Salt enrichment and dynamics in the interface of supercooled aqueous droplets

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Abstract

The interconversion reaction of NaCl between the contact-ion pair (CIP) and the solvent-separated ion pair (SSIP) as well as the free-ion state in cold droplets have not been yet investigated. We report direct computational evidence that the lower the temperature the closer to the surface the ion interconversion reaction takes place. In supercooled droplets the enrichment of the subsurface in salt becomes more evident. The stability of the SSIP relative to the CIP increases as the ion-pairing is transferred toward the droplet’s outer layers. In the free ion form, the number density of Cl^- in nanodroplets shows a broad maximum in the interior in addition to the well-known maximum in the surface. In the study of the reaction dynamics, we find a weak coupling between the interionic NaCl distance reaction coordinate and the solvent degrees of freedom, which contrasts the diffusive crossing of the free energy barrier found in bulk solution modeling. The H_2O self-diffusion coefficient is found to be at least an order of magnitude larger than that in the bulk solution. This fast diffusion decreases the coupling of the solvent with the interionic distance reaction coordinate. We propose to exploit the enhanced surface ion concentration at low temperature to eliminate salts from droplets in native mass spectrometry ionization methods.

Reduction of adduct formation between macromolecules and salt may open up the possibility to directly ionize a biological sample from a physiological solution in experiments.

Introduction

Cold aqueous droplets containing ion pairs play an important role in atmospheric chemistry and technology. In particular, they participate in thundercloud processes in the upper troposphere, where the temperature may be as low as 220 K. In technology, they are used in cryo-preservation,^{1,2} and potentially they can be used in geo- and climate-engineering. Cold droplets also show particular physical properties. A notable example is the preservation within nanodroplets of the supercooled liquid state, in contrast to the bulk, where practically unavoidable crystallization prevents the liquid from existing in the temperature range of $T = 150 \text{ K}$ to 230 K at $P = 1 \text{ atm}$ of pressure.^{3–16} In a broader context, the distinct physical chemistry in small-volume cold systems has been demonstrated by the formation of new ice structures that cannot be seen in the bulk.^{3–14,17}

Cold aqueous nanodroplets have a surprisingly complex internal structure that varies with temperature and size, as revealed by computer simulations of the TIP4P/2005 model of

water.¹⁸ While the interior P of small droplets reaches over 100 MPa on account of a surface tension that increases with decreasing T , two other factors conspire to create a heterogeneous environment: densification of the liquid at the vapour interface, and a bulk-like interior that reflects the bulk behavior of water, including a tetrahedral network that expands and becomes more compressible with decreasing T . By $T = 220$ K, the outer water layers can become significantly denser compared to the interior of the droplet. The interior core density continues to follow bulk values for the given T and interior P . For droplets with number of molecules $N \geq 360$, the droplet interior exhibits a temperature of maximum density below which the density decreases, creating a density contrast between the lower density core and higher density (sub)surface, a contrast that sharpens with decreasing T . For $T \leq 200$, the density differences between core and subsurface exceeds 5%. The above scenario means that simulated supercooled droplets (for $N \geq 200$) exhibit structural heterogeneity manifested by three radial regions: low-density interior, high-density subsurface (thickness $\approx 0.7 - 0.8$ nm) and surface (thickness ≈ 0.3 nm). These regions are depicted in Fig. 1. This structure provides an interesting chemical environment that contrasts that of a simpler nanodroplet at ambient conditions, where the density is approximately constant, showing a decrease (mainly due to shape fluctuations) only at the liquid-vapor interface.

The study of the distinct chemical reactivity within supercooled droplets,² and more generally in cold droplets is still in its infancy. Here, we model the NaCl ion-pairing, one of the fundamental reactions in chemistry, in mesoscopic clusters in the temperature range of 200 K-300 K. The mesoscopic clusters are also called nanodroplets.

Experiments and computations of NaCl ion-pairs in clusters have been mainly performed in systems composed of up to a few tens of H₂O molecules.²⁰⁻³⁰ Fourier transform microwave spectroscopy²⁴ has shown that the distance between the ions in a NaCl pair increases by gradually adding up to 3 H₂O molecules and

