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Models and mechanisms of Hofmeister effects in electrolyte solutions, and colloid and protein systems revisited

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Specific effects of electrolytes have posed a challenge since the 1880's. The pioneering work was that of Franz Hofmeister who studied specific salt induced protein precipitation. These effects are the rule rather the exception and are ubiquitous in chemistry and biology. Conventional electrostatic theories (Debye–Hückel, DLVO, *etc.*) cannot explain such effects. Over the past decades it has been recognised that additional quantum mechanical dispersion forces with associated hydration effects acting on ions are missing from theory. In parallel Collins has proposed a phenomenological set of rules (the *law of matching water affinities*, LMWA) which explain and bring to order the order of ion–ion and ion–surface site interactions at a qualitative level. The two approaches appear to conflict. Although the need for inclusion of quantum dispersion forces in one form or another is not questioned, the modelling has often been misleading and inappropriate. It does not properly describe the chemical nature (kosmotropic/chaotropic or hard/soft) of the interacting species. The success of the LMWA rules lies in the fact that they do. Here we point to the way that the two apparently opposing approaches might be reconciled. Notwithstanding, there are more challenges, which deal with the effect of dissolved gas and its connection to 'hydrophobic' interactions, the problem of water at different temperatures and 'water structure' in the presence of solutes. They take us to another dimension that requires the rebuilding of theoretical foundations.

1. Introduction

'Hofmeister', 'lyotropic' or 'salting in *vs.* salting out' effects are synonyms for the same ion specific phenomenon.[1–4] They are not explained by standard theories of electrolytes.[5–7] The term 'ion specificity' in fact puts the 'cart before the horse'. Specificity is the rule rather than the exception and exists everywhere in chemistry and biology.[4,5] Examples of these phenomena include the Born energy,[8] electrolyte activities,[9] buffers,[10,11] viscosities,[12] bubble coalescence,[13] surfactant and microemulsion phases,[14,15] ionic liquids,[16] polymer solubility,[17,18] cation and protein adsorption at silica surfaces,[19–21] optical rotation of amino acids,[22] enzyme activities,[23–28] protein cloud points,[29,30] protein surface charges[31] and electrophoretic mobilities,[32,33] electrochemistry of redox enzymes,[34] growth rates of microorganisms,[35] and many others. For an overview of the situation see some recent books[6,36] and reviews.[5,7,37–42]

Classical theories of electrolytes 'work' qualitatively but never quantitatively without many fitting parameters, *e.g.* those developed systematically in the widely used Pitzer scheme.[43] Fitting parameters like hydrated ion size that fit one experiment are different for another.

The situation has frustrated physical chemists since Hofmeister's original work on ion specificity that showed up with precipitation of proteins about 130 years ago.[1,2] It is a frustration also because without any evident systematics all attempts to exploit Hofmeister effects in applications are doomed.[4]

We make a distinction between specific ion effects in electrolyte solutions and those in more complex colloids like proteins. Two recent developments appeared to throw light on the problem. In one, Collins[44] found a set of rules that brings many observations to order. The rules take cognizance of electrostatic interactions and systematise (unquantified) hydration interactions between ions, and between ions and surface sites of opposite charge. But they ignore quantum mechanical (and ion specific) dispersion forces, which have to be included in a complete theory. Attempts to take these into account have been made by one of us and coworkers.[45–49] Ion specificity emerged, but the first theoretical attempts ignored hydration. Note however that Hofmeister effects also do exist in non-aqueous solvents.[50,51] The initial work on ionic dispersion forces also failed to take account of ion size variations. At first sight this might seem totally wrong. However the formulae required polarisability and radii of ions scale (see Section 6.3).

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Nonetheless, the two approaches, ion specificity expressed *via* hydration (Collins' rules) *vs.* specificity explicit with ionic dispersion forces, appeared to conflict.

