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To cite this version:

Mathieu Salanne, Sami Tazi, Rodolphe Vuilleumier, Benjamin Rotenberg. Ca 2+ -Cl − Association in Water Revisited: the Role of Cation Hydration. ChemPhysChem, 2017, 18 (19), pp.2807 - 2811. 10.1002/cphc.201700286 . hal-01634885

HAL Id: hal-01634885

https://hal.sorbonne-universite.fr/hal-01634885

Submitted on 14 Nov 2017

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Ca^{2+} - Cl^{-} association in water revisited: the role of cation hydration

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May 16, 2017

1 Abstract

We investigate the dissociation of a Ca^{2+}-Cl^{-} pair in water using classical molecular dynamics simulations with a polarizable interaction potential, parameterized from *ab initio* calculations. By computing the potential of mean force as a function not only of the interionic distance but also of the coordination numbers by water molecules, we show it is necessary to use a collective variable describing the cation hydration in order to capture the dissociation mechanism. In the contact ion pair, the Ca^{2+} cation has a first coordination sphere containing 5 or 6 water molecules. The minimum free-energy path for dissociation involves a two-step process: First one or two additional water molecules enter the cation coordination shell, increasing the coordination number up to 7 with an almost fixed interionic distance. Then the dissociation of the ionic pair occurs at this fixed coordination number.

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2 Introduction

Aqueous calcium and chloride ions play determinant roles in various biological or environmental phenomena, and understanding their thermodynamics is of primary importance [1]. Among the microscopic quantities that remain to be characterized, the formation of associated Ca^{2+}-Cl^{-} pairs, despite its apparent simplicity, is not well understood yet. Indeed, such a chemical reaction, which involves electrostatic interactions only, cannot be probed directly from experiments. Due to the presence of four diffracting nuclei (Ca, Cl, O and H) in aqueous solutions of calcium chloride, the interpretation of diffraction data is not univocal and leads to different conclusions: For example, a neutron diffraction study concluded on the virtual absence of Ca^{2+}-Cl^{-} contact ion pairing even at high concentration [2] (*i.e.* up to 6.4 mol L^{-1}) while the same year an X-ray diffraction study, evidence of both contact and solvent-separated ion pair formation was obtained [3] at concentrations starting from 4 mol L^{-1}. The latter conclusions were similar to the ones obtained subsequently by XAFS. [4]

From the computational point of view, a first attempt to determine the Ca^{2+}-Cl^{-} potential of mean force (PMF) was made by Guardia *et al.*[5]. Their work was criticized by Dang and Smith because of the absence of inclusion of polarization effects in their molecular dynamics (MD) simulations [6]. Nevertheless, Dang *et al.* showed that the PMF obtained with polarizable force fields is largely dependent on the parameters used for describing the ion pair interactions[7]. In all these classical simulation works, the Ca^{2+}-Cl^{-} distance was chosen as a single reaction coordinate. Yet, it was unambiguously shown by Geissler *et al.* by using the transition path sampling method[8], that the dissociation of ionic pairs involves a wide range of transition pathways in which collective solvent motions play an important role [9]. In particular they have shown that in the case of NaCl aqueous solutions the entrance of water molecules in the Na^{+} ion solvation shell is a driving force for dissociation of the ionic pair. More recently, Ballard and Dellago analyzed the enthalpic and entropic contributions to the PMF for NaCl and demonstrated with transition path analysis that the dissociation event is sensitive to the solvent fluctuations [10]. Fennell *et al.* have computed water density profiles around alkali-halide ion pairs at fixed separations and found clear correlations between the PMF and the solvent organization, which depend on the nature of both the cation and the anion. [11]

The Ca^{2+}-Cl^{-} PMF has also been extracted from a series of constrained *ab initio* MD calculation [12]. In this study, the role of cation hydration in the pair dissociation was considered and a mechanism based on the entrance of a sixth water molecule in the Ca^{2+} solvation shell occurring at an interionic distance of 3.5 Å was proposed. Dai *et al.* used Density Function Theory (DFT) and molecular dynamics to investigate ion pairing of calcium chloride in water clusters and in solution [13], and concluded that contact ion pairs may not be neglected, even though they are less frequent than solvent shared ion pairs. Wang *et al.* used the same approach to analyze the stability of high-order Ca-Cl complexes (with several chloride ligands) in concentrated mixed calcium and lithium chloride solutions [14]. Baer and Mundy computed the PMF from *ab*

initio MD and emphasized the importance of including a dispersion correction to DFT scheme in order to correctly account for the solvation of the ions [15]. They further used these results to discuss the relative merits of several classical force fields for the description of this PMF, finding a better agreement with the dispersion-corrected DFT in the case of a model with rescaled charges to account for electronic polarization, introduced by Kohagen *et al.* [16, 17]