Figure 1: Typical snapshot of a supercooled droplet composed of $N = 776$ H₂O molecules and a sole NaCl ion pair. Only the O sites are depicted in the colored shells, the Na⁺ is depicted by the large red-colored sphere, and the Cl⁻ by the blue-colored sphere. Three regions are distinguished where the H₂O molecules are organized differently: (a) A bulk-like interior (orange-colored) that extends from the droplet center of mass (COM) to a distance $r = R_B$. This region is characterized by a lower density and a better formed tetrahedral network than the outer layers. (b) The subsurface region $R_B < r < R_V$ (green-colored), that is characterized by a higher density, and lower degree of tetrahedrality than the interior. (c) The surface region $R_V < r < R_e$ (grey-colored), where R_e is the equimolar radius. The determination of R_B and R_V is presented in Ref.¹⁹ A few H₂O molecules (O sites are depicted by small red-colored spheres) are found at $r > R_e$.

reaches the value of 2.9 Å, which is the contact-ion pair (CIP) distance found in the bulk solution. Anion photoelectron spectroscopy²⁵ of clusters comprising NaCl and up to 12 H₂O molecules found that at 9–12 H₂O molecules, the CIP and SSIP (solvent-separated ion pair) formations are almost degenerate in energy. In larger clusters, characteristics different from those of minute or macroscopic sizes, such as the large shape fluctuations, prevail and may affect the reaction mechanisms. The experi-

mental and computational studies of salt ion-pairing in larger cluster are more limited. Clusters of 150–400 H_2O molecules containing NaCl have been studied by X-ray photoelectron spectroscopy.^{31,31,32}

Nanodroplets are characterized by a large surface-to-volume ratio, thus, when they are neutral and sufficiently large, they may have commonalities with the ion-pairing features in planar interfaces. The NaCl ion pairing in the planar water interface at room temperature has been extensively studied.^{26,33–41} It has been found that the CIP and SSIP are stabilized differently in the interface and in the bulk. There is a high degree of agreement that the ion dissociation is suppressed in the interface^{33,34,38} relative to bulk solution.

The study of the ion pairing in cold systems is more challenging because of the slow dynamics.^{42,43} The ion-pairing mechanism has been only recently explored in the premelting ice surface.⁴⁴ It has been found that the ice interface may play the dominant role in the reaction dynamics and that the dissociation dynamics of water molecules in the premelting layer differ significantly from those in bulk solution.

In this article we use the example of NaCl in an aqueous nanodroplet to examine via molecular modeling how the water structure and dynamics at cooling, and more evidently at supercooling, affect the ion-pairing. Differently from the simulations of ion pairs in planar interfaces,³⁸ where the ions are restricted to remain in the interface, in the droplet simulations the ions are free to explore the entire volume. We hypothesize that the colder the droplet, the more likely is for the CIP to SSIP interconversion reaction to occur in the droplet subsurface and surface. The dynamics in the droplets is characterized by the H_2O self-diffusion coefficient and the rate constant for the CIP to SSIP transition. As it will be discussed later, the salt enrichment of the interface at low temperature may be exploited to optimize the ionization conditions in mass spectrometry (MS).

Results

Equilibrium

To examine how the particular structure of a cold droplet affects the ion-pairing we mainly study systems comprising $N = 776$ H_2O molecules and a sole NaCl pair in the temperature range of 200 K to 300 K. The droplet size is large enough for the results to be transferable to larger droplets. We model the systems with the TIP4P/2005 set of parameters and with the polarizable SWM4-NDP force field.⁴⁵ TIP4P/2005 allows one to model the systems at supercooling, but it lacks the electronic polarization. In previous research it has been found that the SWM4-NDP model yields non-physical water density at low temperature,^{19,46,47} and for this reason we can only study the trends in dynamic and equilibrium properties in the temperature range $T = 260$ K–300 K.

The TIP4P/2005 model shows that the number of transitions between CIP and SSIP as well as between SSIP and the free ions (Fig. S1 in SI) is sufficient to provide good enough statistics to directly calculate free energy differences along the $\text{Na}^+\text{-Cl}^-$ interionic distance. Indicatively, at $T = 200$ K there are 7 transitions from CIP to SSIP within $2.8 \mu\text{s}$, and at $T = 220$ K 10 transitions within $0.8 \mu\text{s}$ (Fig. S1 in SI). In Fig. 2 (a) (for TIP4P/2005 model) the free energy along the $\text{Na}^+\text{-Cl}^-$ interionic distance at $T = 200$ K and 300 K are shown. The CIP is defined within the basin where the $\text{Na}^+\text{-Cl}^-$ interionic distance is in the range of $2.5 \text{ \AA}$ – $3.5 \text{ \AA}$, the SSIP in $3.5 \text{ \AA}$ – $5.7.0 \text{ \AA}$, and the free ions when they are $> 5.7 \text{ \AA}$ apart. The equilibrium constant for $\text{CIP} \rightleftharpoons \text{SSIP}$ and the free energy differences along the interionic distance are shown in Table 1. It is found that at $T = 300$ K the CIP is stabilized more than at 200 K and that at 200 K, the free energy difference between CIP and SSIP decreases.

