

Ions at Aqueous Interfaces

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Abstract

Studies of aqueous interfaces and of the behavior of ions therein have been profiting from a recent remarkable progress in surface selective spectroscopies, as well as from developments in molecular simulations. Here, we summarize and place in context our investigations of ions at aqueous interfaces employing molecular dynamics simulations and electronic structure methods, performed in close contact with experiment. For the simplest of these interfaces, i.e., the open water surface we demonstrate that the traditional picture of an ion-free surface is not valid for large soft (polarizable) ions such as the heavier halides. Both simulations and spectroscopic measurements indicate that these ions can be present and even enhanced at surface of water. In addition we show that that ionic product of water exhibits a peculiar surface behavior with hydronium but not hydroxide accumulating at the air/water and alkane/water interfaces. This result is supported by surface selective spectroscopic experiments and surface tension measurements. However, it contradicts the interpretation of electrophoretic and titration experiments in terms of strong surface adsorption of hydroxide; an issue which is further discussed here.

The applicability of the observed behavior of ions at the water surface to investigations of their affinity for the interface between proteins and aqueous solutions is explored. Simulations

show that for alkali cations the dominant mechanism of specific interactions with the surface of hydrated proteins is via ion pairing with negatively charged amino acid residues and with the backbone amide groups. As far as halide anions are concerned, the lighter ones tend to pair with positively charged amino acid residues, while heavier halides exhibit affinity to non-polar protein patches, which resembles their behavior at the air/water interface. These findings, together with results for more complex molecular ions, allow us to formulate a local model of interactions of ions with proteins with the aim to rationalize at the molecular level ion-specific Hofmeister effects, e.g., salting out of proteins.

1. Introduction

Structure, dynamics, and chemistry of aqueous interfaces have attracted considerable attention in the last years, as also reflected in the theme of the 141. Faraday Discussion. The present Discussion focuses on a range of important areas concerning interfacial behavior of aqueous systems; from the surface charge of liquid water, over ice interfaces, to confined (nanoscale) systems, and to electrochemical and biological interfaces. Overviews of latest scientific problems concerning interfacial water including many of these topics can also be found in the April 2006 special issue of Chemical Reviews and in dedicated monographs [1, 2]. Within the present contribution we narrow the focus to issues connected with our studies of ions at aqueous interfaces.

Aqueous electrolytes including their interfaces emerged as subjects of intensive scientific scrutiny already in the nineteen-hundreds with the basic theory thereof being built up by the first half of the 20th century [3, 4]. More recently, studies of aqueous electrolytes and specific ion effects have been undergoing a remarkable renaissance with a particular emphasis on interfacial

systems [5]. The reason for the renewed interest in aqueous interfaces is at least twofold. First, processes at aqueous interfaces have been shown to play a prominent role in widely studied problems in a variety of fields ranging from chemistry of atmospheric aerosols and heterogeneous catalysis [6-8] to biophysics and biochemistry [9]. Second, new surface-selective spectroscopic techniques and computational methods have allowed for investigations of aqueous interfaces with atomistic detail revealing how incompletely they have been understood so far [10].

The present paper focuses on our recent attempts to characterize ions at aqueous interfaces at a molecular level. Since it is not supposed to be a review but rather an account on our limited contributions, it does not aim at providing a complete overview of the present state of matters within this ever broadening field. Solely due to our particular choice of systems under investigation several exciting areas concerning, e.g., ions at water/non-polar liquid or water/solid (insulator or metal) interfaces will be omitted or only briefly touched upon here. This paper thus provides a limited and necessarily personally-biased account on the development of our understanding of interfacial behavior of aqueous ions based on molecular simulations, which we performed in close contact with surface-selective spectroscopic experiments.

Other researchers in the field might tell the story of ions at aqueous interfaces differently (and better), however, we hope that useful general patterns will emerge from this somewhat personal narrative. Chronologically, we started about a decade ago with investigations of inorganic ions at the air/water interface, being motivated by unresolved issues concerning heterogeneous chemistry of atmospheric aqueous sea salt aerosols [11, 12]. Having collected a “database“ of computational results which allowed us to unravel certain general patterns of ionic surface affinities, our interest has shifted lately toward the behavior of ions at the interface

between a biomolecule and the surrounding aqueous solution, focusing on specific ion effects on proteins [13-15]. This path has lead us (somewhat accidentally) from the simplest aqueous interface to arguably one of the most complex ones. Since the reader may find it pedagogic moving from simple to complex interfaces, we stick to this route also in this paper. In the following chapters we thus discuss first the behavior of ions at the air/water interface, proceeding later to issues concerning ions at hydrated proteins. Doing this, we present also the latest (mostly unpublished) computational results, putting special emphasis on controversial and not completely resolved issues.

2. Inorganic ions at the Air/Water Interface

2.1 Simulations of Surfaces of Aqueous Salt Solutions

At the simplest aqueous interface, i.e., that between water and air or vapor, the behavior of salt ions should be according to the textbook knowledge rather straightforward [4, 16-18]. Namely, viewing this interface as a plane between a high and low dielectric constant media, ions should be repelled from it into the water phase by the electrostatic image force (see Figure 1). This situation is pertinent inorganic ions. Large organic ions, e.g., containing long alkyl chains are also subject to the image force, however, they are attracted to the surface due their hydrophobicity [19]. But even for inorganic ions the picture turns out to be more complicated than Figure 1 suggests. These ions are indeed repelled from the surface by the image force, however, the free energy penalty for bringing a monovalent ion from the aqueous phase right to the interface is only of the order of several kT (the rest of the free energy penalty being paid only when the ion is fully desolvated in the air) [20]. Such a relatively weak electrostatic repulsion from the water surface can in principle be overwhelmed by other forces connected with ion-

specific interaction with water, e.g., due to ion cavitation and polarization [21]. Ion-specific dispersion forces can also come into play [22], but are likely of secondary importance in strongly polar solvents.

Consequently, large and polarizable (soft) inorganic ions, such as heavier halides, can be found in the topmost water layer and can even exhibit surface enhancement, followed by subsurface depletion [12, 23-26]. This is demonstrated in Figure 2, which shows density profiles of surface attracted bromide and surface repelled sodium in a slab of roughly molar aqueous solution of NaBr [12]. As a matter of fact, surface affinity of iodide, bromide, and to a lesser extent also of chloride was first observed in pioneering polarizable molecular dynamics (MD) simulations of water clusters [27-30], being only later found computationally also for extended aqueous slabs [12, 23-26]. We should stress here, that even for the largest and softest investigated halide, i.e., iodide, the interfacial enhancement is rather modest, the peak surface concentration exceeding that of the bulk by no more than a factor of 2-3 [12]. Inorganic ions thus do not behave as typical surfactants with many orders of magnitude of surface enhancement, nevertheless, some of them can act as surface active species. This concerns particularly anions, which are large and polarizable (with few exceptions such as fluoride); small hard positively charged ions, e.g., alkali cations, being always repelled from the surface [21, 31]. Surface depletion is also pertinent to polyvalent ions, where much stronger (compared to monovalent ions) image charge repulsion overwhelms surface driving forces [32].

Propensity for the air/water interface was also observed in MD simulations of more complex inorganic salts containing molecular ions. There, the situation is complicated by difficulties in deriving accurate polarizable force fields for non-spherical ions possessing internal structure. Therefore, only a limited set of such ions has been investigated so far. Surface affinity

has been observed, e.g., for azide [33] and thiocyanate [34]. For the latter case, the concentration dependence of the surface enhancement has been investigated in the molar range showing, similarly to heavier halides, a gradual saturation of the surface effect. A particularly difficult case has been that of nitrate anion, where first calculations indicated some surface enhancement [35]. Subsequent more converged simulations with a refined force field revealed that nitrate is repelled, albeit weakly from the top layer and rather prefers to reside in the immediate subsurface [36, 37]. This demonstrates the sensitivity of the results on simulation conditions, in particular on the force field. Rough estimates of ionic surface affinities can be already obtained from nanosecond simulations with relatively simple (but polarizable) potentials with several hundreds of water molecules in the unit cell of the slab. However, to be more quantitative, force fields must be refined and longer simulations with larger unit cells are needed.

2.2 Experimental Considerations for Surfaces of Aqueous Salt Solutions

The above computational findings of surface affinities of large and soft inorganic ions were first met with skepticism, since they were in conflict with the textbook notion of an essentially ion free electrolyte surface due to image charge repulsion [16-18]. Moreover, inorganic salts in general increase the surface tension of water. It follows from the Gibbs adsorption equation [38]

$$\partial\gamma/\partial\mu = 1/kT \times \partial\gamma/\partial(\ln fx) = -\Gamma \quad (1)$$

that a positive change in surface tension γ with salt ion chemical potential μ means a negative surface excess Γ of the ions. (The chemical potential of the ion species is related to the logarithm of its mole fraction x times activity coefficient f , the latter being close to unity at small

concentrations.) Note, however, surface excess is an integral quantity over the whole interfacial region. As such, it can still be negative if surface accumulation of ions is overcompensated by subsurface depletion. Qualitatively, such a situation is indeed observed, e.g., for heavier halides (Figure 2), although it is difficult to obtain computationally a converged value of the subsurface ion depletion due to its slow convergence into the bulk and the necessarily finite width of the simulated slab [21, 25].

