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Hofmeister effects in supramolecular and biological systems

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Abstract

Specific ion effects, representative of near-universal Hofmeister phenomena, are illustrated in three different systems. These are the formation of supramolecular assemblies from cyclodextrins, the optical rotation of L-serine, and the growth rate of two kinds of microorganisms (*Staphylococcus aureus* and *Pseudomonas aeruginosa*). The strong specific ion effects can be correlated with the anion polarizabilities and related physico-chemical parameters. The results show the relevance of dispersion (non-electrostatic) forces in these phenomena.

Keywords: Hofmeister series; Specific ion effect; Supramolecular assembly; Optical activity; Bacteria; Polarizability; Dispersion forces; Interactions

1. Introduction

Hofmeister or specific ion effects are ubiquitous. They occur, e.g., in aqueous solutions of electrolytes, in water dispersions of macromolecules, and in self-assembled amphiphilic structures, where large interfaces separate phases with different hydrophobicity [1,2]. Despite the huge number of studies devoted to this issue that date back more than a century, their origin is still debated. Classical theories of solution, colloid and surface chemistry embodied in electrostatic models, DLVO type theories of molecular, surface, and interparticle interactions, with a continuum model for water, are inadequate in accounting for the experimental specificity at high salt concentrations [3,4]. What constitutes high salt concentration is different in model and real, e.g., biological or chemical engineering systems. For in the real system, the importance of electrostatic forces as measured by the Debye length is much reduced due to the presence of even a minute amount of multivalent contaminant. So the effects show up at low apparent salt [5]. One source of specific ion effects is missing in standard theories that separate electrostatic forces from electrodynamic, quantum mechanical (Lifshitz) forces. The latter include many body dipole–dipole, dipole–induced dipole, and induced dipole–induced dipole forces. In dilute media, these are the familiar Keesom, Debye and London dispersion forces. For mnemonic convenience only, we refer to them all as dispersion forces. The proper treatment of dispersion forces–where for ions the polarizability and the ionization potential of the intervening species play a major role–does give ion specificity, surface specificity, and also explains the fact that usually anions (richer in electrons) produce larger effects than cations [4,6–8]. In previous papers, we have shown that some Hofmeister phenomena can be at least partially understood in terms of dispersion forces [9–11]. These interactions include correlation contributions for all frequency ranges [12].

The conventional picture on the occurrence of specific ion effects is that they are directly related to the water structure effect induced by ions and neutral molecules. Cations, anions, and other solutes (such as sugars and urea) have been divided into water structure makers (or cosmotropes) and water structure breakers (or chaotropes). Supposedly, the former type enhances the strength of the hydrogen-bonding network of bulk water, while the latter goes the opposite way. When a cosmotropic ion (typically Li^+, Ca^{2+}, F^- or SO_4^{2-}) is introduced

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into bulk water, it binds the nearest solvent molecules more strongly than bulk water molecules, so producing a significant reorientation of the molecular dipoles around its electric field, and a lowering in the freedom of motion of the solvent molecules in the hydrated shells. On the other hand, the presence of a chaotropic ion (i.e., Cs^+, I^- or ClO_4^-) results in a disturbance of the hydrogen bonding network that is not followed by the formation of stronger ion–solvent interactions. As a consequence, bulk water will repel chaotropic ions toward interfaces (air/water or oil/water), and tend to keep cosmotropic species in the bulk [6]. Experimental data and molecular dynamics calculations predict that, in solution, fluoride and chloride ions remain in the bulk phase, while iodide and bromide ions approach the air/water interface. A confirmation of this process seems to be the asymmetric distribution of halide ions in seawater aerosols [13]. In fact the two approaches are not in conflict, as the inclusion of ionic dispersion energy along with the electrostatic Born energy in a continuum water model gives the same results as the cosmotropic–chaotropic picture [14,15].

Recent reports show that although a strong effect of the solutes can be reasonably expected to modify the hydrogen bonding in the nearest hydration shells, a long-range influence on the hydrogen bonding network of bulk water has not been detected [16,17]. However, other authors relate Hofmeister phenomena to changes in water nature/structure [18,19].