Figure 2 (b) and (c) show the location at which the ion-pairing takes place at 200 K and 300 K, respectively. The free-ion configurations accounts for $\approx 70\%$ of the total number. In previous research¹⁹ we have found that the supercooled droplets with $N > 200$ exhibit het-

Table 1: Free energy differences ($\Delta W_{1,2}$) along the $\text{Na}^+\text{-Cl}^-$ distance at various temperatures for TIP4P/2005 and SWM4-NDP models. BT denotes the free energy barrier top along this reaction coordinate. The number in parentheses is $\Delta W_{1,2}$ in units of $k_B T$, where k_B is the Boltzmann constant. K_{eq} is the equilibrium constant for $\text{CIP} \rightleftharpoons \text{SSIP}$. The statistical error in the free energy estimates is ± 0.15 kcal/mol.

Model	T (K)	ΔW_1 (kcal/mol) CIP $\rightarrow$ BT	ΔW_2 (kcal/mol) SSIP $\rightarrow$ BT	K_{eq}
TIP4P/2005	300	2.8 (4.7)	1.8 (3.0)	0.74
	260	2.6 (5.1)	2.1 (4.0)	1.09
	240	2.8 (5.8)	2.5 (5.2)	1.52
	210	2.3 (5.4)	2.1 (5.0)	1.92
	200	2.5 (6.3)	2.4 (6.0)	1.77
SWM4-NDP	300	1.4 (2.35)	2.2 (3.7)	10.2
	280	1.3 (2.34)	2.3 (4.1)	19.9
	260	1.3 (2.52)	2.3 (4.5)	22.5

erogeneity that is manifested by three regions: a bulk-like interior, a subsurface, and a surface (Fig 1). In $N = 776$ the distances from the droplet’s COM that delimit these regions are $R_B = 7.4$ Å, $R_V = 14.8$ Å, and $R_e = 17.7$ Å (where R_e denotes the equimolar radius), respectively. At 200 K, the CIP and SSIP show a distinct propensity to be in the middle of the subsurface. In contrast, at 300 K, the probability of formation of CIP, SSIP is significant throughout the volume of the droplet but with a slightly higher probability in the subsurface. We define the angle between the dipole moment of the CIP and SSIP (dipole moment is defined from the negative site to the positive site) and the vector defined from the droplet’s COM to the ion-pair COM. At $T = 300$ K the orientation of the CIP spans all the angles, but at 200 K, the cosine of the angle is peaks in the range 0.0-0.2, which corresponds to an angle of $90^\circ - 78^\circ$ (Fig. S2 in SI). The orientation of the NaCl is clearly more pronounced within the SWM4-NDP model (Fig. S2 in SI). The CIP orientation indicates a slight preference of the Cl^- site toward the droplet’s surface. Even though Fig. 2 only shows the $\text{CIP} \rightleftharpoons \text{SSIP}$ equilibrium at two significantly different temperatures, the propensity of the ions toward the subsurface increases gradually as the temperature decreases as shown in Fig. S3 and Fig. S4 in SI. Specifically, we find that TIP4P/2005 at 200 K expels Na^+ stronger than Cl^- (Fig. S4 (d) in

SI).

We think that the increased expulsion of the ions in the subsurface as temperature decreases is due to an improved H-bonded coordinated network in the droplet interior. The differences in the H-bonded network in the interior and subsurface in supercooled droplets have been presented in our previous research.¹⁹ At supercooling, both the CIP and SSIP are mainly formed in the outer portion of the subsurface, where the dielectric constant is expected to be higher than that at 300 K. The higher dielectric constant at lower temperature may lead to a decrease in the free energy difference between the CIP and SSIP, which is consistent with the free energy profile at 200 K shown in Fig 2 (a).