Recent studies of Duignan *et al.*[52–55] subsume recent encouraging steps by Lund *et al.*[56] and Levin *et al.*[57,58] that point the way to reconciliation of the two apparently opposing approaches. The development quantifies ion specific dispersion forces and ion size *via ab initio* quantum mechanics that also includes hydration and thus 'Collins' rules'. Promising quantification and predictability is emerging. This will be illustrated explicitly by means of examples of ion specific phenomena in bulk, colloid, and protein systems.

The outline of the review is as follows.

– We lay out the background to the phenomena and difficulties that face us in protein, solution, and colloid chemistry (Sections 2–4).

– We explain Collins' rules and illustrate their application (Section 5).

– We then give a brief account of theory that includes quantum dispersion forces missing from classical theory, and show how hydration and ion size are taken account of systematically (Section 6).

– We discuss how the Collins' and 'missing dispersion forces' approaches might be reconciled (Section 7).

– Finally we summarise the present state of affairs covered in this review, with a focus on future challenges (Section 8).

2. Background to ion specific phenomena

2.1. Hofmeister's and other early 'ion specific' experiments

In 1888 and subsequently Franz Hofmeister quantified specific effects of salts on egg white protein precipitation.[1] For salts having the same cation the anions could be ordered in a series that reflected their efficiency in precipitating proteins. The series orders the increasing concentration required to do the job:

$$SO_4^{2-} > HPO_4^{2-} > F^- > CH_3COO^- > Cl^- > Br^- > NO_3^- > I^- > ClO_4^- > SCN^-$$

Similarly, for salts with the same anion the cation order is:

$$(CH_3)_4N^+ > Rb^+ > K^+ > Na^+ > Li^+ > Mg^{2+} > Ca^{2+}$$

Such experiments were carried out in the context of a background where pH was unquantified and no theory of electrolytes like the Debye–Hückel theory existed.

Hofmeister remained bemused on whether his effects should be attributed to bulk water (withdrawing power) or surface effects due to salts. As a pharmacologist, the withdrawal power of magnesium sulfate used as a laxative was evident! And while the weight of opinion opposes such long range effects, nagging questions like the existence of extremely dilute gels that comprise jellyfish remain an unsolved issue.[59]

Besides Hofmeister's studies in the 1880s, attempts to account for the phenomena in the early years of the 20th century can be seen in the major studies of Robertson,[60] Loeb,[61] and Gustavson.[62] We note that these post-Hofmeister studies were conducted in 1911, 1920, and 1926, indicating the venerability of the problem, which is still unexplained.

A remarkable example of ion-specific effects in a protein system was reported by Green[63] in 1932 who studied the solubility of carboxy-hemoglobin in different aqueous salt solutions. By considering the ratios of protein solubility S in the presence of salts, and solubility S_0 in the absence of salts, the entity $\log S/S_0$ followed a bell shaped trend as a function of the square root of the ionic strength I (Fig. 1). Experimental data could be fitted by using an empirical equation which is

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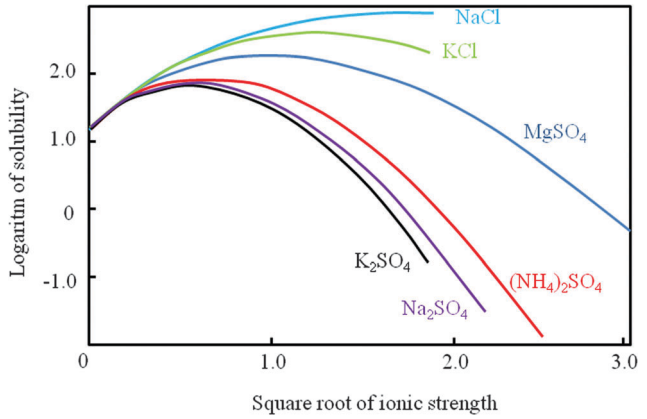

Fig. 1 Solubility of carboxyhemoglobin in various electrolyte solutions at 25 °C. Adapted with permission from ref. 63. Copyright (1932), by the American Society for Biochemistry and Molecular Biology.