Specific ion effects occur in aqueous solutions of electrolytes and are reflected in consistent variations of a number of physico-chemical parameters (such as viscosity, partial molar volume, conductivity, pH, surface tension, etc.); however, Hofmeister phenomena are particularly relevant in the presence of a third component such as a polymer or a colloidal dispersion [19]. This introduces a further difficulty in the description of the mechanism that rules specific ion effects, because of the particular interactions between the third component, the ions, and the solvent, especially when a new large interface is introduced (for example, with a biopolymer such as a protein or a polysaccharide).

As pointed out by Jungwirth and Kunz, the complexity of Hofmeister phenomena embraces so many factors that it is impossible at the present moment to elaborate a predictive and quantitative universal model [20]. Certainly, polarizability and dispersion forces are two of the key factors that determine the different behavior of cations and anions in the Hofmeister rank. But other features, such as hydrogen bonding and ion pairs, will play a relevant role in Hofmeister phenomena [21].

In this paper, we analyze the effect of varying monovalent anions on three different illustrative systems:

(1) the formation of a supramolecular assembly, a polypseudorotaxane, produced by a polymeric chain with β-cyclodextrin in water (Fig. 1). Pseudopolyrotaxanes are formed when aqueous solutions of a fairly hydrophobic polymer (for example, PEG or PPG) are mixed with concentrated solutions of cyclodextrins (CDs). The onset of strong turbidity reveals the formation and precipitation of large aggregates. These are constituted by inclusion of the polymer chain in the internal hydrophobic cavity of beads formed by CD hosts. Hydrophobic interactions are the driving force for the formation of these supramolecular assemblies [22], and polypseudorotaxanes are interesting models that mimic real biological systems such as ribosomes and complexes of nucleic acids, proteins or antigen–antibody pairs, where specific molecular recognition is involved [23].

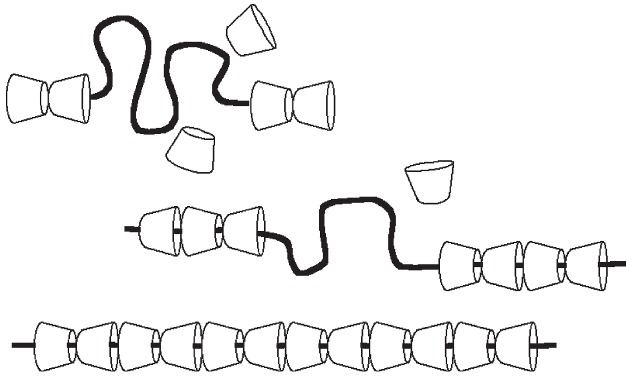

Fig. 1. Threading of a polymeric chain with β-cyclodextrin molecules.

(2) the optical rotation of L-serine in water. The value of optical activity [α] of this amino acid changes when different electrolytes are added to the solution at the same concentration and temperature. The optical activity of a chiral molecule is mainly determined by its conformation [24] and transition dipole moments [25].

(3) the growth of *Staphylococcus aureus* and *Pseudomonas aeruginosa* in aqueous media. The growth of the two strains of bacteria depends on the nature of the anions that are dissolved in the environment. *S. aureus* is a Gram-positive halophilic microorganism, while *P. aeruginosa* grows preferentially in diluted aqueous media [26]. These microorganisms react differently to the presence of salts. The mechanism seems to depend on ion adsorption at the microorganism membrane or wall, or on the rate-limiting step of specific enzymes involved in division and/or metabolism. Adsorption of anions at the active site changes hydrophobicity of the cavity and stops catalysis, as previously reported [27].

In this report we discuss the experimental results keeping in mind the dispersion forces that determine the specific interactions of ions with interfaces and molecular solutes. These forces are reflected too by some physico-chemical parameters such as the polarizability, the molar surface tension increment $\sigma = \partial(\Delta\gamma)/\partial c$ [28], and the lyotropic number [29]. These parameters all depend, more or less directly, on dispersion forces and can be used to evaluate and quantify Hofmeister phenomena [12]. In particular, we will show that:

(i) The effect induced by the anions in the three different systems is similar to that observed in other Hofmeister phenomena such as the precipitation of polysaccharides and the variation of the cloud point of surfactant solutions.