The calculated surface enhancement (e.g., for bromide and iodide) or at least presence at the interface (e.g., for chloride) helped to rationalize atmospheric observations and laboratory experiments concerning heterogeneous chemistry on aqueous sea salt aerosols [6, 11]. Subsequently, surface selective spectroscopies, such as vibrational sum frequency generation (VSFG) [39-42], second harmonic generation (SHG) [43-45], photoelectron spectroscopy (PES) [46-48], and atomic scattering techniques [49, 50] allowed for an indirect or direct observation of ions within the interfacial layer between an aqueous electrolyte solution and its vapor. All these techniques showed that inorganic salt ions can influence the interfacial layer. SHG and PES methods were moreover capable to directly detect the interfacial ionic signal as a function of bulk concentration, revealing surface adsorption of anions like bromide, iodide, or thiocyanate, but not of alkali cations [44, 48, 51]. Although more work is needed to obtain fully quantitative results for each individual system, we can conclude that affinity of large soft inorganic anions for the air/water interface is reasonable well established by now, both computationally and experimentally.

2.3 Simulations of Hydronium and Hydroxide at Aqueous Interfaces

Aqueous electrolytes encompass not only salts but also solutions of acids and bases. Strong acids and bases practically completely dissociate in water releasing into the solution two important ions which have been not discussed yet – hydronium and hydroxide. Even pure water contains these ions, albeit at a very low amounts of 10^{-7} M. The issue of surface affinity of H_3O^+ and OH^- has been subject of vigorous computational and experimental investigations recently [52-61]. Researchers generally agree that these two ions exhibit a non-trivial surface behavior. However, as reflected also in this Faraday Discussion, there is disagreement not only on the quantitative amount of ionic surface adsorption but also on a more qualitative issue, namely which of these two ions exhibits larger surface enhancement [62-64].

Similarly as for salt ions, the first computational indication about an interesting surface behavior of hydronium and hydroxide came from medium-sized to large cluster studies [65-69]. Note that one needs at least about 20 water molecules in order to start distinguishing between surface and internal ion solvation. For hydronium, calculations revealed a strong preference for cluster surfaces [65-69]. This may come as a surprise since naively one could assume that proton as a small ion with zero polarizability should prefer internal solvation. The trick is, of course, that hydrated proton chemically reacts with water, the two limiting resulting structures being the Eigen (H_3O^+) and Zundel (H_5O_2^+) cations [70, 71], which dramatically alters its properties and interfacial behavior (*vide infra*). For hydroxide, computational studies show a systematic shift from an affinity for the surface to delocalization over the whole cluster upon increasing the cluster size [69, 72, 73].

While cluster studies can provide useful hints, there is need for investigating extended aqueous surfaces in order to directly connect with experimentally scrutinized surfaces of bulk

aqueous systems. MD simulations of hydronium in aqueous slabs employing a polarizable classical force field [52, 54] or a more sophisticated Effective Valence Bond scheme [53, 60] allowing for proton transfer revealed that hydronium is attracted to or at least not repelled from the water surface. In contrast, hydroxide was found to be weakly repelled from the surface, although it did occasionally penetrate all the way to the topmost water layer [54].

Most recently, we have performed a series of simulations [58, 62, 74] to check the above early predictions. The principal aim of these calculations has been to establish the free energy difference connected with transferring hydronium or hydroxide from the aqueous bulk to the surface. Our approach to this problem has been a pragmatic combination of three computational methods – classical MD with polarizable potentials, ab initio MD based on Density Functional Theory (DFT) methods, and accurate ab initio (MP2 or Coupled Cluster) calculations. A similar methodology has been already applied in our studies of salt ions at the air/water interface [21] with that the combination of empirical and electronic structure techniques becomes particularly topical for the "difficult", chemically non-trivial hydronium and hydroxide ions. In the following paragraphs we, therefore, briefly summarize the employed computational strategy.

Each of the above three computational approaches has its advantages and disadvantages. Classical MD simulations can be easily performed for relatively large systems containing hundreds to thousands of water molecules in periodic unit cells mimicking extended aqueous interfaces. We have been employing unit cells of the form of a rectangular prism where the system acquires the shape of a periodic slab with a bulk region in-between two air/water interfaces (Figure 3). Depending on the actual system size, the area of each of these interfaces in the unit cell has varied between 3 and 9 nm². This computational approach is fast enough to allow collecting data for varying amounts of dissolved species from just a single ion to several

moles per liter. Also, long enough (nanosecond to microsecond) runs can be performed so that thermodynamic quantities such as free energy differences can be converged either directly or using advanced simulation techniques. The basic drawback of classical MD is that the empirical potential does not allow for proton hopping unless special approaches such as the EVB are employed [60, 75, 76]. Neither does it properly describe the partial charge transfer character of strong ion-water interactions, although a polarizable force field partially accounts for this effect [64].

Ab initio MD allows to get rid of an empirical potential and to describe explicitly the electronic structure of the whole system accounting naturally for proton hopping and charge transfer effects. The price is a dramatic increase in computational load. Consequently only smaller slab systems with up to about couple hundred water molecules in the unit cell can be studied [77]. Also, the accessible picosecond rather than nanosecond timescales allow for studying dynamics but typically not thermodynamics. Nevertheless, a most recent “tour de force” ab initio MD simulation showed that free energy differences are becoming within reach of this method [78]. Another issue is that ab initio MD techniques are based on DFT methods, typically employing non-hybrid functionals such as BLYP or PBE [79]. These functionals are necessarily of an approximate character (e.g., in many cases they tend to overdelocalize the electron density) which also translates to the accuracy with which they describe aqueous systems. Currently, hybrid functionals, which provide generally a better description (e.g., by reducing the self-interaction error), are being introduced to ab initio MD. Finally, accurate ab initio calculations at the MP2 or even Coupled Cluster level can be employed for small cluster systems containing a hydronium or hydroxide ion with several water molecules. Such calculations provide valuable

information per se and also serve as benchmarks for developing and testing empirical potentials for the ionic product of water [62].

In our studies of hydronium and/or hydroxide in aqueous slabs, we have most heavily relied on classical MD simulations employing polarizable force fields [54, 58, 62, 64, 74]. Using a thermodynamic integration method we established for the hydronium cation either in the Eigen or Zundel form a free energy surface minimum of -2 to -3 kcal/mol. This surface enhancement is in accord with results of EVB calculations, which allow for proton hopping [53, 60]. In contrast, we found that hydroxide has a very weak preference for the bulk of about 1 kcal/mol (with the statistical error of all of our free energy estimates being ± 1 kcal/mol with 85 % confidence). In other words, simulations show that hydronium accumulates at the water surface, while hydroxide has at best the same concentration there as in the bulk. Therefore, in the topmost layer of water there shall be an excess of hydronium over hydroxide. We denote this situation as an “acidic” surface of water [58]. We use the quotation marks since pH is strictly speaking a bulk property related to proton activity, nevertheless, we operationally define as “acidic” an aqueous surface with a number excess of hydronium over hydroxide.

A simple qualitative rationalization of this effect is as follows. While H_3O^+ makes three strong donating hydrogen bonds, its oxygen is a dysfunctional hydrogen bond acceptor due to its very low negative charge compared, e.g., to the O atom of a water molecule (Figure 4). From this perspective, hydronium has been labeled as the smallest “amphiphilic” species [53] and as such prefers to reside at the surface with the O-atom exposed into the vapor. Qualitatively, the situation for OH^- is the opposite with its oxygen being an excellent hydrogen bond acceptor and hydrogen a poor donor. However, quantitatively this “amphiphilic” effect is weaker since the H atom is small and so is the reduction of its partial charge compared to hydrogen in a water

molecule. Hydroxide is, therefore, able to develop also a donating hydrogen bond, albeit a weak one (Figure 4). As a result, it does not exhibit surface enhancement although it can occasionally penetrate all the way to the surface layer.

Classical MD allows, provided long (beyond nanosecond) simulations are performed, to obtain the free energy difference between an ion solvated in the bulk and at the surface. However, these simulations are only as good as is the empirical interaction potential and without sufficient care a “garbage in – garbage out” scenario may become applicable. A dynamical approach which bypasses the use of empirical potentials is the *ab initio* MD where energies and forces are calculated using DFT-based methods [80]. We employed the BLYP functional to investigate the behavior of hydronium or hydroxide in clusters with 48 water molecules and in small aqueous slabs with 72 waters [58, 62]. Picosecond timescale trajectories revealed that hydronium prefers to reside at the surface, while hydroxide tends to move from the surface to the subsurface layers. For a set of optimized cluster structures we estimated the surface preference of hydronium to be at least as strong (if not stronger) using DFT than that obtained using polarizable empirical potentials. Most recently, we have launched a larger scale *ab initio* simulation of a single OH^- ion in an aqueous slab containing 216 water molecules in a unit cell [81]. Such size has been shown previously to be sufficient for the system to develop a well defined bulk region between the two water/vapor interfaces [77]. In a simulation lasting ten picoseconds we see a hydroxide ion initially placed at the surface starting to “dive” into the subsurface within 50 fs and then exploring this region of the slab (Figure 5). This indicates that there are no special “binding sites” for hydroxide at the water surface and that the free energy profile connected with the motion of OH^- toward the bulk lacks an appreciable surface minimum. This result is also supported by most recent massive (~500 ps) *ab initio* MD simulations of a very similar system

which allowed to extract the free energy difference between a surface and bulk position of hydroxide [78]. The obtained value is roughly zero, this result falling within the statistical error of 1 kcal/mol of the value obtained from MD with an empirical polarizable potential [58, 62, 78]. Nevertheless, aqueous hydroxide described within DFT has a more delocalized charge (particularly at the interface) than its counterpart modelled with a polarizable force field, which is a factor which tends to reduce its repulsion from the surface [78].