Table 1 Literature values of some ion specific parameters. Mobility (μ_i) of aqueous ions at infinite dilution at 25 °C.[64] Jones–Dole Viscosity B coefficient (B).[69] Hydration enthalpies ($\Delta H_{hydration}$).[70] Ionic size (hard sphere radius, a).[6] Static polarisabilities (α_0)[6]

Ion	μ_i ($cm^2\ V^{-1}\ s^{-1} \times 10^4$)	B	$\Delta H_{hydration}$ (kJ mol^{-1})	a (Å)	α_0 (Å^3)
CH_3COO^-	4.23	0.236	−425	—	—
F^-	5.70	—	−515	1.12	1.218
Cl^-	7.91	−0.007	−381	1.86	4.220
Br^-	8.13	−0.032	−347	2.16	6.028
NO_3^-	7.40	−0.046	−314	2.21	4.008
I^-	7.95	−0.080	−305	2.33	8.967
SCN^-	—	−0.103	−310	2.39	7.428
Li^+	4.01	0.147	−519	0.42	0.028
Na^+	5.19	0.086	−409	0.67	0.131
K^+	7.62	−0.007	−322	1.06	0.795
NH_4^+	7.60	−0.007	−307	—	—
Rb^+	7.92	−0.029	−293	1.23	1.348
Cs^+	7.96	−0.045	−264	1.62	2.354

exactly equivalent to the extended Debye–Hückel equation for mean activity coefficients of electrolyte solutions,

$$\log \frac{S}{S_0} = \frac{0.5 z_1 z_2 \sqrt{I}}{1 + A\sqrt{I}} - K_s I \quad (1)$$

where z_1 and z_2 are ion valences, and K_s is the 'salting out' coefficient, analogous to the Jones–Dole B coefficient for viscosity (see next paragraph).

2.2. First attempts to come to grips with ion specificity

It was supposed at the beginning that ion specificity was intimately related to the specific interactions that ions have with water. This is reflected in many easily measurable physico-chemical parameters of aqueous salt solutions. We consider the insights that can be gleaned from two of these, namely conductivity and viscosity.

2.2.1. First ion specific parameters and water structure. In 1876 Kohlraush measured the conductivity of electrolyte solutions.[64] His mechanism for conductivity was the 'independent migration' of ions through the solution caused by the presence of an electric field. Positive ions migrate towards the negative electrode and negative ions toward the positive electrode. The current through the solution is given by the product of the velocity of the ion and its charge. The electrochemical mobility, μ_i ($cm^2\ V^{-1}\ s^{-1}$), is given by the ratio between the velocity and the applied electric field.

One would expect that the mobility is high for small ions and low for big ions. In fact the order of mobility for alkali metal cations is $Cs^+ > Rb^+ > K^+ > Na^+ > Li^+$ and for halides is $Br^- > I^- > Cl^- > F^-$ (Table 1). That is the opposite of what was expected. The accepted explanation is that the actual effective size of ions in water is very different from that in a crystal. Small ions (*e.g.* Li^+, F^-) are strongly hydrated and move bearing several water molecules with them and so they move slowly compared with bigger, poorly hydrated ions (*e.g.* Cs^+, Br^-).

The first pioneering experiment on electrolyte viscosities was that of Poiseuille[65] in 1847. Jones and Dole measured the viscosities of salt aqueous solutions about 80 years later.[12] They found that salt solutions can be either more or less viscous than pure water depending on the nature of the salts. The relationship between the relative viscosity (η/η_0) and the salt concentration c is:

$$\eta/\eta_0 = A\sqrt{c} + Bc \quad (2)$$

where A is an 'electrostatic' parameter about equal for all salts, and B is an 'ion specific' parameter known as the 'Jones Dole Viscosity B coefficient' (Table 1).