Figure 3 (a) shows the free energy of the interconversion between CIP and SSIP as a function of the NaCl interionic distance using SWM4-NDP model. The K_{eq} values and the free energy differences are shown in Table 1. The free-ion configurations account for $\approx 85 - 87\%$ of the total production run. Figure 3 (b) and (c) show that the CIP is formed near the surface at 300 K and 260 K. The probability to encounter the ions in the interior and subsurface decreases considerably relative to the TIP4P/2005. The polarizable model finds the Cl^- to be nearer to the vapor-liquid interface than Na^+ . The closer proximity of Cl^- to the surface is in agreement with previous studies^{22,26,48-50} that have been performed at room temperature. The temper-

(a)

Figure 2: (a) Free energy for $\text{CIP} \rightleftharpoons \text{SSIP}$ inter-conversion reaction at 200 K and 300 K along the Na^+ - Cl^- interionic distance. TIP4P/2005 model is used. (b) Distribution of Na^+ (red) and Cl^- (blue) sites in the CIP, SSIP and Free ions (F) basins at 200 K as a function of the distance from the droplet's COM (y-axis) (the profiles are not normalized by the volume of the spherical shell). (c) Same as (b) but at 300 K.

ature effect, that has not been studied previously, shows that the lower the temperature (a)

(a)

Figure 3: (a) Same as Fig. 2 (a) but for the SWM4-NDP polarizable model at various temperatures. (b) and (c) same as Fig. 2 (b) and (c), respectively, but for SWM4-NDP.

the higher the Cl^- probability density in the surface (see also Fig. S5 and Fig. S6 in SI), (b) the free energy differences between the CIP and SSIP and the BT (barrier top) are not very sensitive to the temperature. We attribute this lack of sensitivity to the fact that the polarizable model predicts the most probable location of the ions near the surface in the temperature range 260 K-300 K. The location does

Figure 4: Probability density profiles of Na^+ and Cl^- sites (measured in units of concentration in the right y-axis), and H_2O density profiles (measured in units of g/cm^3) in the left y-axis) at $T = 300$ K in droplets comprising $N = 776$ H_2O molecules and a sole NaCl pair. For reference, the probability density of a sole Cl^- in $N = 776$ is included. The SWM4-NDP polarizable model is used.

not change significantly with temperature. We note that we have also performed simulations with different values of the Langevin damping (Fig. S7 in SI), and all the free energy profiles are in agreement.

Here, we point out a significant difference in the relative stability of CIP and SSIP between the present study and that of Dang et al. using a polarizable model when the pair is confined in the Gibbs dividing surface of a planar interface.³⁸ In the latter case, it is found that the CIP is formed with a higher probability than the SSIP. We think that when the pair is confined in the Gibbs dividing surface both Na^+ and Cl^- are partially solvated, which promotes pairing due to the low dielectric constant environment. In our systems, the Cl^- lies on the surface, but the Na^+ is well solvated in the borderline of the subsurface and surface or within the subsurface. The likelihood of the CIP formation relative to the SSIP decreases because of the particular requirements for the orientation of the H_2O molecules near the interface.

The SSIP basin (Fig. 3 (a)) is wide and shows a fine structure of two small local minima. This structure is consistent throughout the temperature range 260 K-300 K and agrees very well

with the structure observed in the PMF reported by Dang et al. using a different polarizable model.³⁸ Possibly the structure seen in the SSIP basin is due to a different orientation of the bridging H_2O molecules. As we are going to see later, this structure is consistent even in the presence of four NaCl pairs.

In summary, even though the polarizable and the non-polarizable force fields show different location of the ion-pairing at room temperature, both models indicate that the lower the temperature the farther from the droplet's COM the ion pairing takes place. The models are also in agreement that the stability of the SSIP relative to the CIP increases as the ion-pairing is transferred toward the droplet's outer layers and that when the CIP is formed the Cl^- is found more in the exterior than when it is in the SSIP or free-ion form.

In order to have a closer look to the free-ion state we compare the Na^+ and Cl^- number density with that of the sole ions using the SWM4-NDP model at 300 K as shown in Fig. 4. The free ion-state is the most likely state of the ion pair (87% of the total number of configurations). We find that the Na^+ number density, is higher in the interior in agreement with previous research.^{19,51,52} We computed the number density of Cl^- at $T = 300$ K as a function of the distance from the droplet's COM. The number density shows two broad maxima. The basin of the one maximum near the surface extends from the subsurface to the surface region (1.2 Å-1.9 Å) and corresponds to a free energy minimum of $1.7 k_B T$ measured from the barrier top, which is located at 1.2 Å. This free energy estimate is in good agreement with the value of $\approx 1.0 k_B T$ reported by Coleman et al.⁵¹ at $T = 293.15$ K, using the same polarizable model as we do, in a cluster of radius equal to 1.1 nm, which corresponds to $N \approx 145 - 150$ H_2O molecules. The value of this free energy as a function of the distance from the droplet's COM is affected by the shape fluctuations. The smaller the droplet, the larger the effect. Our free energy estimate (and the Ref.⁵¹) includes the contribution from the pure entropic effect due to the spherical geometry. If the free energy due to the geometric effect is subtracted,

