Supporting Information for

Hofmeister Series: Insights of Ion Specificity from Amphiphilic Assembly and Interface Property

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THEORETICAL EXPLANATION OF HOFMEISTER SERIES

HS has usually been used to describe the interactions among ions, water, and macromolecular ions in bulk solution and at interface.[1] Since the pioneer work of Franz Hofmeister over 120 years ago, many scientists have attempted to account for this phenomenon. In order to give a satisfactory and fairly predictive explanation, femtosecond time-resolved infrared spectroscopy (FS-IR),[2] dielectric relaxation (DR) spectroscopy,[3] optical Kerr-effect spectroscopy,[4] molecular dynamic simulation,[5] vibration sum frequency spectroscopy (VSFS),[6-8] differential scanning calorimetry (DSC),[9] and core-hole x-ray emission spectroscopy (XES),[10] *in situ* Raman spectroscopy[11] measurements have been performed to detect the interactions between the ions and the proteins. However, though vast amounts of experiments have been carried out, an underlying molecular level explanation of the mechanism of HS is still extremely intricate and far from completion. To date, two common models are used to interpret the mechanism: (i) indirect mechanism of action, i.e., the hydrated ions interacting with water around the proteins or macromolecules and causing precipitation; (ii) direct mechanism of action, i.e., the direct binding of the ions to the biomolecules by electrostatic interaction and hydrogen bonding (superchaotropic ions), being the key point for the biomolecule precipitation.[10,12,13] In this section, the two models are elaborately reviewed.

The first model leads to the term of structure makers/structure breakers, depending on the ions type, i.e., a completion between the strength of ion-water and bulk water-water interactions existing in the protein solution when electrolyte was added. The strength of the ion-water and water-water intermolecular forces is a consequence of charge density and hydrogen bonding, respectively.[10] In the HS, both anions and cations can be classified into kosmotropes and chaotropes, i.e., lyotropic ones and

hydrotropic ones, respectively, according to their properties of enhancing or weakening the hydrogen bonding network of water molecules.[14] Ions that interact with water more strongly than water itself are known as structure makers (kosmotropes). They break the hydrogen bonding in the surrounding water molecules resulting in rearrangement of the rest water molecules in a higher order hydration structure. The ions that interact with water weakly and are weakly hydrated are classified as structure breakers (chaotropes).They interact weakly with the nearby water molecules and make the surrounding water more disordered.[15,16]

The effect of different solutes on the water structure is realized by the way that water molecules arrange themselves around the solutes. Nau briefly reviewed the water-solutes interaction introduced by Herzfeld[17] and Colloins,[18] and gave a visualized explanation for water-solutes interaction at the molecular level, as shown in Figure S1.[19] Each water molecule has a tetrahedral coordination pattern, whose relative orientation to the convex solute surface (apical, lateral, and basal) and involved interaction sites at the apex, edge or base (hydrogen atoms or electron lone pairs) are specified. The solvation of a solute need the formation of a cavity (Figure S1d) around which water molecules arrange themselves on the principle of keeping the stability of the original hydrogen bonding network. Without regard to the interaction with the solute, no preferential orientation of the individual water molecules towards the surfaces of the cavity appears, resulting in both hydrogen atoms and lone pairs pointing to the convex surface of solutes. For kosmotropic anions, the positioning in the cavity cause highly directional hydrogen bonding or coordinative interaction, leading to a strong apical orientation of the water molecules (Figure S1a). While for chaotropic anions, its positioning in the cavity induce the less directional ion–dipole interactions for dominant, resulting in a lateral orientation of

the water molecules under alignment of their dipole moment (Figure S1b). The positioning of a hydrophobic solute in the cavity is mainly dependent on the distance-dependent dispersion interactions, which give rise to the preferred basal orientation of the water molecules, maximizing the proximity to bonding electrons, lone pairs, and the oxygen atom (Figure S1c). For cations, the principle orientations of the water molecules (apical or lateral) retain the same except that the interactions exist through the lone pairs instead of the hydrogens.