Finally, we performed accurate benchmark ab initio calculations at the MP2 and CCSD(T) levels employing the aug-cc-pvtz basis set for small clusters containing a single proton or hydroxide ion and up to six water molecules [58], similarly to previous computational studies on these systems [82, 83]. Optimized geometries of H_3O^+ with three, H_5O_2^+ with four, and OH^- with four tightly bound water molecules are depicted in Figure 6. Note that the latter structure is not the global minimum but rather a hypercoordinated geometry close to those being prevalent in the liquid [84]. Such calculations serve as benchmarks allowing to refine polarizable force fields for hydronium (both in the Eigen and Zundel forms) and for hydroxide [58].

2.4 Experiments Concerning Hydronium and Hydroxide at Aqueous Interfaces

The present computationally-based picture of an “acidic” surface of water with an excess of hydronium over hydroxide in the topmost layer is in accord with a broad range of surface selective spectroscopic measurements. Indirectly, the effect of hydronium or hydroxide on water molecules at the interface between air and acid or base solution was investigated using the Vibrational Sum Frequency Generation (VSFG) spectroscopy [54, 57, 59]. These measurements reveal a strong effect of hydronium but only a weak influence of hydroxide on the water molecules in the interfacial layer. Similarly, isotope exchange IR measurements of cold aqueous

nanoparticles show enhanced isotopic scrambling at the surface traced to an increased presence there of protons but not of hydroxide [58, 62]. The Second Harmonic Generation (SHG) spectroscopy allows to probe interfacial OH⁻ directly via excitation to charge-transfer-to-solvent states [61]. A concentration dependence study in the millimolar to molar range provides data that are best fitted by a Langmuir adsorption isotherm with zero or positive value of the surface free energy (compared to the bulk) and clearly excluded strong surface adsorption beyond ΔG of -1 kcal/mol [61]. This technique also allows to indirectly probe interfacial concentration of hydronium by comparing a salt and acid with a common anion [55]. Such a study of aqueous HI vs NaI or KI has revealed a strong interfacial enhancement of hydronium with respect to alkali cations [55]. Most recently, surface behavior of OH⁻, which has a distinct signature both in the valence and core regions, has been probed directly by photoelectron spectroscopy (PES) in aqueous microjets [81]. For a proper choice of photon wavelengths PES probes only the top ~5-10 Å of the liquid, i.e., about two to three highest water layers [51]. A concentration study shows a linear dependence of the surface signal on the amount of hydroxide in the bulk from which no surface adsorption of OH⁻ is inferred [81]. Additionally, no PES signature of hydroxide at the surface of neat water has been observed [85].

A direct way how to relate the above molecular level calculations and experiments to macroscopic observations is via surface tension. Measurements show that adding alkali hydroxides to water leads, similarly as for inorganic salts, to an increase in surface tension [86, 87]. In this context it is interesting to note that for some salts a tiny dip in surface tension by about 0.02 % has been observed in the millimolar region in the 1930-40 (the so called Jones-Ray effect) [88]. This effect was later interpreted as an artifact of the measurements [89], however, it has been invoked recently in interpretation of SHG experiments [90, 91]. Whether the Jones-Ray

effect is real or artificial, for the sake of present discussion it suffices to say that it has only been observed in salt and not in hydroxide solutions. In contrast to hydroxides, acids, including strong, fully dissociating ones such as HCl, HBr, or HI, decrease the surface tension of water [86]. A straightforward application of the Gibbs adsorption equation (Equation 1) to these results leads to a conclusion that hydroxide is repelled from while hydronium attracted to the water surface. Surface tension is, however, an integral property of the whole interfacial layer and we have shown before that for large soft inorganic ions a surface tension increase does not necessarily exclude a surface peak [21]. Nevertheless, in order to maintain a net negative surface excess such peak has to be relatively small (say maximally a several fold increase compared to the bulk) and should be overcompensated by subsurface depletion. Therefore, it is safe to conclude at this point that based on surface tension measurements hydronium exhibits surface activity, while hydroxide is repelled from or at most shows a small peak at water surface.

While calculations and surface selective spectroscopies are in agreement with surface tension experiments, comparison with other macroscopic measurements is more controversial. Measurements of small water droplets sprayed in the laboratory or in nature (the so called waterfall effect), which have been performed in the late 19th and early 20th century and have been revisited recently showed that these water particles mostly carry a negative charge [92, 93]. In addition, electrophoretic mobility measurements of gas bubbles in water yielded negative ζ -potentials of about -35 mV [56, 94], while even lower negative values were obtained for oil droplets in water at pH = 7 [95, 96]. An isoelectric point (IP) around pH = 4.5 was observed for gas bubbles in water [56, 94]. The titration curve tended to level off on both sides of IP indicating surface accumulation of negative charge above and of positive charge below this point. Similar behavior was also observed for oil droplets in water, where it was deduced from

pH-stat measurements that the surface concentration of the negative charge at pH = 7 amounts to -5 to -7 $\mu\text{C cm}^{-2}$ [63, 95, 96]. This corresponds to about one negative charge per 3 nm² or, assuming (rather generously) a 1 nm width of the interfacial layer of neat water, to a roughly 0.5 M of surface charge. This negative surface charge, which has been assumed as originating from OH⁻ ions [56, 94-97], has been also invoked in interpreting disjoining pressure measurements determining stabilities of thin aqueous films [98, 99].

It is instructive to relate the above suggested surface adsorption of hydroxide to surface tension effects. Using the Gibbs adsorption equation (Equation 1) one can directly deduce the surface tension change with pH, which would be caused by a net surface excess of hydroxide of $3 \cdot 10^{13} \text{ cm}^{-2}$ (corresponding to the negative surface charge of -5 $\mu\text{C cm}^{-2}$ observed for pH neutral water [63, 95, 96]). At pH = 7 one would thus obtain a change in surface tension of $\sim 3 \text{ mN/m}$ per pH unit. The accuracy of surface tension measurement is typically in the 0.01 – 0.1 mN/m range, therefore, such a large change should be easily detectable. Instead, there is no observable difference in surface tension within a broad range of pH values around pH 7 and, as for inorganic salts, one needs orders of magnitude higher (at least millimolar or larger) concentrations of hydroxide or hydronium to start detecting measurable changes in surface tension [86, 87]. The only way to make a surface excess of OH⁻ of $3 \cdot 10^{13} \text{ cm}^{-2}$ consistent with a vanishing change of surface tension with pH around pH = 7 is to assume an unrealistically (several millimeter) thick subsurface layer completely depleted of hydroxide.

The suggested interpretation of the above macroscopic experiments in terms of an extremely strong (i.e., by about six orders of magnitude) surface enhancement of hydroxide [56, 94-97] is thus at odds with results of calculations, surface selective spectroscopies, and surface tension measurements which span a broad range of concentrations from neat water to several

moles per liter. Full resolution of the existing controversy may be difficult since electrophoretic mobilities and titration measurements are experiments which neither directly reveal the chemical nature of the observed surface charge, nor do they tell us where exactly and within how thick of a layer does the charge reside.

What can be done on the computational side to enhance our understanding of the behavior of hydronium and hydroxide at aqueous interfaces? Many of the macroscopic measurements are performed for the oil/water rather than the air/water interface. Simulations are, therefore, being performed for different aqueous hydrophobic interfaces, in particular those between water and oil (alkane) and water and a rigid hydrophobic wall (graphene) [64, 74, 100, 101]. Classical MD simulations employing polarizable potentials show that hydronium and hydroxide exhibit at the oil/water interface a behavior very similar to that at the air/water interface, i.e., surface attraction for the former but not for the latter ion [64] (see Figure 7). The situation is somewhat different at the interface between water and a rigid hydrophobic wall, which causes density oscillations and strong orientational structuring within the interfacial water layers [74]. As a result, hydronium exhibits a strong and sharp surface peak, while hydroxide is also slightly enhanced in the subsurface layer (Figure 7). A more general picture of the behavior of H_3O^+ and OH^- is thus emerging from these calculations which, admittedly, does not bring us much closer to the resolution of the existing controversy with some macroscopic experiments.

In the near future, progress in hardware and software will allow simulating larger systems (i.e., bigger unit cells in periodic systems) for longer timescales and with improving description of the intermolecular interactions. Ab initio MD simulations going beyond the limitations of empirical force fields will become an invaluable tool for obtaining accurate thermodynamic quantities, particularly if the accuracy of the employed density functionals is further improved.

This will lead to a refinement of the present view on hydronium, hydroxide, as well as other ions at aqueous interfaces, however, it is unlikely that the computational picture will change qualitatively.

3. Beyond the Air/Water Interface

Do the lessons we have learnt (or have not learnt yet) from ion affinities to the free surface of water help us in understanding their behavior at more complex aqueous interfaces? These are the interfaces between water and non-polar liquids, metals, insulating solids including ice, or large (bio)molecules [102-104]. The prominent question concerning ions at these interfaces is as follows: How transferable is the finding from the air/water interface that the surface affinity is connected with ionic size, polarizability, and other specific ion issues such as ion-water hydrogen bonding patterns? As an example, we have seen in the previous section that, e.g., the behavior of hydronium and hydroxide at the soft oil/water interface is similar to that at the open water surface, while a hard hydrophobic wall behaves somewhat differently. Several other cases of ions at these aqueous interfaces have been studied [105, 106], nevertheless at present, our understanding falls short of being able to fully answer the above question. Rather, we report here on our limited explorations in this direction focusing solely on the last of the above mentioned interfaces. To this end, we have started recently a systematic investigation of interfaces between proteins and their aqueous environment aimed at understanding surface affinities of biologically relevant ions.