In this work we address quantitatively the importance of Ca^{2+} hydration in its association with Cl^- from classical MD simulations. We compute the potential of mean force for this process along two collective variables. The first one is the conventional interionic distance, while the second is the cation coordination number in water molecules. The simulations involve a polarizable force field of first-principles accuracy, which was parametrized using DFT calculations and validated against experimental data pertaining to the solvation structure, dynamics and thermodynamics [18, 19]. Simulation details are given in Section 3, while results are presented and discussed in Section 4.

3 Methods

The molecular dynamics simulations were performed with the CP2K package. The simulation cell of cubic shape (with a lateral length of 27.6 Å) contained 700 water molecules, one Ca^{2+} and one Cl^-. The trajectories were gathered in the NVT ensemble, with a timestep of 1 fs. Temperature was maintained constant through the use of a chain of Nose-Hoover thermostat with a time constant of 1 ps. The polarizable force field provided in reference [19] was used to describe the interactions involving the ions, combined with the Dang-Chang water force field [20]. This force field includes repulsion, dispersion, Coulombic and polarization terms. It neglects charge transfer since it was developed for closed-shell ions only. It is able to reproduce experimental data on the solvation structure (including in the case of calcium a direct comparison of the EXAFS signal from experiments and from the configurations sampled from molecular dynamics), thermodynamics (hydration free energy) and dynamics (ion diffusion coefficient). In addition, the interactions between calcium and chloride also allow to reproduce the density of crystalline $CaCl_2$ within 5%, whereas its crystal structure is even unstable with many classical force fields [19]. The Ewald summation method was employed for the interactions involving point charges and induced dipoles [21, 22, 23], with a real-space cut-off set to 13.8 Å (a similar cut-off distance was taken for the short-ranged repulsion and dispersion interactions).

The two collective variables were extracted from the trajectories. The cation coordination number in water molecules was calculated following Sprik [24]:

$$N_{\mathrm{H_2O}}(\mathbf{r}^N) = \sum_j \frac{1}{1 + \exp[\kappa(r_j - r_c)]} \tag{1}$$

where the sum runs over all the water molecules, r_j is the distance between the Ca^{2+} cation and the oxygen atom of the jth water molecule, r_c is the coordi-

nation radius taken equal to the first minimum of the Ca-O radial distribution function ($r_c = 3.5$ Å) and κ^{-1} is the width of the transition region (here 0.1 Å), in which a water molecule accounts for a number smaller than 1 in the coordination number. The Cl^- anion coordination number N'_{H_2O} is defined in a similar way (with $r_c = 3.7$ Å).

The Ca-Cl distance was restrained to 16 r_0 values evenly distributed between 2.3 and 8.0 Å by an harmonic potential $V(r) = \frac{k}{2}(r - r_0)^2$. The spring constant was set to 6 kcal/mol, except for distances ranging between 2.3 and 3.5 Å, for which additional sampling was performed for values of 12 and 24 kcal/mol. The total simulation time for each target distance ranged between 1.8 and 2.2 ns. The two-dimensional PMF was then obtained using the weighted histogram analysis method (WHAM). [25] Note that we use a bias only in the interionic distance and not in the coordination number so that only configurations accessible to thermal fluctuations are sampled along this latter variable. However the two-dimensional PMF can easily be reconstructed with WHAM provided that the metastable basins are connected by sufficiently low free energy barriers in the unbiased direction. The sampling of two collective variables over simulations biased in a single one (possibly different from the two sampled) is similar to the Indirect Umbrella Sampling (INDUS) approach of Patel *et al.* [26]