then the effect due to the ion-H₂O interactions equals $0.90 k_B T$. The $N = 776$ droplet showed another broad maximum at $0.7 \text{ \AA}$. The basin that is associated with it is in the range of $0.2 \text{ \AA}$ - $1.1 \text{ \AA}$. It is likely, that the basin extends up to the droplet’s COM, but it is harder to distinguish that because of the larger statistical uncertainty near the center. To our knowledge the second maximum has not been previously reported in the literature. The interior basin ($0.2 \text{ \AA}$ - $1.2 \text{ \AA}$) corresponds to a free energy that is more shallow than that on the surface, but it is wider, which indicates a substantial probability to encounter the Cl^- in the interior. The equilibrium constant estimated directly by the number of configurations in the exterior basin over the interior is 3.2, however, if we estimate the ratio of probability densities in the two basins, then the value is 1.1. The presence of Na^+ increases slightly the residence time of the Cl^- on the surface, which decreases the number density of the Cl^- in the interior.

To analyse the retention of salt in the droplet interior at supercooled droplets, we also examined droplets comprised 776 H₂O molecules and four NaCl pairs, using the SWM4-NDP at 260 K and 300 K and TIP4P/2005 at 300 K down to 200 K. The probability density profiles (Fig.S8 and Fig.S9 in SI) and free energy profiles as a function of the interionic distance are shown in Fig. S10 and Fig. S11 in SI. The striking feature at lower temperature is the increased Na^+ and Cl^- probability density in the subsurface (distance from the COM $> 1.2 \text{ nm}$) relative to that at 300 K. The distance 1.2 nm separates two basins. For SWM4-NDP the equilibrium constant as a ratio of configurations in the outer basin over the inner basin for Cl^- is 12.2 at 260 K vs 3.3 at 300 K. This ratio for Na^+ is very similar ≈ 0.84 at both temperatures. The enrichment of the subsurface in ions at lower temperature is attributed to the expulsion of the ions from the bulk-like interior due to a better coordinated H-bonded network. The reduced shape fluctuations may contribute to this increase as well. We find here that the internal H-bonded network is maintained even at the higher concentration of NaCl. It is interesting to note that Fig. S8 in SI may create the

impression that at room temperature the ions are deeper in the interior measured from the surface than at lower temperature. The depth of the ions from the surface is the same at the various temperatures. The visual misconception arises from the fact that the distance from the COM order parameter masks the droplet’s shape fluctuations. Comparison of the location of Na^+ and Cl^- between the single pair in the droplet and the multiple pairs, shows that in the supersaturated droplet the ions have higher propensity toward the exterior. The free energy differences of CIP and SSIP (Fig. S10 and Fig. S11 in SI) are in excellent agreement with those for the single NaCl (Fig. 3 (a) and Table 1), which verifies the convergence of the runs.

It is interesting to note that for several ions in TIP4P/2005 we have consistently found that near R_B the probability density shows a minimum. This unfavourable region indicates the presence of an energetic barrier, arising from the different quality of the H-bonded network, in the crossing of the ion from the subsurface to the interior.

Finally, we can examine the effect of the lower temperature in the location of the multiple ions in charged droplets, where ions of the same sign are in excess. We have studied droplets composed of 3000 H₂O molecules and $24\text{Na}^+-8\text{Cl}^-$ ions or $24\text{Cl}^- - 8\text{Na}^+$ ions at $T = 240 \text{ K}$ and 300 K using TIP4P/2005. The data and analysis are presented in Sec. S8 in SI. The key idea of the surface enrichment in salts also appears in the highly charged droplets. TIP4P/2005 shows the trend for the enrichment, and we expect that a polarizable model will show an even higher enhancement of the surface concentration. In native mass spectrometry (MS) droplets are heated up in order to quickly evaporate but in this process ions may form undesirable adducts with the analytes. We propose that by initial cooling a droplet instead of heating, or by alternating heating and cooling the ions may accumulate near the surface. Possibly, bombardment with other molecules may assist in the detachment of solvated ions or their salt complexes from the surface.