3.1 Ions at the Protein/Water Interface

The influence of salt ions on collective properties of hydrated proteins (i.e., Hofmeister effects [107, 108]) is viewed traditionally as coming from specific ion-water interactions in the aqueous bulk [109]. Indeed, ions are classified in textbooks as either cosmotropes (“structure makers”) or chaotropes (“structure breakers”) according to their ability to structure water molecules around themselves [110]. In simple terms, cosmotropes should organize layers of water molecules around themselves, “stealing” thus effectively the solvent from proteins, which leads to salting-out, while chaotropes are not able to do that. However, there is mounting experimental evidence that monovalent ions (even cosmotropic ones) are not able to affect more than their immediate solvent shell [111-113]. Therefore, other possible explanations of salt action on protein are being looked for. If it is not the bulk solvent, then the prime suspect for Hofmeister effects becomes the interface between the protein and the surrounding salt solution [9].

As a first case study [14] we have investigated the behavior of sodium and potassium at surfaces of hydrated proteins. Na^+ and K^+ are the biologically most relevant monovalent salt cations. Moreover, they represent simple hard atomic ions the behavior of which at the air/water interface is straightforward – they are both equally repelled from it [21, 31]. Surface tension arguments invoking the air/water interface have been used recently to rationalize interactions of ions (both cations and anions) with surfaces of hydrated proteins [114, 115]. In a similar spirit, an old model representing globular proteins as spheres with a low dielectric constant and with a dipole or a smeared charge distribution [116] has been recently revived and dressed with dispersion interactions to account for specific ion effects [117]. We found it, therefore, instructive to explore using MD simulations ion specific interactions of Na^+ and K^+ with proteins

and to check the applicability of the above models. To this end we selected a set of five very different proteins – actin as a structural protein, bovine pancreatic trypsin inhibitor (BPTI) as an enzyme inhibiting protein, ubiquitin as the “kiss of death” protein marker, rubredoxin as an electron-transfer system, and ribonuclease A as an enzyme [14]. Each of these systems was simulated in a mixed solution of varying but equal amounts (typically 0.25 M) of NaCl and KCl for several nanoseconds to ensure statistically meaningful results

Figure 8 summarizes the affinities of sodium and potassium for surfaces of aqueous proteins [14]. They are expressed in terms of distributions of individual ions (in layers with a given distance from the protein surface) and integrals thereof. The latter are the cumulative sums providing the number of ions of each type which can be found within a certain distance from the surface of the protein. From the first column of Figure 8 two non-trivial results emerge. First, both cations exhibit affinity for protein surface. Second, this surface enhancement is about a factor of two stronger for sodium than for potassium and this remarkable ion specificity is preserved for all the aqueous proteins under study. Analyzing the MD trajectories it is easy to trace the origins of this effect. Affinity and selectivity comes for alkali cations primarily from interactions with the carboxylic side chain groups of the negatively charged glutamate and aspartate residues (second column of Figure 8) and from the electro-negative oxygens of the backbone amide group (third column), the rest of the protein surface being relatively unimportant (last column).

Similar results are born out of MD simulations of short polypeptides and individual glutamates and aspartates and by ab initio calculations of cationic pairing with acetate and formate in water [14]. The computational predictions are also supported by conductivity measurements and X-ray absorption spectroscopy [14, 118, 119]. Finally, the preferential affinity

of sodium over potassium for the COO^- group is in accord with the empirical law of matching water affinities [120]. According to this rule of thumb, cations preferentially interact in water with anions or anionic groups with similar hydration enthalpies. In other word, a small cation (sodium) exhibits a stronger affinity for a small anionic group (COO^-) than a larger cation (potassium). We can thus conclude that, unlike the air/water interface, the protein/water interface exhibits affinity and selectivity for alkali cations. This effect is primarily due to the presence COO^- and C=O groups at the protein surface. It is, therefore, an example of ion-pairing rather than segregation of ions at an interface between low and high dielectric constant media. Due to this and due to the fact that binding between alkali cations and negatively charged groups at the protein surface is not very strong a local ion-pairing model for these interactions can be utilized at least as a first approximation. Therefore, a lot can be learned already from studying interactions of alkali cations with aqueous negatively charged polypeptides, terminated amino acids, or even carboxylate anions [14].

Let us now switch the electric polarity and ask ourselves which *anions* preferentially interact with *positively* charged amino acid residues. As a first choice for addressing this question, we employed the series of halide anions – fluoride, chloride, bromide, and iodide [121]. Among amino acids there are three residues which bear a positive charge on their side chain; arginine with guanidinium, lysine with ammonium, and protonated histidine with the imidazolium group. Using extensive MD simulations lasting tens to hundreds of nanoseconds and employing both polarizable and non-polarizable force fields, we have thus investigated interactions of these (terminated) amino acids with halides in aqueous solutions. Results of these simulations are presented in Figure 9 as 3D density plots, i.e., distributions of each of the halide

anions around the three amino acids. These were obtained with a non-polarizable force field, the results with polarizable potentials being similar (*vide infra*).

The following conclusions can be drawn from these simulations. Halides exhibit a tendency for pairing with the cationic side chain groups which decreases as we move down the periodic table, fluoride showing the strongest affinity for the positively charged side chain groups. While proteins have only one anionic side chain group (COO⁻), there are three positively charged amino acids. Among these, guanidinium interacts most strongly with the lighter halides, followed by imidazolium and ammonium. Qualitatively, the results are the same for both polarizable and non-polarizable force fields. Quantitatively, inclusion of polarizability reduces the strength of the ion pairing. However, it underlines another effect present for heavier halides, namely the tendency of Br⁻ and I⁻ to accumulate in the vicinity of the non-polar regions of the (terminated) amino acids (Figure 9). This is a behavior similar to their affinity to the air/water interface which we observed previously. For soft ions, the combined effect of ion pairing and segregation at the interface between water and non-polar protein surface region thus hints to a need to extend the local model which we invoked earlier for the description of the interaction of alkali cations with aqueous proteins. Further refinement of this model may also be necessary for more complex molecular ions, particularly polyvalent ones (e.g., alkali earth dications or sulfate) which have a tendency for very strong ion pairing interactions, both with charged amino acid residues and with counter-ions in the bulk solvent [13, 122-124].

3.2 Ion Mediated Protein Interactions

While affinity of ions for aqueous proteins is an interesting issue *per se*, from the biophysical and biochemical point of view a more important question is how specific ion

interactions influence processes involving proteins such as association (salting-out), crystallization, denaturation, and enzymatic activity. As a matter of fact, it was via studying salting-out of proteins how specific ion effects were discovered 120 years ago. In 1888, Franz Hofmeister with his students at the Pharmacological Institute in Prague ordered separately common anions and cations according to their ability to salt-out egg white from aqueous solutions [107, 108]. The result is the lyotropic or Hofmeister series, which separately for the most common anions and cations reads as $\text{SO}_4^{2-} > \text{Cl}^- > \text{NO}_3^- > \text{Br}^- > \text{I}^- > \text{ClO}_4^- > \text{SCN}^-$ and $\text{NH}_4^+ > \text{K}^+ > \text{Na}^+ > \text{Mg}^{2+}$. It follows from it that weakly hydrated anions and strongly hydrated cations are efficient salting-out agents, with the effect of anions being much more pronounced than that of cations. It should be stressed that the Hofmeister series is an empirical rule rather than a “law of nature” and as such has many exceptions. Nevertheless, it represents a very useful concept for rationalizing specific ion effects, which has been invoked also in other phenomena than salting-out, such as enzymatic activities, crystallization of proteins, swelling of tissues, ion exchange, surface tension, etc. Note, however, that the concept of Hofmeister series is hardly applicable to situations where a very particular geometric arrangement of the protein is built in order to accommodate a given ion such as is the situation for ion channels or for metal ion binding positions in active sites of enzymes.

With the protein surface rather than the aqueous bulk being established as the primary suspect for Hofmeister effects [9] it is thus tempting to ask ourselves how the ion-protein interactions characterized in the previous section translate to protein-protein interactions. To this end, we have recently started investigating association of model proteins – lysozymes, in aqueous solutions using atomistic MD together with a coarse-grained Monte Carlo approach [125]. Lysozyme is a rather exceptional protein in that it carries at neutral and slightly acidic pH

a large positive charge (+9 at pH = 4.5). This charge can be effectively screened (neutralized) by salt anions which leads to protein association in aqueous solutions. Measurements of the second virial coefficient show that in this case iodide is a more efficient salting-out agent than chloride in a reversed Hofmeister ordering [126]. Our coarse-grained Monte Carlo calculations using effective ion-amino acid interactions extracted from atomistic MD reproduce this effect showing a deeper free energy minimum for an associated lysozyme pair in NaI than in NaCl [125]. This is despite the fact that our MD simulations show a stronger binding of Cl⁻ over I⁻ to positively charged amino acid residues [121]. The key here is the stronger binding of iodide to non-polar residues, which overwhelms the ion-pairing effect. At (somewhat unrealistic) pH of 12.5 leading to a net charge of lysozyme of -5 the subtle balance between ion-pairing and segregation at non-polar parts of the protein surface reverses and chloride becomes more efficient than iodide in salting-out (Figure 10) [127], which is the normal Hofmeister ordering.