4 Results and discussion

The potential of mean force is reported in figure 1 as a function of two collective variables: on the one hand interionic distance r between Ca^{2+} and Cl^-, on the other hand the water coordination number N_{H_2O} for either Ca^{2+} or Cl^- ions. In the former case, along the horizontal axis, the contact ion pair (CIP, $r < 3.9$ Å) and solvent-separated ion pair (SSIP, 3.9 Å $< r <$ 6.0 Å) regions can clearly be identified. In both cases, as well as for larger distances, several basins are then observed along the vertical axis. In the case of the CIP, they correspond to values of 5, 6 or 7 for N_{H_2O}, while the preferred coordination numbers for the Ca^{2+} ion either involved in a SSIP or as an isolated ion are 7 or 8. Therefore, it appears clearly that the coordination number of Ca^{2+} cation is a relevant collective variable and that neglecting it only provides a partial information on the association and dissociation processes. Unsurprisingly, for the Cl^- ion the coordination number is of lesser importance, as indicated by the funnel-like landscape with no well-defined basins at fixed interionic distances. Therefore we will mainly focus on the case of Ca^{2+}.

In order to analyze further the dissociation process, we have projected the variations of the PMF along a given collective variable for different basins along the other one. More precisely, the projected PMF along x for the region defined by the values $y \in \mathrm{A}$ is:

$$\mathrm{PMF}_{y\in\mathrm{A}}(x) = -k_B T \ln \int_{\mathrm{A}} \mathrm{d}y \; e^{-\mathrm{PMF}(x,y)/k_B T} \tag{2}$$

In a first step, we focus on the CIP. From figure 2, it is immediately seen that

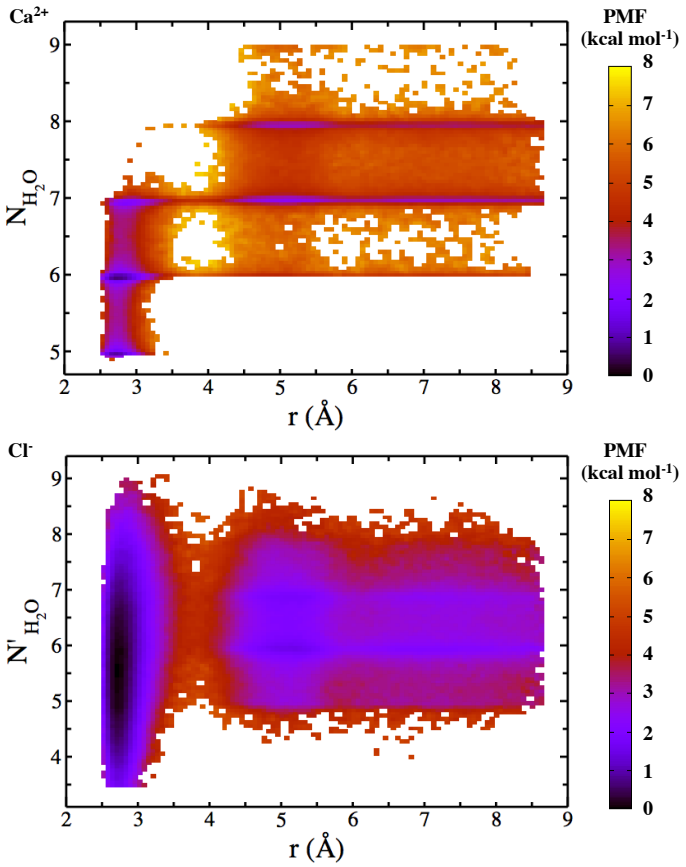

Figure 1: Two-dimensional potential of mean force for the Ca^{2+}-Cl^{-} dissociation. In addition to the interionic distance, which appears on the horizontal axis, the Ca^{2+} (top) / Cl^{-} (bottom) coordination numbers in water molecules is used as a second collective variable, along the vertical axis.

the depth of the basins corresponding to $N_{H_2O} = 5$ or 6 are almost identical, while the PMF for $N_{H_2O} = 7$ is higher by ≈1.2 kcal mol^{-1} at the Cl^{-} concentration of our simulation. Note that this value (and those reported below) depends in principle on the choice of the width κ^{-1} to define the continuous coordination number in Eq. 1. However this does not change the conclusion that a coordination of 7 is less probable than 6 and 5 in the CIP. Integrating e^{-PMF/k_BT} over the three basins, we obtain relative weights of 32, 51 and 17% for 5, 6 and 7 water molecules, respectively (hence an average of ~ 5.9).