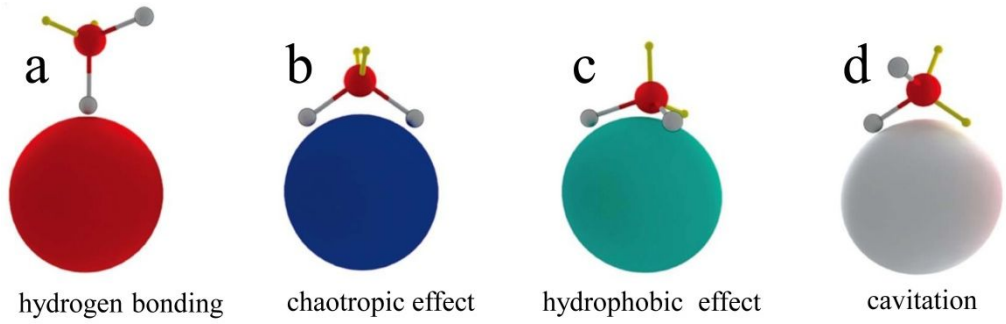

Figure S1. The favorable orientation of water molecules around a cavity and at the surface of different solutes: kosmotropic (a) and chaotropic (b) ions, hydrophobic molecules (c), and void space (d). Electron lone pairs are visualized in yellow. Reprinted with permission from ref 19. Copyright 2018, Wiley-VCH.

Collins conceptually divides the interfacial region near a protein molecule into three layers with each layer being the thickness of one water molecule.[18] The first water layer is directly adjacent to the proteins surface, called solvation layer; the second water layer is the designated transition layer; and the third water layer is neighboring the bulk surface. Proteins determine the behavior of the solvation layer. The bulk solution affects the property of bulk surface and both the solvation layer and bulk surface compete for the hydrogen bonding with transition layer. The third water layer (bulk surface) indirectly affects the solvation layer *via* transition layer and further influence the solubility of proteins, as shown in Figure S2a. When a strongly hydrated

anion (kosmotropic anion) is inserted into the third water layer, the second water layer busily participates in solvating the anion and weakens its interactions with the solvation layer, which decreases the hydration of solvation layer and the solubility of proteins, leading to a salting-out behavior. When a weakly hydrated anion (chaotropic anion) is inserted into the third water layer, the large volume and strong polarizability of the chaoreopic anion facilitate to promote the interactions between the transition layer and solvation layer, increasing the solubility of proteins and showing a salting-in behavior.

The reversal HS in the protein solution after changing the counterions can be interpreted by the law of matching water affinities, put forward by Collins, which describes the ion-ion and ion-charged site interactions.[1,18,20,21] Ions are approximately considered as a sphere with just a point charge in the center. When the ions are small, the surrounding water molecules are tightly bound (the ions are hard or kosmotropic). When the ions are big, the hydration shell is loosely bound (the ions are soft or chaotropic). When two strongly hydrated small ions with opposite charge come together, very strong attraction occurs between them, since the point charge at their centers could get closer to each other than those at the center of water molecules. Thus, they can form direct ion pairs and extrude the hydration spheres between them, as shown in Figure S2b. For two weakly hydrated soft big ions with opposite charges, they will also come together because the released water molecules can form stronger medium-medium interaction. However, small ions will not dehydrate spontaneously to form an inner sphere ion pair with an oppositely charged large ion because the point charge at the center of the small ion can get closer to the point charge at the center of the oppositely charged portion of water molecule than to the point charge at the center of an oppositely charged larger ion. Thus, we can conclude that oppositely

charged ions in bulk solution initiatively form inner sphere ion pairs only when they have equal water affinities, which qualitatively interpret of the reversal HS phenomenon in the solution.