(ii) The specific ion effect is strictly related to some physico-chemical parameters, such as the molar surface tension increment (σ) and the ion polarizability in solution (ρ) that are directly related to the dispersion forces that the ions experience in solution. In the paper, we will designate the polarizability as ρ (instead of α) to avoid any confusion with the optical activity.

(iii) The Hofmeister phenomena observed in these systems can be explained in terms of ions adsorption at interfaces, or of interactions with specific linkages.

2. Materials and methods

Sodium fluoride, hydroxide, chloride, bromide, dihydrogen phosphate, hydrogen carbonate, nitrate, iodide, thiocyanate, iodate, perchlorate, poly(propylene glycol)-bis-2-aminopropyl ether (PPG-Am_2; MW ≈ 2000), β-cyclodextrin (β-CD) and L-serine were purchased from Aldrich-Fluka (Milan, Italy) and used as received. All solutions were made with bidistilled Milli-Q water system (Organex) supplied by Millipore (resistivity > 18 MΩ·cm).

2.1. Formation of polypseudorotaxanes

The formation of polypseudorotaxanes was obtained by mixing proper amounts of water solutions of poly(propylene glycol)-bis-2-aminopropyl ether (PPG-Am2; 0.075 mM) and β-cyclodextrin (β-CD; 8.37 mM). Salt solutions were 0.1 M. Absorbance data at 400 nm were collected with a Lambda 5 Perkin-Elmer spectrophotometer at 25°±0.1 °C. The threading time, τ (see Fig. 2) was evaluated as previously reported [30].

2.2. Optical rotation

The optical activity of L-serine was measured with a Perkin-Elmer 343 polarimeter as $[\alpha]_\lambda^T = \frac{100\cdot\alpha}{c\cdot d}$, where α is the optical rotation in degrees, d is the path length across the cell (100 mm), λ the wavelength of light (589 nm), T the absolute temperature, and c is the concentration of L-serine (in g/mL). If the solvent contains other solutes (such as salts), the data need to be corrected for the change in refractive index of the solvent (water): $[\alpha] = [\alpha]_{\mathrm{EXP}} \cdot \frac{n_w^2+2}{n_s^2+2}$, where $[\alpha]$ and $[\alpha]_{\mathrm{EXP}}$ are the corrected and experimental values, n_w and n_s are the refractive indices of water and of the aqueous solution of the particular salt at the same T and λ, respectively [31]. All measurements were carried out at 20°±0.1 °C, and all electrolyte concentrations in the cell were 0.5 M. The final concentration of L-serine in the cell was 0.20 M. Refractive index measurements of 0.5 M electrolyte solutions were performed at a constant temperature (20 °C) with a modified Abbé Refractometer (Atago 3T).

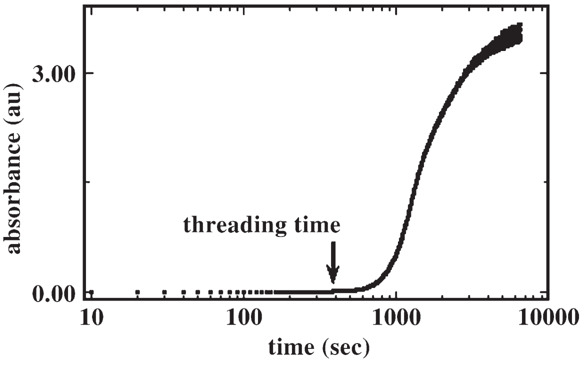

Fig. 2. Turbidity change during the formation of a polypseudorotaxane from PPG-Am_2 (MW ≈ 2000) and β-CD. The arrow indicates the threading time (τ).

2.3. Growth of bacteria

The strains of *S. aureus* and *P. aeruginosa* were ATCC 25953 and ATCC 27853, respectively (Oxoid, Milan, Italy). The study was carried out according to the procedure already described [32]. The growth of bacteria is expressed as log (C/C_0), where C is the count in the presence of the different added salts (0.9 M), and C_0 in the blank growing medium.