One also observes in figure 1 a slight shift of the interionic distance for which the PMF as a function of N_{H_2O} for the CIP: It increases from 2.72 Å for $N_{H_2O} = 5$ to 2.78 Å for $N_{H_2O} = 6$ and 2.90 Å for $N_{H_2O} = 7$. We therefore

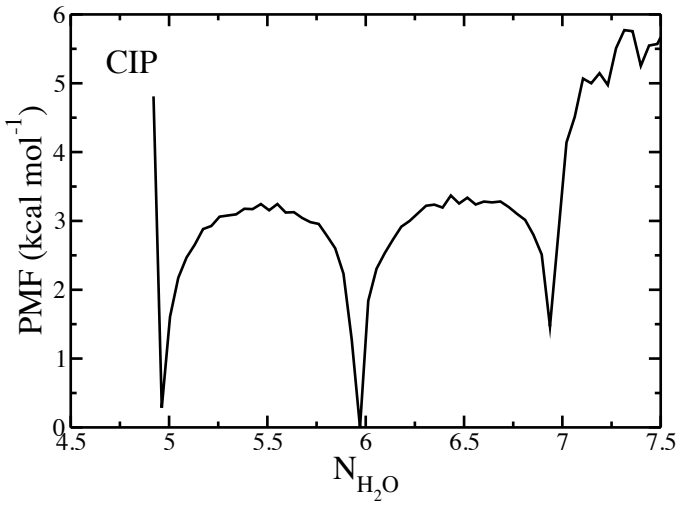

Figure 2: One-dimensional PMF as a function of the Ca^{2+} coordination number (water molecules only) for interionic distances corresponding to the CIP region, calculated from the two-dimensional one using Eq. (2).

expect a more likely distance of 2.7–2.8 Å for the CIP. This result is in excellent agreement with a X-Ray diffraction study performed in concentrated $CaCl_2$ solutions[3], from which a distance of 2.7 Å is reported. This distance also corresponds to the shortest distance in crystalline $CaCl_2$. In their *ab initio* based study of the PMF as a function of the interionic distance, Timko *et al.* report a slightly shorter distance [12] of 2.57 Å which differs from the results obtained in another (unconstrained) *ab initio* MD study, in which Ca^{2+}-Cl^- bonds of length 2.7–2.8 Å were obtained [27]. We can therefore conclude that the correct CIP distance is more likely to be around 2.7 Å.

When considering the PMF variation with interionic distances for fixed coordination numbers, which are shown on figure 3, strong differences are observed. Compared to the CIP, the PMF value at the SSIP interionic distance is somewhat lower for large coordination numbers, decreasing from 4.0 kcal mol^{-1} for $N_{H_2O} = 6$ to 1.1 kcal mol^{-1} for $N_{H_2O} = 7$. Even more drastic are the changes in the barrier height for the CIP $\rightarrow$ SSIP transition: It could not be evaluated for $N_{H_2O} = 5$ (but it is larger than 7 kcal mol^{-1}) and takes values of 5.6 and 3.4 kcal mol^{-1}, respectively for $N_{H_2O} = 6$ and 7. The fact that the transition cannot take place at ambient conditions for a five-fold coordinated Ca^{2+} cation was already observed by Timko *et al.*[12]. In this study, the PMF corresponds to $N_{H_2O} = 5$ in the CIP region and to $N_{H_2O} = 6$ beyond (*i.e.* for distances greater than 3.5 Å). The authors have concluded that the Ca^{2+}-Cl^- dissociation involves the entrance of a water molecule in the cation solvation shell at $r \approx 3.5$ Å, but this proposed mechanism was only supported by observations