Dynamics

The dynamics of the ion-pair interconversion reaction may be affected by the self-diffusion of the H_2O molecules. We compute the self-diffusion coefficient using the fluctuation-dissipation theorem where we combine a correlation function formalism with the macroscopic description of the diffusion within a spherical cavity. The details of the method are described in the Methods Section. The diffusion coefficient as a function of temperature is shown in Table 2 and Fig. 5. An example of the decay of $\langle \delta J_{k,l,m}^*(0) \delta J_{k,l,m}(t) \rangle$ is shown in Fig. S13 in SI. At $T = 300$ K, both TIP4P/2005 and SWM4-NDP predict a diffusion coefficient value approximately 23 and 44 times larger than that of the bulk at room temperature (exp. $D = 2.30 \text{ nm}^2/\text{ns}$), respectively. Near 200 K, the diffusion coefficient in the $N = 776$ droplet approaches the experimental value of supercooled water⁵³ at 260.1 K.

We attribute this large value relative to the bulk water to the fact that in $N = 776$ droplets the 93% of the molecules are found in the sub-surface (411 H_2O molecules out of 776) and surface (108 H_2O molecules out of 776), where molecules diffuse fast via a “jump” mechanism, which does not exist in bulk solution. The high value of diffusion coefficient is consistent with experimental suggestions that reactions in microdroplets that accelerate by orders of magnitude relative to the bulk solution may also indicate a significant increase in the value of the diffusion coefficient.^{54,55} The diffusion is expected to be much higher in nanoscopic droplets because of the larger surface contribution and the significant contribution of the shape fluctuations.

We find the forward rate constant ($\text{CIP} \rightarrow \text{SSIP}$) by using the time evolution of the interionic distance of the MD trajectories. We compute the time-correlation function of a state variable n_{CIP} that has the value of 1 if the interionic distance is less than $3.3 \text{ \AA}$ (for SWM4-NDP) and 0 if it is greater than this value. The correlation function is fitted to $\phi(t) = p_{\text{CIP}} p_{\text{SSIP}} \exp(-k_f t) + p_{\text{CIP}} p_{\text{CIP}}$, where p_{CIP} and p_{SSIP} denote probabilities of CIP and SSIP,

Figure 5: Diffusion coefficient of H_2O as a function of temperature for $N = 776$. The red points are for TIP4P/2005 and the blue for SWM4-NDP.

respectively. An example of the decay of $\langle n_{\text{CIP}}(t) n_{\text{CIP}}(0) \rangle$ is shown in Fig. S14 in SI and the values are presented in Table 2. The back rate constant ($\text{SSIP} \rightarrow \text{CIP}$) can be computed by $k_b = k_f / K_{eq}$, where K_{eq} is shown in Table 1. As it is expected, the reaction rate decreases with temperature for both models. Overall, the rate constant is higher in the TIP4P/2005 model than in SWM4-NDP. In SWM4-NDP the transitions are very few but the life-time of CIP is longer than in TIP4P/2005. The difference is attributed to the fact that in SWM4-NDP the CIP-SSIP transition occurs closer to the surface than in the TIP4P/2005. Near the surface it is expected for the CIP to live longer than in the TIP4P/2005 model because of the much lower dielectric constant in this location. The droplet electric field on the surface also may contribute in this stabilization because the ion pair is oriented with the negative site (Cl^-) toward the hydrogen-site richer surface.

The dynamics of the interconversion reaction is affected by two factors that are not present in bulk solution. Firstly, the Cl^- is less solvated than the Na^+ ion since it is found almost at the surface, therefore, it is mainly the motions

Table 2: Self-diffusion coefficient of H₂O and rate coefficient (k_f) of the conversion of CIP to SSIP vs T for TIP4P/2005 and SWM4-NDP. The values of D shown in Fig. 5 are found in Table S4 in SI. As a reference, the experimental value of D for water is 2.30 nm²/ns at room temperature and SWM4-NDP has been parametrized to reproduce this value (2.33 nm²/ns $\pm$ 0.02 from Ref.⁴⁵). τ is the dissociation lifetime (1/ k_f).

Model	T (K)	D (nm ² /ns)	k_f (1/ns)	τ (ns)	error in τ
TIP4P/2005	300	53.1	7.04	0.142	0.007
	260	19.6	2.34	0.428	0.012
	220	6.01	0.19	5.360	0.112
SWM4-NDP	300	101.8	2.43	0.412	0.019
	280	47.0	0.64	1.561	0.048
	260	26.7	0.35	2.837	0.055

of the solvent molecules around Na⁺ that determine the dynamics.²² Secondly, the much faster diffusion of the solvent molecules in the droplet relative to the bulk solution counterpart, especially, in the subsurface and surface. These factors may decrease the coupling of the interionic distance reaction coordinate with the solvent. As a result, no diffusive barrier crossing is found in the direct monitoring of the CIP-SSIP transitions. Fig. S15 in SI shows representative trajectory segments with CIP-SSIP transitions from a trajectory at $T = 260$ K using SWM4-NDP. Lack of diffusive motion at the barrier top is also found for TIP4P/2005, which shows that the weak coupling is extended in the entire subsurface. In contrast, in the bulk solution as it has been demonstrated by other authors^{38,56} there is a strong coupling between the solvent and the interionic distance reaction coordinate, which leads to several re-crossing at the barrier top of the free energy profile.