3. Results and discussion

3.1. Formation of polypseudorotaxanes

The threading process that involves the threading of polymer chains (as guests) through a number of cyclodextrin cavities (as hosts) leads to the formation of polypseudorotaxanes. This has been described and discussed in previous papers [22,33]. The process can be monitored through turbidity measurements. After mixing the solutions of the two reactants, the absorbance remains constant and this region defines the threading time (τ). After some time, depending on temperature, solvent nature and composition of the reactants, the solution becomes more and more turbid (Fig. 2), as the polypseudorotaxanes aggregate and precipitate [33]. The addition of salts significantly changes the threading time τ for PPG-Am_2/β-CD mixtures by either accelerating or retarding the formation of the supramolecular assemblies. The experimental values are reported in Table 1. This evidence indicates that some ions stabilize the reactants and slow the reaction (fluoride), while others like iodide favor the formation of the host–guest compound, and increase the reaction rate, according to the following trend, the standard Hofmeister series:

$$F^- > OH^- > H_2O > Cl^- > Br^- > H_2PO_4^- > HCO_3^- > NO_3^- \approx I^- \approx SCN^- > IO_3^-.$$

3.2. Optical activity of L-serine

The specific effect of some sodium salts on the optical rotation of L-serine, HO–CH_2–CH(NH_3^+)–COO^-, has been investigated at constant temperature and solutes concentration (see Table 1). In pure water, $[\alpha]$ reaches the highest (absolute) value. Then it reduces quite regularly in going from the cosmotropic (hard) anions (like F^-) to the chaotropic (soft) species (such as I^-) according to the following trend:

$$H_2O > H_2PO_4^- > F^- > Cl^- > NO_3^- \approx Br^- > ClO_4^- > I^- \approx SCN^-.$$

Table 1
Polarizability (ρ in Å^3), molar surface tension increment (σ in mN·L/m·mol), lyotropic number (N), threading time of polypseudorotaxane (τ in seconds, ±10), corrected optical activity ([α], ±0.06), and bacteria growth (log C/C_0, ±0.5) for *S. aureus* and *P. aeruginosa*

Anion	ρ	σ	N	τ	[α]	log (C/C_0)	
						S. aureus	*P. aeruginosa*
F^-	1.36	1.96	4.8	118	−7.09		
OH^-	2.25	1.84	5.8	103			
Cl^-	3.73	1.63	10.0	79	−6.88	2.4	−0.5
Br^-	5.07	1.31	11.3	63	−6.78	1.4	−1.9
$H_2PO_4^-$	(4.5)		8.2	55			
HCO_3^-				40			
NO_3^-	4.48	1.18	11.6	36	−6.70	1.6	−1.4
I^-	7.16	1.02	12.5	35	−6.45	−1.0	−3.8
SCN^-	7.41	1.06	13.2	30	−6.44	−0.6	−3.8
IO_3^-	8.00		6.2	25			
ClO_4^-	5.26		11.8		−6.54		
(Water)				97	−7.59	−1.0	2.9

The value of ρ for $H_2PO_4^-$ was estimated from the refractive index of $NaH_2PO_4 \cdot H_2O$ averaged over the three crystal axes [47].

3.3. Growth of bacteria

The bacteria growth rates were quantified through the parameter log(C/C_0), where C represents the counts obtained after adding the electrolyte to the growing medium, and C_0 the counts measured without that salt. The data are reported in Table 1 and can be ordered in the following trends:

$$S.\ aureus\text{: } Cl^- > NO_3^- > Br^- > SCN^- > I^- \approx H_2O$$

$$P.\ aeruginosa\text{: } H_2O \gg Cl^- > NO_3^- > Br^- > SCN^- \approx I^-$$

The main difference is that *S. aureus* grows preferentially in the presence of some salts (chloride, nitrate and bromide) rather than in water, at least for the electrolytes and concentrations considered. By contrast, *P. aeruginosa* prefers water to any salt solution. This difference is reflected in the value and sign of log (C/C_0) and is probably due to the different structure of the bacterial walls and membranes in the two species.