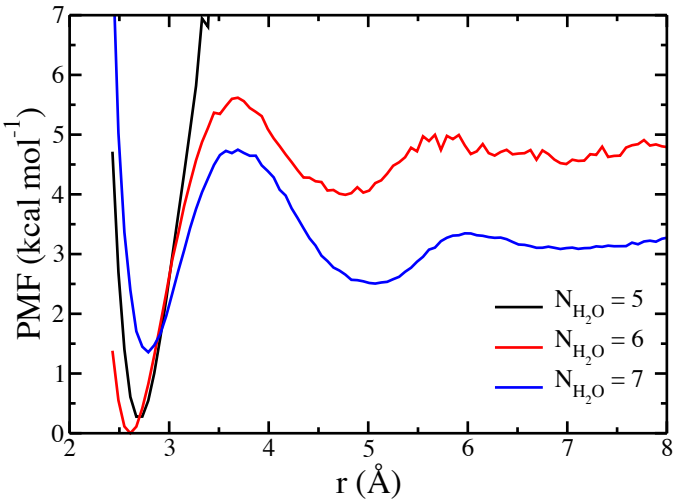

Figure 3: One-dimensional PMF as a function of the interionic distance for fixed cation coordination number in water molecules ($N_{\mathrm{H_2O}} = 5$, 6 or 7), calculated from the two-dimensional one using Eq. (2).

on a series of very short (20-30 ps) trajectories, due to the use of *ab initio* MD simulations.

Here, the two-dimensional PMF clearly shows that, starting from the global minimum ($r = 2.78$ Å, $N_{\mathrm{H_2O}} = 6$), the minimum free-energy path involves an increase in the coordination number up to 7 with an almost fixed interionic distance followed by the dissociation of the ionic pair at fixed coordination number. This path involves two successive barriers of 3.3 and 3.4 kcal mol^{-1} (Figure 1), while the direct path in which the dissociation of the ionic pair occurs at a fixed coordination number of 6 involves a substantially larger barrier of 5.6 kcal mol^{-1} (Figure 3). A system starting at the secondary minimum ($r = 2.72$ Å, $N_{\mathrm{H_2O}} = 5$) would therefore need to cross an additional barrier of 3.4 kcal mol^{-1} for adding a first water molecule to the Ca^{2+} ion.

We now turn to the relative weight of the CIP ($r \sim 2.7 - 2.8$ and $N = 5$ or 6) and the SSIP ($r \sim 4.8 - 5.2$ and $N = 7$), for which we observe a difference of 2.5 kcal mol^{-1}. This result differs from the one by Timko *et al.*, who found similar PMF values for these two states. Again, as pointed out by the authors of this study, it is difficult to evaluate the average force in some of the windows in the transition region due to the limited simulation time in *ab initio* MD, which renders the comparison difficult. Nevertheless, in the SSIP minimum region, an excellent agreement is obtained with our PMF obtained for a fixed $N_{\mathrm{H_2O}} = 6$.

Dang *et al.* have proposed two PMFs corresponding to different parameterization of the Ca^{2+} - Cl^{-} interaction. [7] With a first set of parameters, which were obtained using the Lorentz-Berthelot mixing rules, a deep mini-

mum was observed for the CIP, which had a lower free energy than the SSIP by 4.1 kcal mol^{-1}. On the contrary, when determining the parameters for this interaction from gas-phase electronic structure calculations, no stable CIP was found. This shows that an accurate parameterization of the ion-ion interaction, which is often neglected in the building of common force fields, is crucial. In our case, the parameters were extracted from a generalized force-matching procedure [28] involving *ab initio* reference data obtained on crystalline $CaCl_2$ and on solvated Ca^{2+} and Cl^-. The advantage of this approach is that all the interactions are then sampled in a condensed-phase environment, where the electronic structure differs substantially from that in the gas phase [29] (this can for example be seen in the polarizability of the Cl^- anion which decreases from 5.5 $Å^3$ in the gas phase to 3.5 $Å^3$ in aqueous solution [18]). In addition, our force field takes into account short-range damping effects, which are known to play an important role on the polarization of the ions and of the water molecules. [30, 23]

Finally, the last important feature observed from the two-dimensional PMF in figure 1 is that for large interionic distances, *i.e.* for the SSIP and beyond, the most stable coordination number is $N_{H_2O} = 7$. The 8-fold coordinated Ca^{2+} species also corresponds to local free energy minima and occurrence of both $N_{H_2O} = 6$ and 9 are also expected, although with lower frequency. This is again in agreement with previous experimental studies, from which the most commonly proposed coordination numbers are of 6, 7 and 8 (see Table 1 in reference [27] for a review of the X-Ray diffraction, neutron diffraction and EXAFS experiments).

