atomistic simulations on short PA chains in water in the presence of Ca^{2+} ions, using metadynamics to accelerate the standard MD and quantitatively reconstruct the free energy surface. We have elucidated the nature of the strong “site binding” of Ca^{2+} ions to the polymers in solution (−6 kcal/mol for initial binding, up to −18 kcal/mol for the most stable configurations) and confirmed its entropic nature. Our results show a low probability for coiling of single PA chains at high PA and Ca^{2+} concentration due to the local rigidity induced in the initially stretched short chain when many Ca^{2+} ions coordinate. In this manner the formation of the preferred highly coiled conformations with many Ca−COO^- bonds is kinetically hindered, and interchain interactions are favored. Furthermore, we demonstrated how at low NaPA concentration the system has the opportunity to achieve highly coiled stable conformations, with local crystal-like features where many calcium ions cluster together, sharing several COO^- groups. We suggest that these crystal-like features are responsible for the tendency for the CaPA complex to desolvate at low Ca^{2+} concentrations. Stiffer backbones in combination with higher flexibility of the side chains should allow for better encapsulation of an individual calcium ion and more efficient binding to each monomer. This would prevent the formation of local crystal-like structures and the occurrence of coiling and desolvation.

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