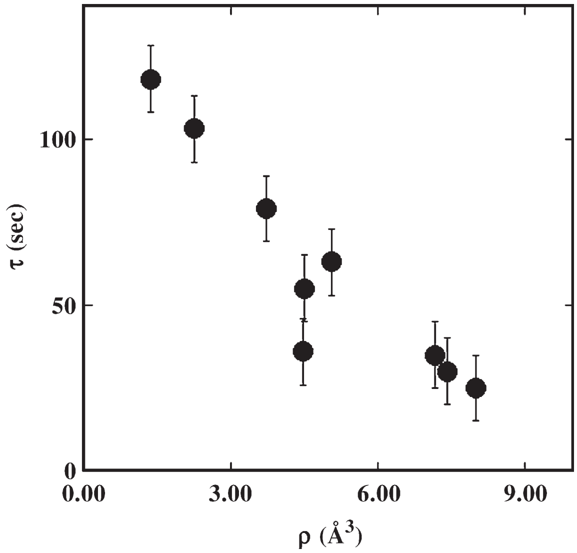

Fig. 3. Threading time (τ) during the formation of polypseudorotaxanes from PPG-Am$_2$ and β-CD in water as a function of the ion polarizability in solution (ρ).

The effect of salts on bacterial strains has been already investigated and reported. Some species are halophilic or halotolerant [34], but usually microorganisms react to hyper-osmotic shocks by the osmoregulating activity of compatible cosmotropic solutes [5]. In other cases, more specific mechanisms take place, with preferential interactions between salts and bacterial membranes, or the modification of proteins or enzymes structure, folding and activity [6,27,36,37]. Chaotropic anions adsorb at interfaces and can permeate across the membrane or reduce the membrane lipid order and change the membrane composition [6,38], possibly affecting cellular communication and biological signaling [39]. Our results indicate that both strains are inhibited by the presence of the more chaotropic anions (iodide and thiocyanate), while the effect of chloride, bromide and nitrate is smaller (in the case of *P. aeruginosa*) or even positive (for *S. aureus*).

3.4. Correlation with other physico-chemical parameters

In order to explain the experimental findings, we proceed to correlate the change in τ, [α], and log(C/C_0) with some typical physico-chemical parameters that all provide traces of "Hofmeister fingerprints." We limit our discussion here to the ionic polarizability ρ, the molar surface tension increment σ, and the lyotropic number N. The latter was introduced by Voet to quantify the effect of salts in salting-out of polysaccharides [29].

These parameters are more or less directly related to the dispersion non-electrostatic forces that ions experience in the solution. With the term "dispersion forces," we remark again that we mean the totality of frequency-dependent electrodynamic fluctuation forces (i.e., the many-body solvent-dependent generalizations of London, Debye and Keesom interactions)

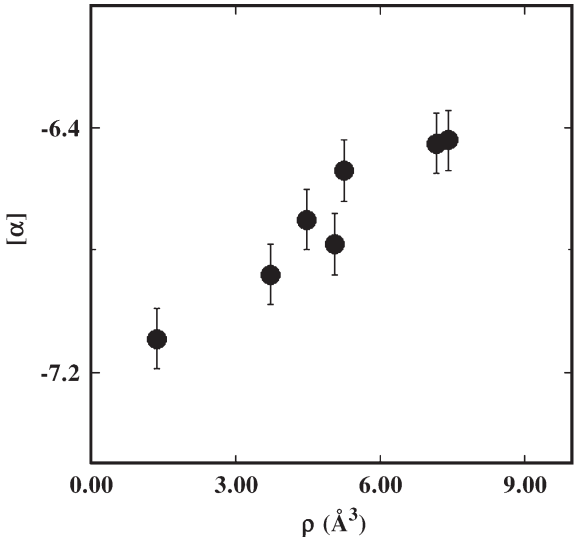

Fig. 4. Optical rotation threading time ([α]) of L-serine in water as a function of the ion polarizability in solution (ρ).

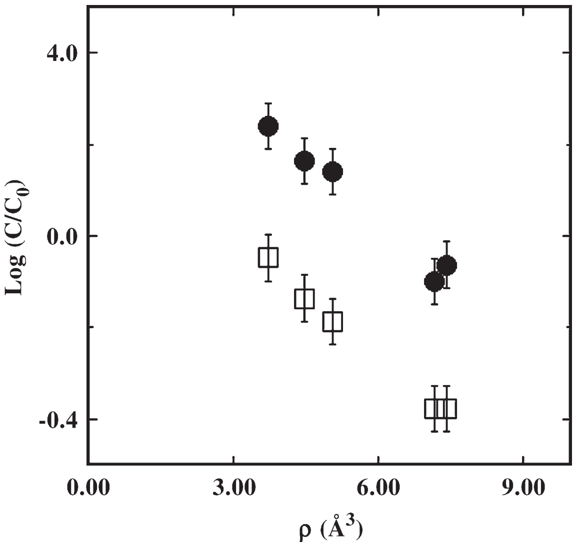

Fig. 5. Growth rate (Log C/C$_0$) of *S.* aureus (●) and *P. aeruginosa* (☐) as a function of the ion polarizability in solution (ρ).