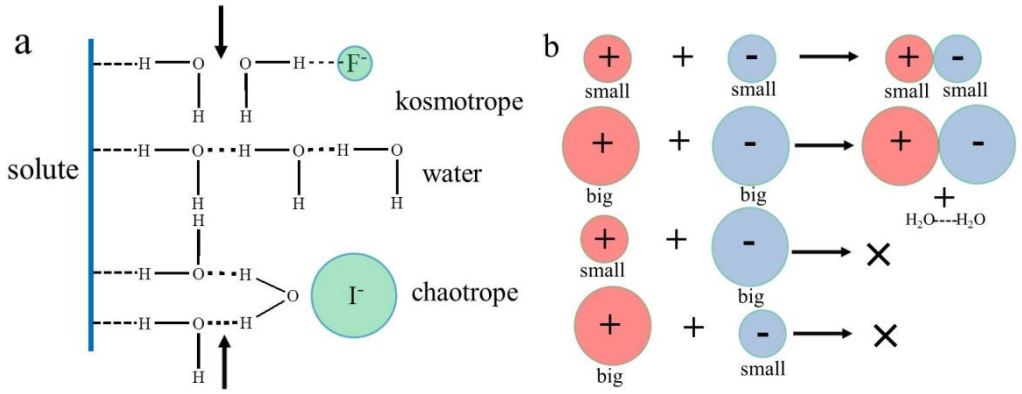

Figure S2. Interfacial water molecule near the polar surface of a test solute (protein molecule). (a) Ions inserted into the third interfacial water layer to modulate the interaction of the second interfacial water layer with the first interfacial water layer (arrows). While the number of hydrogen bonds between the second and first interfacial water layers must increase from the top of the figure to the bottom, the actual number shown is arbitrary. Figure S2a was reprinted with permission from ref 18. Copyright 2004, Elsevier. (b) Schematics of the law of matching water affinities: a kosmotropic (chaotropic) cation would form a contact ion pair with a kosmotropic (chaotropic) anion, whereas a kosmotropic (chaotropic) cation would not form a contact ion pair with a chaotropic (kosmotropic) anion. Figure S2b was reprinted with permission from ref 15. Copyright 2014, Royal Society of Chemistry.

Compared to the indirect mechanism action, the investigation of the direct mechanism of action is relatively less. In recent years, molecule dynamic (MD) simulation has been performed to test the theoretical models of the interactions between salts and proteins, as shown in Figure S3.[5] To understand the influence of salts on the protein backbone solvation and protein secondary structure formation, it is helpful to first analyze the interactions in the multicomponent systems. The carbonyl

of amide group, a good hydrogen bonding acceptor, plays an important role in stabilizing proteins. The change of free hydrogen donor/acceptor availability has a direct effect on the hydration of amide group of proteins. As shown in Figure 4, one can find that cations and anions affect the hydrogen bonding hydrogen donor/acceptor equilibrium in bulk solution, in opposite directions. In addition, ions may interact directly with the amide group of protein; cations can bind the carbonyl oxygen and anions to the amino hydrogen. The highly polarizable anions (chaotropic anions) tend to accumulate near the protein apolar surface and increase the protein solubility.

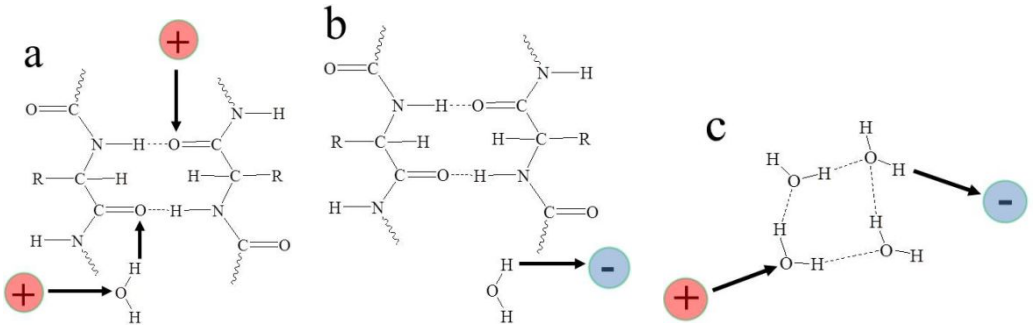

Figure S3. Salt effects on the protein amide hydrogen bonding. (a) The cation can "solvate" carbonyl directly or indirectly by increasing the availability of water hydrogen, (b) the strongly hydrated anion competes with the carbonyl for hydration, and (c) the cation and anion have opposite effects on the hydrogen donor/acceptor equilibrium. Reprinted with permission from ref 5. Copyright 2013, American Chemical Society.

Zhang et al. found that direct interactions exist between the ions and protein by studying the effects of HS on the phase behavior of a triblock copolymer, poly(ethylene oxide)-b-poly(propylene oxide)-b-poly(ethylene oxide), PEO-PPO-PEO.[22] They discovered that poorly hydrated anions affect the phase transition of polymer by changing the interfacial tension at the polymer/aqueous

interface and binding to the hydrophobic portion of the polymer. While the well hydrated anions interact with polymer by changing the hydration around the hydrophobic moieties of the polymer. In fact, the actual solutions are inevitably complicated by a delicate balance of all the interactions (e.g., water-water, water-ion, water-solute, ion-solute, and cation-anion). The two proposed model mechanism action are just from one side. The description of the mechanism is still not discerned the true character of HS phenomenon and more work is still need to dig into the secret behind HS.