We have also recently started addressing questions concerning how specific ions affect enzymatic activities and protein denaturation processes. To this end we have performed several case studies, including investigations of the effect of complex molecular ions such as choline and sulfate on the enzymatic activity of the horseradish peroxidase [13] and most recently also the influence of sodium vs potassium on the activity of the HIV protease and the denaturation abilities of guanidinium and tetrapropylammonium halides and sulfates for model peptides such as mellitin and alanine-based α -helix. Classical MD simulations do not allow to directly follow the enzymatic reactions (for which quantum chemical or mixed approaches are needed), nevertheless they provide information about binding patterns of these ions in the vicinity of the reaction center. Concerning denaturation, MD simulations can indicate binding sites where process can start. In the course of these ongoing studies we are learning that the behavior of

molecular ions is more complex than that of their monovalent atomic counterparts. For example, guanidinium behaves as a rather “promiscuous“ ion, which can associate both with negatively charged and non-polar residues and can even engage in homo-ion pairing. In addition, divalent ions such as sulfate can create “binding pockets“ from positively charged surface residues, distorting thus the protein structure. They also tend to strongly associate with counter-cations in the solutions, which negatively influences the ability of both ions to interact with the protein. While we are only starting to categorize these effects, it is clear already now that they will limit the applicability of the simple local model for ion-protein interactions and of the applicability of separate cationic and anionic Hofmeister series.

5. Conclusions

The field of ions at aqueous interfaces is undergoing a remarkable renaissance thanks to modern computational and spectroscopic techniques, which allow scrutinizing the interfacial region with molecular resolutions. Concerning the air/water interface, the traditional concept of an inactive, ion-free surface of aqueous electrolytes is yielding to a more complex picture, in which inorganic ions with large size and polarizability or specific (“amphiphilic”) interactions with water can appear or even be enhanced at the surface. While the new picture is reasonably well established for inorganic salt ions, the situation is much more controversial for the inherent water ions – hydronium and hydroxide. Researchers agree in general that these ions exhibit an interesting surface behavior, however, there is both quantitative and qualitative disagreement between molecular level calculations, surface-selective spectroscopies, and surface tension measurements on one side and electrophoretic and titration experiments, as well as disjoining pressure measurements on the other side. The former predict surface enhancement of one to two

orders of magnitude of hydronium and virtually no surface enhancement or even weak repulsion of hydroxide, while the latter interpret the measured negative surface charge in terms of roughly six orders of magnitude surface enhancement of hydroxide. Here, we discussed this controversy in detail and while we fell short of fully resolving it, we found the former picture being consistently supported by surface- and molecularly-resolved computational and experimental evidence.

The free water surface is but the simplest interface and it is interesting to investigate how much it can teach us about ionic behavior at more complex aqueous interfacial systems. The closest to the open aqueous surface is the interface between water and soft hydrophobic material such as oil or liquid alkanes. These interfaces are indeed structurally not too far from each other and, as a result, ionic interfacial affinities are also similar. A hard (rigid) hydrophobic interface, such that between water and graphene is already slightly different due to enhanced structuring and density oscillations of water, which provide additional (sub)surface driving force for ions.

Leaving aside other very interesting aqueous interfaces, such as that between water and a solid insulator or metal, we focused on the interface between a protein and its aqueous environment. This interface is much more complex than the air/water or oil/water interfaces, nevertheless lessons learnt about them do come useful. Namely, to the first approximation, the surface of a hydrated protein can be viewed as composed of separate non-polar and polar or charged patches. At the former, ions segregate similarly as at the above hydrophobic interfaces. At the latter, a more appropriate picture is that of ion-pairing with charged or polar amino acid side chain groups and the polar amide group at the protein backbone. Such an approach is clearly not aimed at describing very selective ion bindings, e.g., at the active sites of enzymes or in ion channels, which are due to particular structural and electronic arrangements of whole segments

of the biomolecule. It should be rather applicable for rationalizing the more general but still ion-specific salt effects observed for salting-out, denaturation, crystallization, enzymatic activity, etc. as described phenomenologically via the Hofmeister series. In answering the question why various ions of the same valency affect processes involving proteins differently we are only now starting to see the light at the end of the tunnel, namely the molecular mechanisms responsible for the ion specific behavior.

Acknowledgment

Our calculations presented here are results of an extensive collective effort. I have been blessed by a fantastic generation of students and postdocs (several of them being independent researcher now), including Robert Vácha, Jan Heyda, Mikael Lund, Martina Roeselová, Martin Mucha, Luboš Vrbka, Babak Minofar, Lukasz Cwiklik, and Barbara Jagoda-Cwiklik. I am also indebted to my collaborators, in particular to Doug Tobias, Victoria Buch, Anne Milet, Liem Dang, Barbara Finlayson-Pitts, Werner Kunz, Lai-Sheng Wang, Bernd Winter, Phil Mason, and Jiří Vondrášek. Support from the Czech Ministry of Education (grant LC512), from the Czech Science Foundation (grant 203/08/0114), and from the US-NSF (grant CHE 0431312) is gratefully acknowledged. Work accomplished in the Institute of Organic Chemistry and Biochemistry was also supported via Project Z40550506.

Figure Captions

- Fig. 1:** A schematic picture of water surface as a flat sharp interface between two dielectric continua with $\epsilon = 80$ (water) and $\epsilon = 1$ (air or vapor) [21]. A model spherical ion is repelled from this surface by the electrostatic image force.
- Fig. 2:** Density profiles of bromide, sodium, and water oxygens in a slab of 1.2 M aqueous NaBr [12]. Distributions of ions and water are plotted in layers parallel to the surface; from the center of the slab across the interface into the vapor (only half of the slab is depicted).
- Fig. 3:** Water slab containing 432 water molecules and a single hydronium and hydroxide in a unit cell of dimensions of approximately $19 \times 19 \times 237 \text{ \AA}$ [58]. White lines define the boundary between the the central and neighboring cells.
- Fig. 4:** Solvation shells around bulk located aqueous hydronium (left) and hydroxide (right) from polarizable MD simulations [62]. Color coding: ion oxygens – yellow, ion hydrogens – white, water oxygens – red, and water hydrogens – blue. While H_3O^+ forms 3 strong and very directional donating and no accepting hydrogen bonds, OH^- exhibits 4 – 5 accepting hydrogen bonds and a weak donating one.
- Fig. 5:** Three snapshots from a ab initio MD trajectory of a single hydronium initially placed on the surface of an aqueous slab with 216 water molecules in a $15 \times 15 \times 70 \text{ \AA}$ unit cell [81]. OH^- moves swiftly from the surface to the subsurface, with proton transfer accelerating its mobility. It becomes fully hydrated with no direct exposure to the vapor phase and remains so for the rest of the 10 ps trajectory.

Fig. 6: Ab initio MP2/aug-cc-pvdz structures of H_3O^+ with three, H_5O_2^+ with four, and OH^- with four water molecules, used for benchmarking our polarizable force field [58].

Fig. 7: Density profiles of hydronium, hydroxide, water oxygens, and alkane carbons across the a) water/disordered decane, b) water/ordered decane, c) water/carbon wall, and d) water/vapor interfaces [64]. Insets show snapshots of these four interfaces.

Fig. 8: Distribution functions (dotted lines) and the corresponding integrated sums (full lines) for sodium (green) and potassium in the vicinity of aqueous proteins [14]. Note that both cations exhibit affinity for the protein surface, which is stronger for Na^+ than for K^+ , and that the hotspots for cation binding are the negatively charged carboxylates of glutamates and aspartates, as well as the amide oxygens at the backbone.

Fig. 9: Density distributions of fluoride (black), chloride (yellow), bromide (red), and iodide (blue) around aqueous arginine, lysine, and protonated histidine [121].

Fig. 10: Association of two lysozyme molecules within a coarse-grained model in aqueous salt solutions [125]. At pH 4.5 iodide is more effective salting-out agent causing a deeper free energy minimum than chloride. At a (unrealistically high) pH of 12.5 the order of the anions reverses.