that act on and between ions and substrate [40]. These many-body dispersion forces determine ion adsorption and hydration. In the simplest crude approximation, in the visible and at ultraviolet frequencies, they depend most strongly on the polarizabilities and ionization potentials of the interacting species [40]. Since anions are richer in electrons than cations, they show a greater variation in excess polarizabilities, and therefore in dispersion forces than do the cations. Table 1 reports the values of ρ, N, and σ for the different anions that were taken from the literature [10,41].

Figs. 3–5 show the variation of τ, [α], and log(C/C_0) as a function of ρ, respectively. The plots indicate that the three different systems (the formation of polypseudorotaxanes, the optical activity of L-serine, and the growth of bacteria) show a significant specific ion effect that is quite well represented by the variation of ρ along the series of salts. Ions with large polarizability (such as I^- and SCN^-) accelerate the formation of the polypseudorotaxane, increase the value of [α], and inhibit the growth of the two strains of bacteria. Similar trends are observed when considering the molar surface tension increment. The comparison of τ, [α] and log(C/C_0) with the lyotropic number N indicates that the phenomena we observe here follow the same trend found in classical Hofmeister experiments, such as salting-in/salting-out of proteins [42,43] and polysaccharides [44], and in-phase separation of micellar dispersions of nonionic [45] or zwitterionic surfactants [46].

The polarizability-dependent variation of the experimental observables prompts us to propose the following explanation. In the case of the formation of polypseudorotaxanes, the highly polarizable anions (such as I^-) adsorb at the polymer surface and deplete water around the molecule. In this way, they enhance the unfolding of the polymeric chain that immediately precedes and controls the threading process, and produce faster reactions. Similarly, the anions that mostly inhibit the bacterial growth rates are those that possess high values of ρ and adsorb at the interface between the microorganism and the external environment, or modify the activity of specific enzymes. This mechanism is not limited to large interfacial systems only. Also, in the case of the variation of the optical activity of L-serine, the largest variation is produced by those ions–such as ClO_4^-, I^- and SCN^-–that can modify the molecular conformation of the amino acid, by interacting with specific chemical bonds and/or by changing the transition dipole moments [35].

In summary, these evidences seem to suggest that the basic mechanism that rules specific ion effects is directly related to ion adsorption at interfaces (for example, in the case of the polypseudorotaxane or for the bacterial growth) or to interactions with specific linkages (in the case of L-serine). This conclusion confirms the relevance of dispersion forces in such phenomena and explains the specificity of ions.

4. Conclusions

What we have shown experimentally is that there is a direct relationship between a set of different phenomena where specific ion effects take place. These Hofmeister phenomena–dominated by ion adsorption and specific interactions–occur at interfaces and at the level of specific linkages. The occurrence of Hofmeister effects is near universal. They range over air/water and oil/water interfaces, double layers, hydrophobic surfaces, self-assembled aggregates, microemulsions, enzyme activity, and growth of microorganisms. Our examples, the formation of a supramolecular assembly (polypseudorotaxane), the variation of optical activity of an amino acid in water, and the growth rate of *S. aureus* and *P. aeruginosa* in the presence of different monovalent sodium salts at moderately high concentrations, illustrate the diversity and ubiquity of such effects. They all seem to have the same origin. There is a consistent direct relationship between the effects induced by a set of monovalent salts and the polarizability of the anions in solution, which is strictly related to the dispersion (non-electrostatic) forces experienced by the ions.Our main conclusion is that dispersion forces–that dominate at salt concentrations typical of biological systems (above 0.1 M)–have to be taken into account in the interpretation of Hofmeister phenomena and ion specificity.

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