APPLICATION OF HOFMEISTER EFFECT

Hofmeister series, ions specific effect or lyotropic sequence, refers to the relative effectiveness of anions and cations to produce different specificities on a wide range of phenomena (i.e., ion ability to change the *CMC* value in micellar systems, altering the LCST/UCST of polymers, influencing the phase transition and modifying the interface properties and particles aggregation).[5,23,24] The ions specific effect can be used in a number of physical and chemical processes, e.g., affecting the solubility of hydrophobic solutes in water and the cloud point of polymers and nonionic surfactants; controlling the aggregates transition and the gels formation; adjusting the air/water interface property (the Langmuir monolayer formation and the interfacial free energy). It is found that the ion specificity does not only apply in the biomacromolecule system, such as the enzyme activity, enzyme catalysis, optical rotation of amino acids, and bacterial growth, but also fit for the self-assembly of amphiphilies in electrolytes solution.[25] The Hofmeister effect has been attracting increasingly considerable attention due to their wide applications in electrostatic ion chromatography (EIC),[26] ion-selective electrodes for anions separation, the

determination of ionic drugs *in vitro* and *in vivo*,[27-29] monitoring of organic ions generated *in situ*,[30,31] cell signaling,[5] and "intelligent" materials.[32] It should be pointed that although the ions specific effects have many potential applications, there is still a long way to go before it develops into commercialization. In addition, there have been numerous reports of cation-selective electrodes, but only few anion-selective electrodes were covered, which should be paid much more attention in the further study.

APPENDIX

Acronym	Term
ABCCs	Anions borate cluster compounds
AOT	Sodium bis(2-ethylhexyl)sulfosuccinate
β-CD	*β*-cyclodextrin
$C_{10}NE$	Decyltriethylammonium bromide
$C_{10}SO_3Na$	Sodium decylsulfonate
CFM	Chemical force microscope
CGCs	Critical gelation concentrations
CMC	Critical micelle concentration
C_nEO_m	$C_nH_{2n+1}(OCH_2CH_2)_mH$
CPyCl	Cetylpyridinium chloride
cryo-TEM	Cryogenic transmission electron microscopy
c_{salt}	Salt concentration
CT	Chemical trapping
DLVO	Derjaguin, Landau, Verwey, and Overbeek
DMSO	Dimethylsulfoxide
DPPC	1,2-dipalmitoyl phosphatidylcholine
DR	Dielectric relaxation
DSC	Differential scanning calorimetry
DTAB	Dodecyltrimethylammonium bromide
EIC	Electrostatic ion chromatography
ER	Expansion ratio
EtOH	Ethanol
FS-IR	Femtosecond time-resolved infrared spectroscopy
HIPS	2-hydroxy-3-isopropoxypropyl starches
HS	Hofmeister series
Ils	Ionic liquids
LEP	liquid-expanded phase
LCST	Lower critical solution temperature
LMWGs	Low-molecular-weight gelators

MD	Molecule dynamic
MOF	Metal–organic frameworks
P	Packing parameter
PEO	Poly(ethylene oxide)
PEO-POX	Poly(ethylene oxide)-*block*-poly(2-alkyl oxazoline),
PEO-PPO-PEO	Poly(ethylene oxide)-b-poly(propylene oxide)-b-poly(ethylene oxide)
PMNT	Poly(3-alkoxy-4-methylthiophene)
PMETMASPS	Poly(sulfonium sulfonate)
PMMA	Poly(methyl methacrylate)
PNIPAM	Poly(*N*-isopropylacrylamide)
POMs	Polyoxometalates
PVCL	Poly(N-vinylcaprolactam)
PVP	Poly(vinylpyridine)
R_h	Hydrodynamic radius
SDS	Sodium dodecylsulfate
SL	sodium dodecanoate
T_c	Cloud points
T_{gel}	Gel-sol transition temperature
UCST	Upper critical solution temperature
VSFS	Vibration sum frequency spectroscopy
XRE	X-ray emission

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