Figure 1

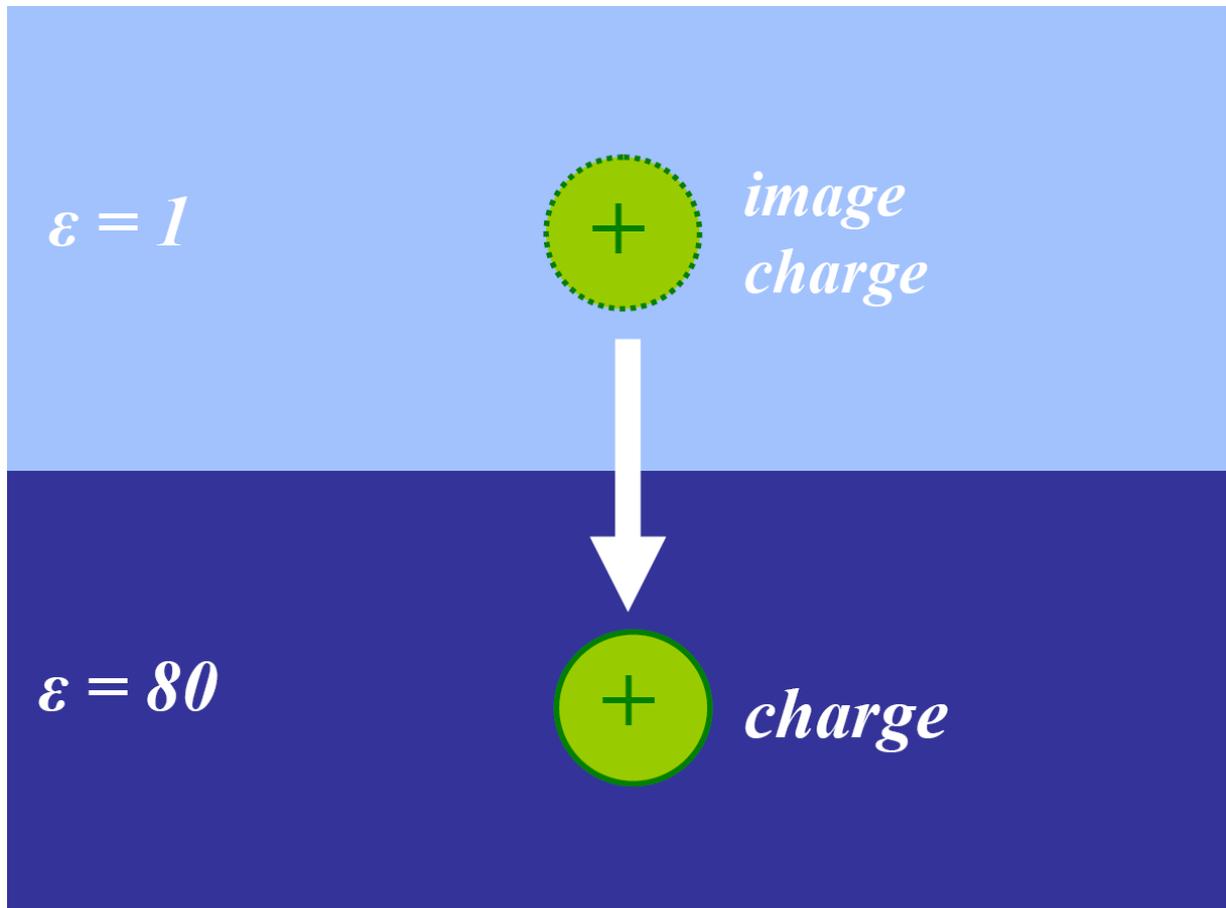


Figure 2:

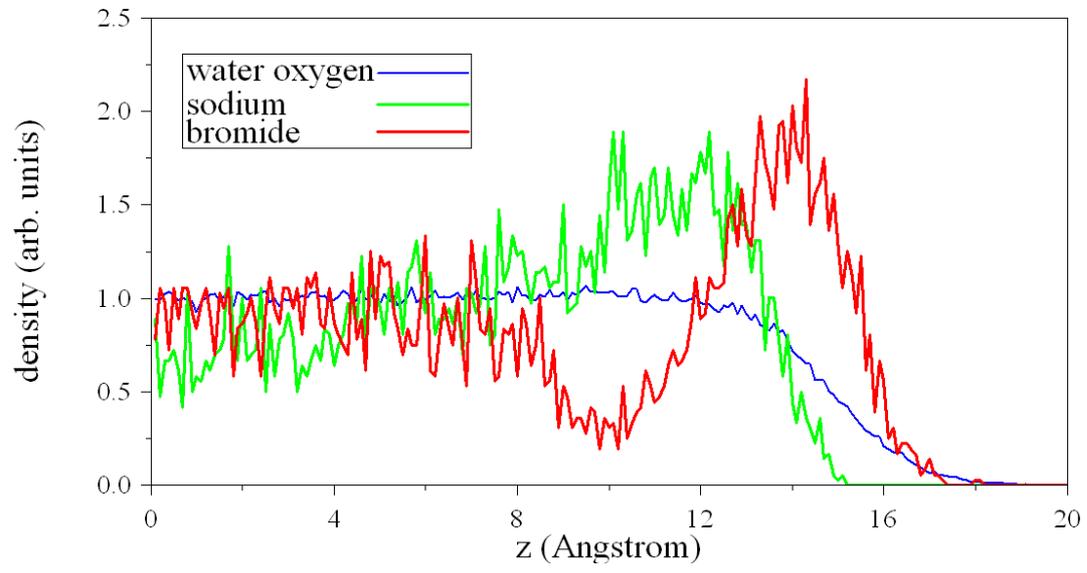


Figure 3:

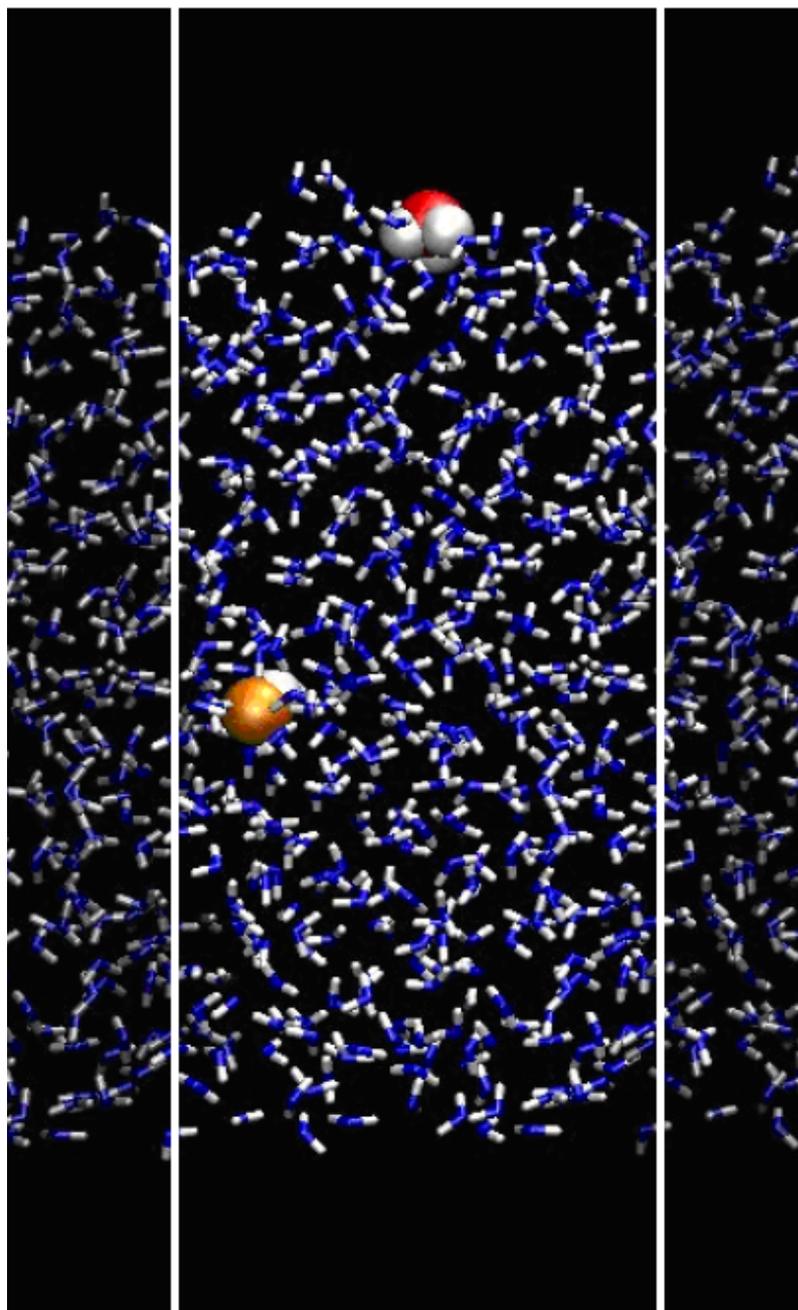


Figure 4:

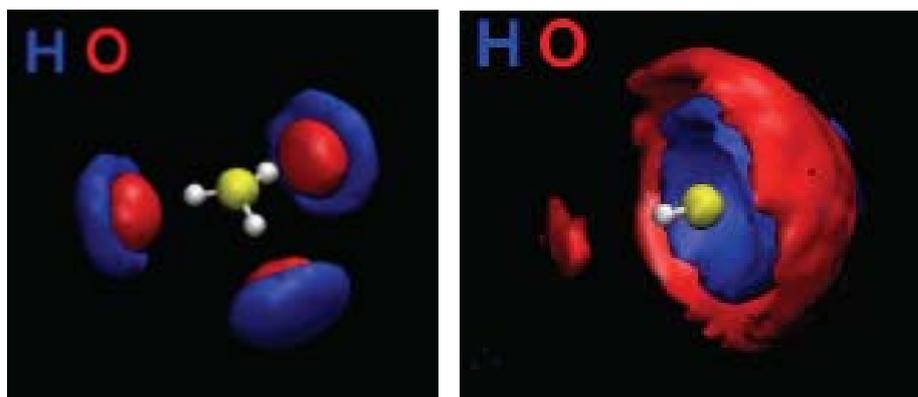


Figure 5:

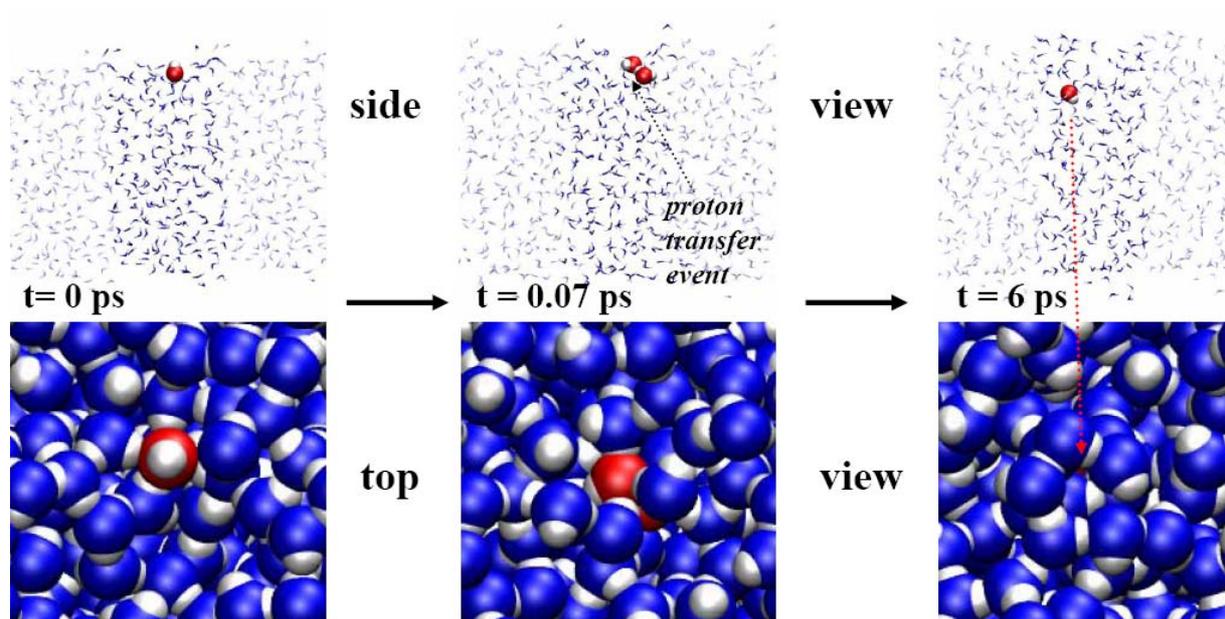


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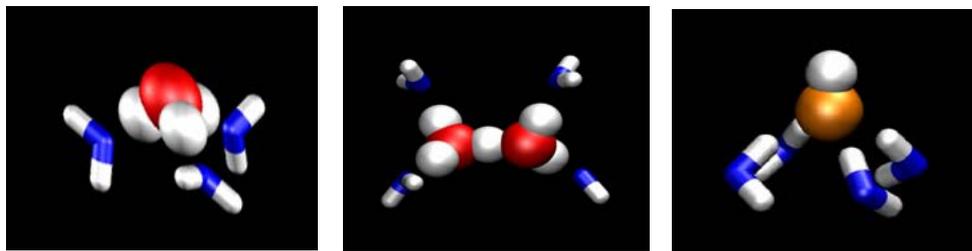


Figure 7:

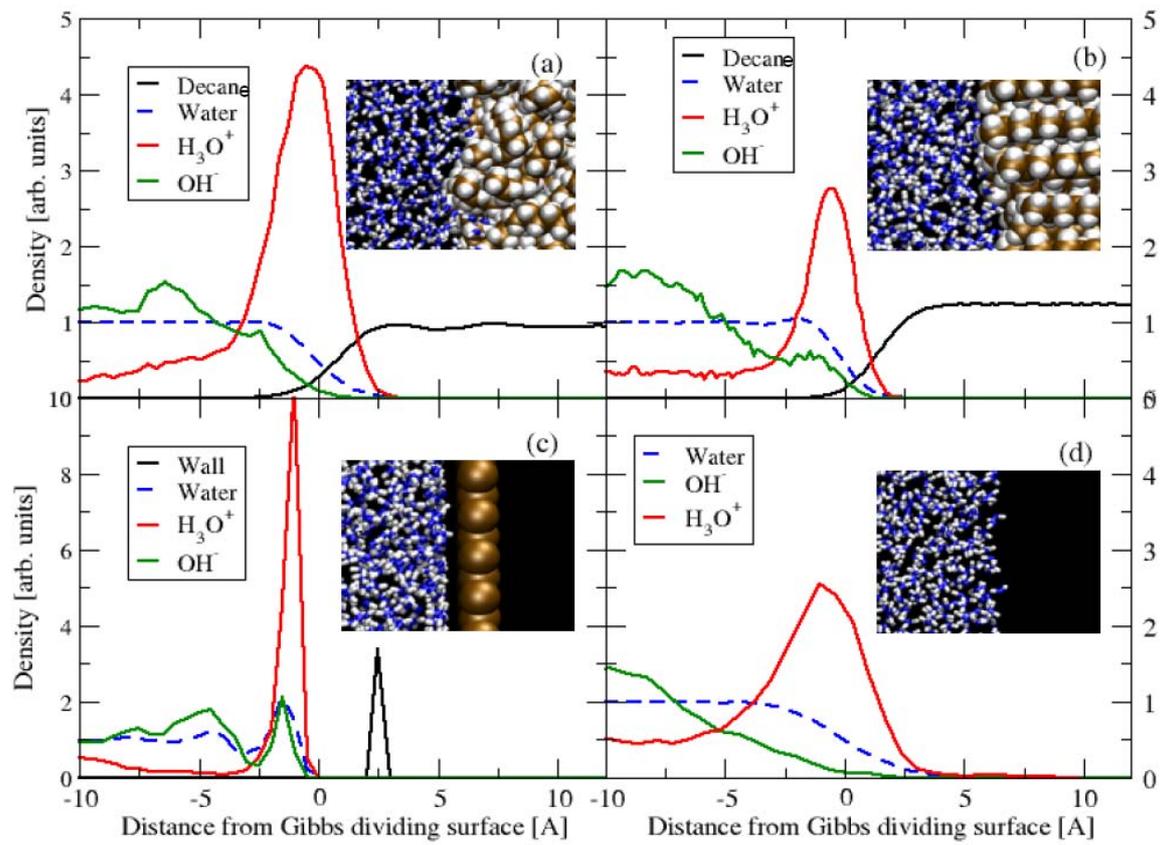


Figure 8:

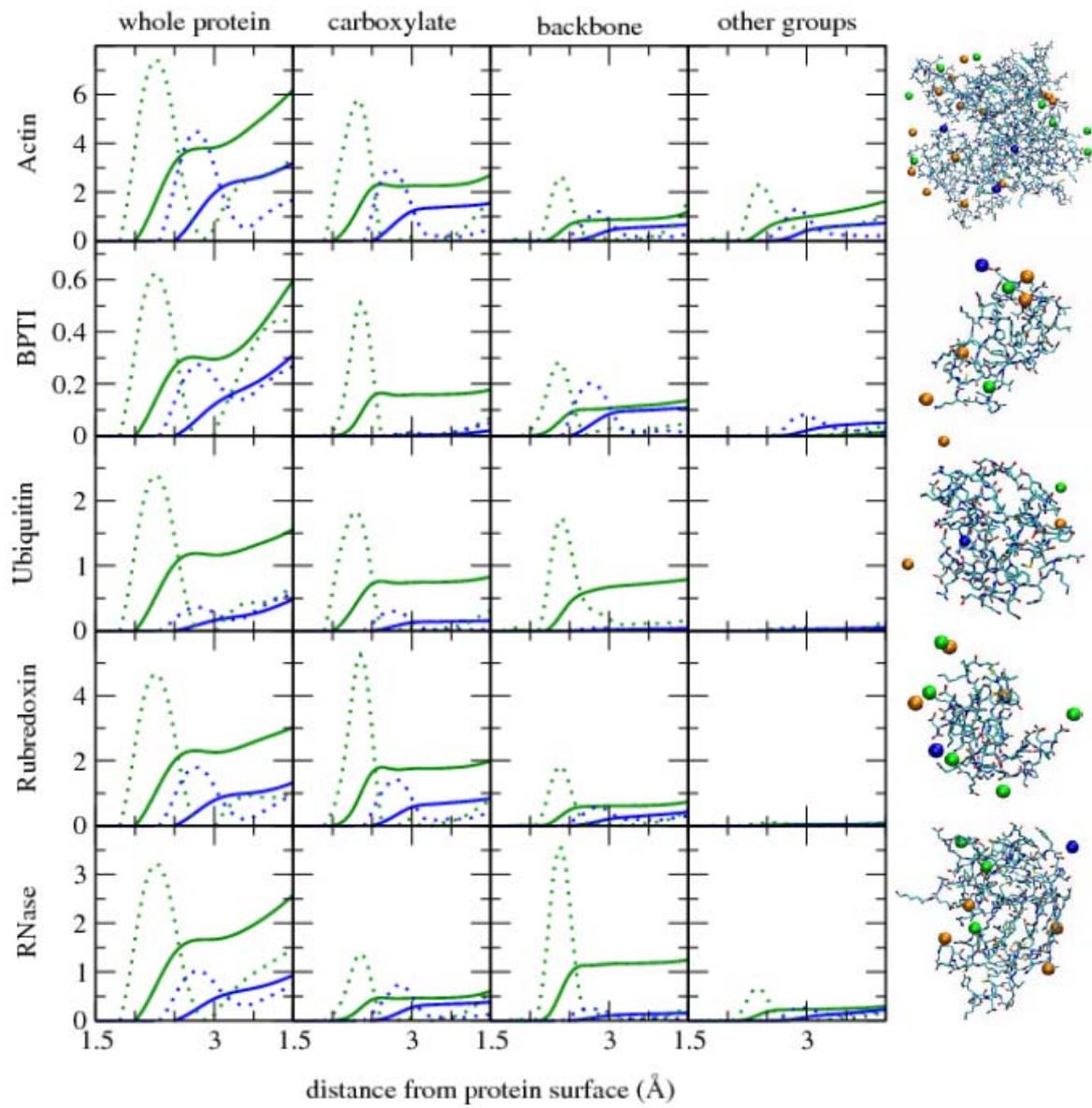


Figure 9:

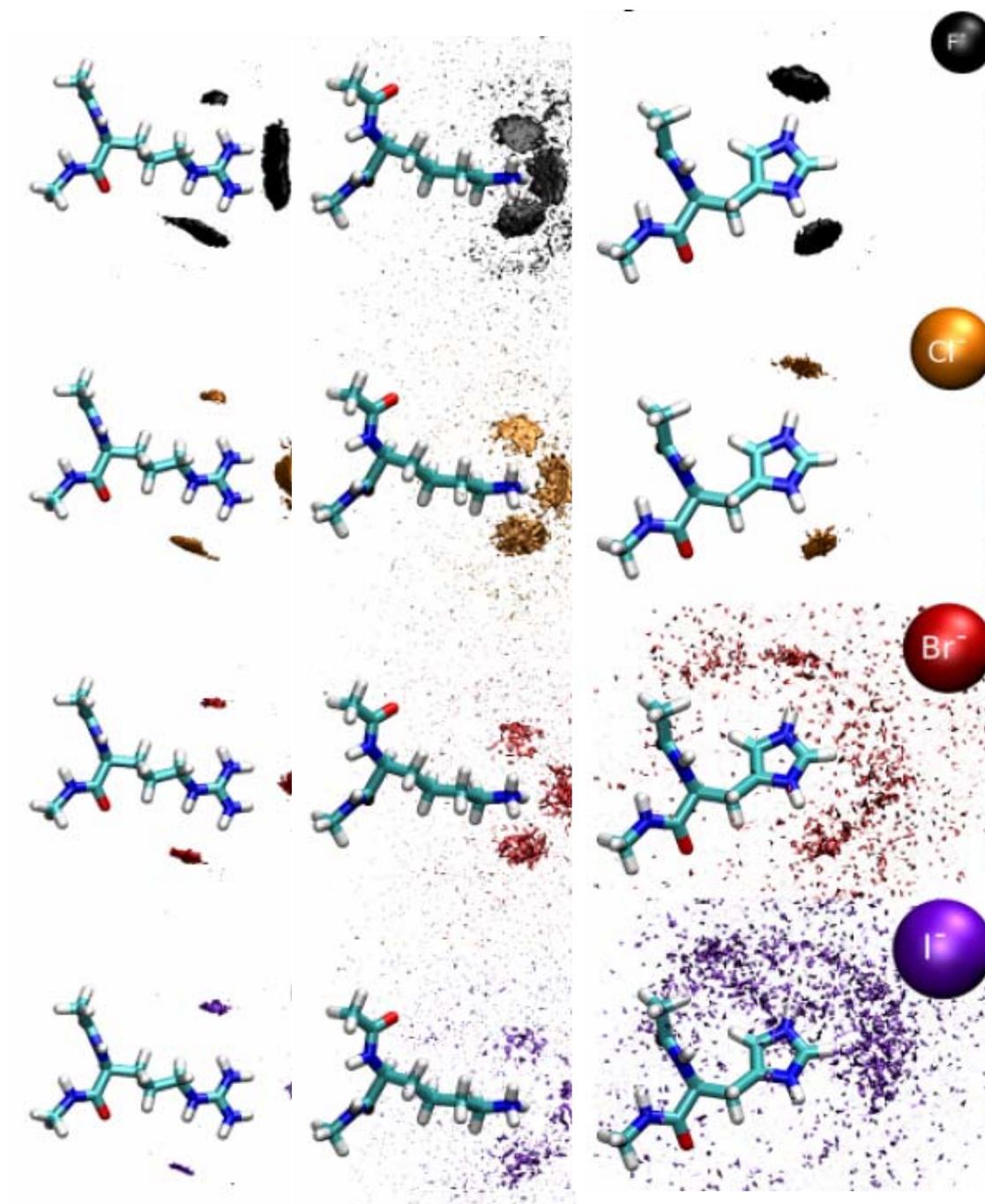
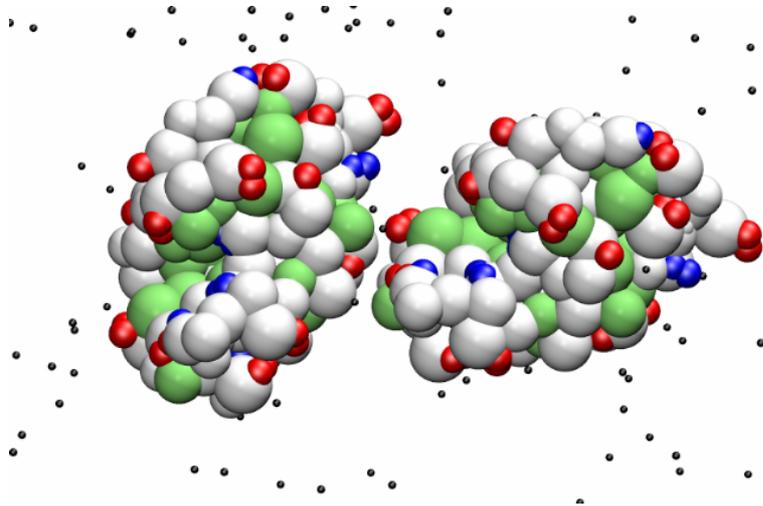
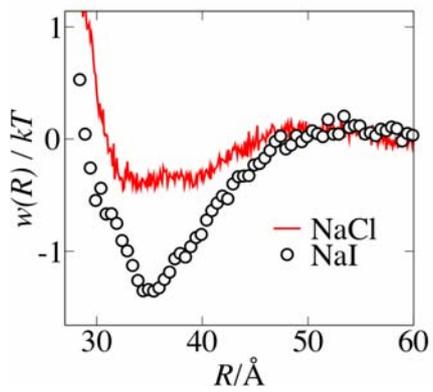


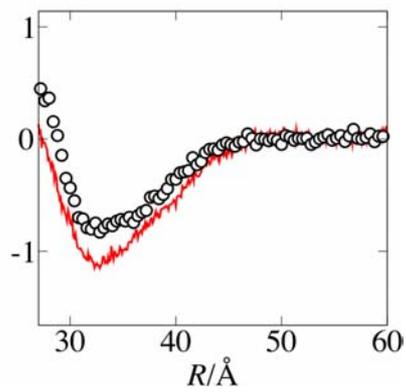
Figure 10:



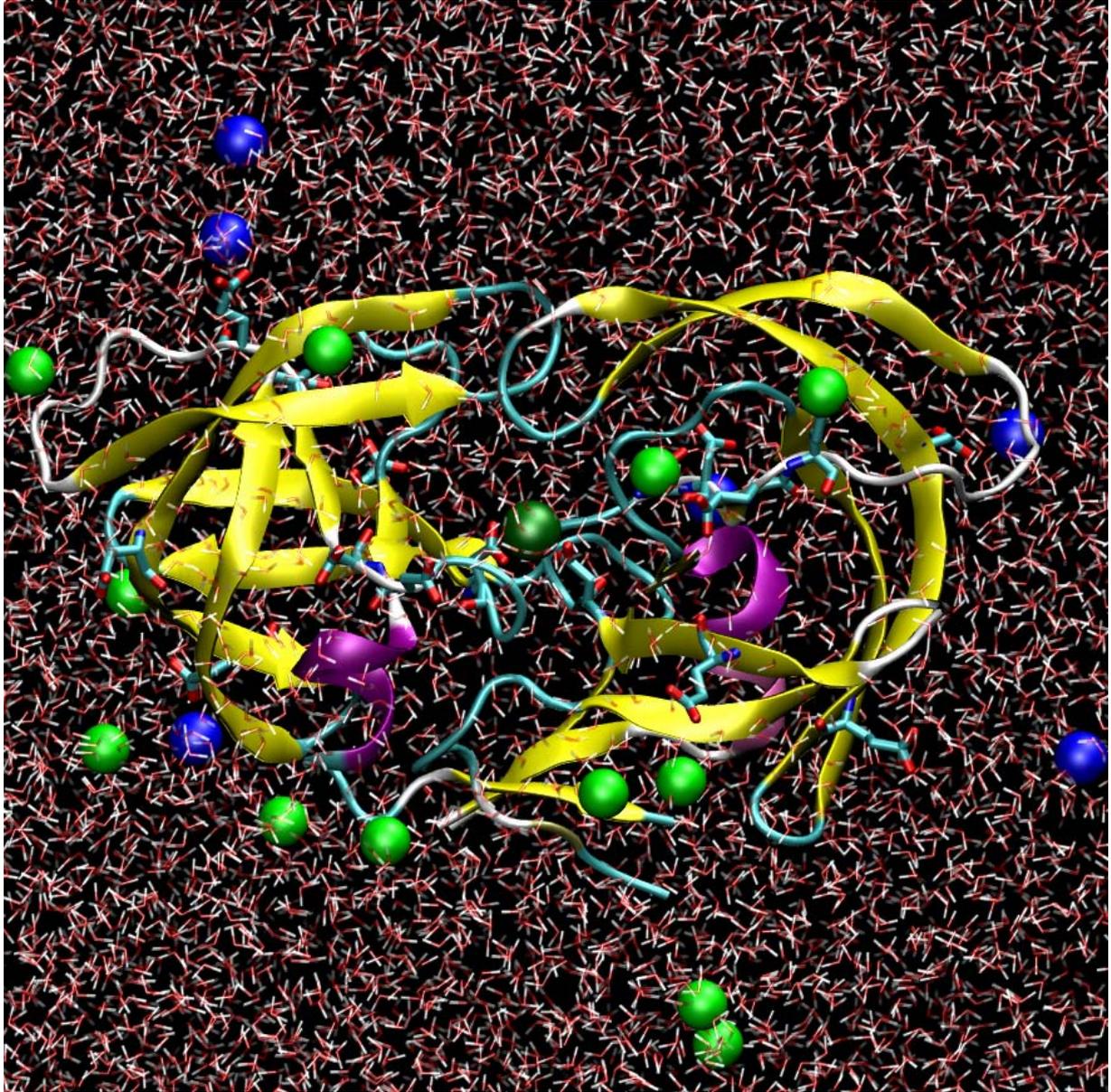
Lysozyme pH 4.5



Lysozyme pH 12.5



Cover Art: Distribution of sodium and potassium cations at the surface of hydrated HIV protease.



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