Conclusion

The modeling of NaCl ion-pairing in cold aqueous droplets showed that in colder droplets ion pairing is more likely to take place near the surface where the stability of the SSIP relative to the CIP increases. This is opposite to the results of bulk solution simulations.^{33,34,38} The polarizable model shows a substantial stabilization of the SSIP relative to CIP not only at low

temperature but also at $T = 300$ K. A side-result of modeling via SWM4-NDP (polarizable model) is an interior broad minimum for Cl⁻ ions in a droplet in addition to the well-known minimum in the surface.^{51,52} This shows that the non-polarizable force fields overemphasize the interior local minimum.

In the study of the reaction dynamics, we found a weak coupling between the interionic NaCl distance reaction coordinate and the solvent degrees of freedom. The reduced coupling is mainly attributed to the presence of Cl⁻ near the surface and to the fast diffusion of H₂O molecules. In contrast to bulk solution where the crossing of the free energy barrier (along the interionic distance) is diffusive, there are no significant re-crossings in droplets. We estimated the self-diffusion of H₂O by introducing a method that resolves the difficulties of employing mean-square displacement and the velocity autocorrelation function for computing the diffusion coefficient in spherical confined geometry. We found that the H₂O self-diffusion coefficient at room temperature is at least an order of magnitude larger than that in bulk solution. It is at ≈ 210 K that the diffusion coefficient of H₂O in the droplet equals the bulk value at room temperature.

Because of the shift in the location of ion distributions and ion-pairing with temperature, we propose to exploit alternating low and high temperature as a way to control the adduct formation with macromolecules in droplet-based

ionization methods used in mass spectrometry. Bombardment of cold charged droplets with other molecules may be a possible way to remove Na^+ ions from the salt enriched interface. Enhanced salt release from droplets that carry the analytes may considerably extend the capability of native mass spectrometry analysis because it may allow for the salinity of the parent bulk solution of a biological sample to be closer to a physiological concentration of NaCl or KCl. Protons are another major ionic species in charged droplets. Experiments and computations have detected enhanced proton activity on ice at 155K.^{58,59} Molecular dynamics simulations predicted that the migration of surface-hydrated protons is ≈ 2800 slower than that of bulk protons at 190 K because they can be locally trapped by the undercoordinated water molecules.^{58,59} Thus, it was deduced that the activity detected in experiments arises from the higher proton concentration.^{58,59} It has also been found that protons are expelled from the ice bulk because of poor solubility in ice.^{60–62} The present study and accumulated evidence from the literature supports the hypothesis that protons in cold aqueous droplets will also be expelled to the surface and their migration may slow down due to local trapping. Therefore, the alternating cooling and heating of droplets may also provide a possible method of controlling the degree of protonation in proteins. We have shown that protonation and sodiation lead to different conformations of macromolecules,⁵⁷ therefore, the migration of ions and their nature may also affect the conformations.

In summary, the expulsion of ions from the interior of a supercooled or ice droplet may be exploited in MS experiments in order to eliminate undesirable salts and control the charge states of biological macromolecules.

We envision that since it is possible for H_2O in supercooled droplets to expel chemical species to the interface that otherwise reside in the interior at room temperature, the question of establishing a deeper relation between the solubility in supercooled H_2O and ice^{63–66} may be addressed. We currently extend the ion-pairing study at low temperature to LiF where, differently from the NaCl pair, both ions show a

propensity for the droplet interior at room temperature.

Methods

Here we present the main points of the computational methods. A detailed account of the methodology is found in Sec. S1 of the SI. The systems that were simulated are shown in Table S1 of the SI. We performed equilibrium molecular dynamics (MD) simulations of aqueous nanodroplets (a) with a single NaCl pair, (b) multiple NaCl pairs, and (c) charged with multiple Na^+ ions with a smaller number of Cl^- counterions and vice versa.