5 Conclusion

In conclusion, we have shown in this paper the importance of accounting for a solvent collective variable to describe the association/dissociation of ionic pairs. In the case of Ca^{2+}-Cl^-, the first coordination sphere of the cation contains predominantly 5 or 6 water molecules in addition to the chloride anion when the CIP is formed. The minimum free-energy path for dissociation involves an increase in the coordination number up to 7 with an almost fixed interionic distance followed by a dissociation of the ionic pair at this fixed coordination number. Then for the SSIP and for larger interionic distance the Ca^{2+} cation has preferred coordination numbers of 7 or 8. This study confirms the important role played by collective solvent fluctuations, underlined for the Na^+-Cl^- ion pair in previous transition path sampling and analysis. [9, 10, 31] While such a study is out of the scope of the present work, it would be instructive to use this approach to investigate the transitions between the various metastable states found here. A first step in this direction could be the use of reaction rate theory in both distance and coordination number space, as an extension of the recent study of Roy *et al.* [32]

The number of metastable states, with several possible hydration states for the CIP, might also contribute to the experimental difficulty in demonstrating the presence or absence of ion pairs in concentrated solutions. The PMF at

infinite dilution considered here reveals no strong tendency towards association. Even though the short-range solvation-dependent part of the PMF only depends weakly on salt concentration up to a few 0.1 molar [33], extrapolation to concentrations of several mol dm^{-3}, at which X-ray and neutron diffraction experiments lead to contradictory conclusions [2, 3, 34], is not possible and resort to the simulation of concentrated solution will provide a better picture of the speciation under these conditions. Taking into account additional collective variables may be even more necessary in the case of complex molecular ions; for example the role of water molecules in the binding between alkali cations and acetate has been underlined. [35, 36] It would therefore be of high interest to perform systematic studies of the multi-dimensional potential of mean force for such systems in order to characterize further the dissociation pathways.

6 Acknowledgements

The authors acknowledge financial support from the Agence Nationale de la Recherche under grant ANR-09-SYSC-012 and from the Ville de Paris (Emergences, project Blue Energy). We also would like to thank David Chandler and Patrick Varilly for useful discussions on the INDUS method.

7 Keywords

Calcium chloride, ion pair, hydration, molecular dynamics, potential of mean force

8 TOC

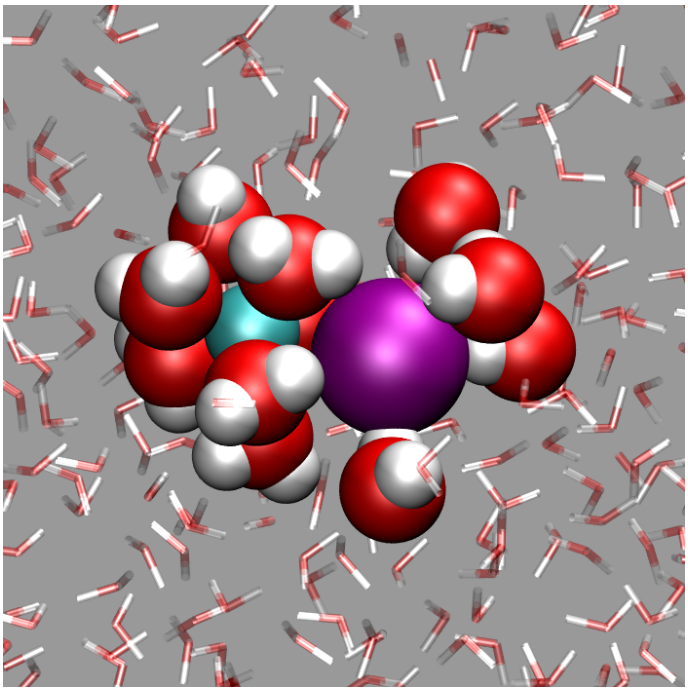

Figure 4: (TOC) **What goes around...** The dissociation of a calcium-chloride ion pair in water (see figure) involves rearrangements of the solvation shell of both ions. We show using molecular simulation that the coordination number of calcium by water molecules should be considered in addition to the interionic distance to investigate this process, in particular when computing the potential of mean force.

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