The majority of the systems were composed of $N = 776$ H_2O molecules ($R_e = 1.77$ nm) and fewer of $N = 3000$ H_2O molecules ($R_e = 2.78$ nm). We selected a droplet of $N = 776$ H_2O to do the majority of the computations because this size is large enough to clearly distinguish the bulk-like interior of a droplet from the subsurface and at the same time this size is computationally feasible to be studied at low temperature and with a polarizable model. The MD simulations were performed using the software NAMD v2.14⁶⁷ and the trajectories were visualized using VMD 1.9.4a47.⁶⁸ The water molecules were modeled with the TIP4P/2005 (transferable intermolecular potential with four points) model⁶⁹ and the SWM4-NDP model.⁴⁵ The ion parameters are described in Sec. S1 of SI and for the TIP4P/2005 are shown in Table S2 of SI. The TIP4P/2005 simulations were performed in the temperature range 200 K–300 K and the SWM4-NDP simulations in 260 K–300 K.

Computation of diffusion coefficient in droplets

Droplets present a confining environment that restricts the range of molecule movement. The use of common formulae that relates the diffusion coefficient to the integral of the velocity correlation function or, equivalently, to the mean-squared displacement poses certain difficulties. The problem has already been pointed

out by B. J. Berne and co-workers⁷⁰ regarding the diffusion coefficient in finite-sized systems. Here we calculate the diffusion coefficient in a droplet using correlation function formalism and the macroscopic description of the diffusion in a spherical cavity.

The evolution of the molecule position is given by the Laplace equation with the Neumann boundary conditions

$$\frac{\partial P(\mathbf{r}, t)}{\partial t} = D \nabla^2 P(\mathbf{r}, t) \quad (1)$$

where P denotes probability density, and D the diffusion coefficient.

The general solution of the Laplace equation is

$$P(\mathbf{r}, t) = \sum_{\substack{k,l,m \\ |m| \leq l}} B_{k,l,m} e^{-Dt/a_{k,l}^2} j_l(r/a_{k,l}) Y_{l,m}(\theta, \phi) \quad (2)$$

where $B_{k,l,m}$ are the numerical coefficients determined by the initial conditions. r, θ, ϕ are the spherical polar coordinates corresponding to the molecule position $\mathbf{r}$. $Y_{l,m}(\theta, \phi)$ is the spherical harmonics of order l and rank m . j_l is the spherical Bessel function of the first kind, $a_{k,l}/R_0$ are the solutions of $j'_l(x) = 0$ imposed by the Neumann boundary conditions and R_0 the droplet's equimolar radius.

Using the orthonormality conditions for the spherical Bessel functions we arrive at the identity

$$B_{k,l,m} e^{-Dt/a_{k,l}^2} = \langle r^2 j_l(r/a_{k,l}) Y_{l,m}^*(\theta, \phi) \rangle = \int_{r \leq R_0} d^3\mathbf{r} r^2 j_l(r/a_{k,l}) Y_{l,m}^*(\theta, \phi) P(\mathbf{r}, t) \quad (3)$$

We introduce a microscopic quantity $\delta J_{k,l,m}$ corresponding to the decay of the probability density of the molecule location using the following identity

$$\delta J_{k,l,m}(t) = r^2 j_l(r_i(t)/a_{k,l}) Y_{l,m}(\theta_i(t), \phi_i(t)) \quad (4)$$

for a molecule i .

Using the linear response ansatz⁷¹ we equate the decay of the macroscopic expectation (3) to the single molecule autocorrelation function

$$\frac{a_{k,l}^2}{D} = \frac{1}{\langle \delta J_{k,l,m}^*(0) \delta J_{k,l,m}(0) \rangle} \int_0^\infty dt \langle \delta J_{k,l,m}^*(0) \delta J_{k,l,m}(t) \rangle \quad (5)$$

We use the spherical Bessel function of order $l = 1$

$$j_1(x) = \frac{\sin x}{x} - \frac{\cos x}{x^2} \quad (6)$$

The first solution of the Neumann b.c. is $a_{1,1} = 2.082 R_0$. From Eq. 5 we can find D by computing the time autocorrelation function (right-hand side of 5) from the MD trajectories and by using the value of $a_{1,1}$. The program for the computation of the diffusion coefficient has been prepared by SC.

Supporting Information

(S1) Details of the computational methods and models. (S2) The trajectories of the distance of Na^+ and Cl^- from the droplet COM and the interionic distance of a sole NaCl pair in a droplet of $N = 776$ H_2O molecules modeled with TIP4P/2005 at various temperatures. (S3) Dipole moment orientation of NaCl. (S4) Ion probability density profiles using TIP4P/2005. (S5 & S6) Ion probability density profiles using SWM4-NDP. (S7) Probability density profiles for droplets with 4 NaCl. (S8) Probability density profiles and discussion for highly charged droplets with counterions. (S9) Dynamics.

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