It was supposed that a 'water structure' (which can be thought as a dynamic fluctuating hydrogen bond network) existed, and that this was specifically affected by electrolytes.[66] (For recent attempts to better fine 'water structure', and water and electrolytes in biology see recent articles by Hyde[67] and Henry.[68]) The ions with a positive value of B increased the viscosity of aqueous solutions and were supposed to 'make the order' in the water structure. They were called 'kosmotropes'. Those with a negative value of B decreased viscosity of aqueous solutions and were supposed to 'break the order' in the water structure. They were called 'chaotropes'.

2.3. Failure of conventional theoretical ideas

On the basis of the previous classification of ions as kosmotropes and chaotropes, one possible explanation for Hofmeister's experiments (salt induced protein precipitation) was that kosmotropic anions withdraw the water molecules of the hydration layer of proteins, thus forcing them to aggregate. Chaotropic anions were thought to act with exactly the opposite mechanism.[71]

Although this seemed to be a qualitatively satisfactory explanation, there are several observations which demonstrate that the mechanism at work is much more complicated. These observations are briefly outlined below.

2.3.1. Effect of cations. The water 'withdrawing power' mechanism appeared to provide some comfort to explain the behavior of anions observed by Hofmeister. But if this was the mechanism at work, the question arises as to why kosmotropic cations salt in (see the cation series above and the recent paper by Schwierz *et al.*[72]) proteins and the chaotropic ones are salting

out? (that is, cations give rise to exactly the opposite effect of anions).

2.3.2. Hofmeister series reversal. It was found that in some situations the series were reversed in order.[60,73] From the beginning this has been the key challenge for any theory. Let us take the ordering of ions that promote protein aggregation listed above as the standard or 'direct Hofmeister series'. This is usually observed at pH values above the protein isoelectric point (IEP). The series reverses at a pH below the IEP (reverse or inverse Hofmeister series).[73] Again, at a pH below IEP the series changes from 'inverse' to 'direct' with increasing salt concentration.[29,60]

Other examples of series reversal are seen by pH measurements in salt solutions. At the same nominal pH of 7, they follow a direct Hofmeister series for phosphate buffer, and reverse for cacodylate buffer.[10] The same kind of reversal is seen with restriction enzymes[23] and activity coefficients (see Section 2.4.2). These and other striking examples are usually ignored completely because they pose too much of a challenge. Such observations imply that both specific surface hydration–ion hydration interactions and hydrated ion–bulk water interactions are involved. The direct and reverse sequences can rearrange in internal ordering depending on the nature of the surface (*e.g.* hydrophobic or hydrophilic, charged or uncharged, zwitterionic).[74] Nonetheless, the idea that there is a fixed universal Hofmeister series persists.

2.3.3. Concentration range. For decades it was thought that Hofmeister effects were associated only with phenomena occurring at high salt concentrations (*i.e.* 0.5–3 M).[63] This belief persists. It was probably due to the unavailability of sensitive enough experimental methods. But even early in the piece, ion specificity was found to also occur at low salt concentrations.[60] That they can occur at very low concentration is a matter predicted theoretically[46] and has been confirmed *e.g.* by Mahiuddin and colleagues.[75] These observations have now become more frequent.[32,33,76] In particular, the occurrence of ion specificity at physiological concentrations ($\sim$0.1 to 0.15 M and below) reflects the fact that ions play a specific key role in most biochemical mechanisms.[77]

2.3.4. Ions do not affect the long range water structure. Besides the open questions above, some experiments have demonstrated that ions do not affect hydrogen bonding of water beyond their first solvation shells.[78] Hence, the hypothesised long range effect of ions on water structure has been put aside. Analogously, the traditional mechanism that assigned Hofmeister effects to salt-induced withdrawal of water from protein surfaces is no longer considered an explanation of ion specific phenomena at a salt concentration of <0.2 M.

These observations imply that, to be acceptable, any approach that explains ion specific phenomena has to account for the different behaviour between anions and cations, the reversal of Hofmeister series, as well as their occurrence at low concentration.

2.4. Bulk electrolytes

If we want to understand ion specificity we necessarily have to consider the behaviour of electrolyte solutions. We recall that the non-ideal behaviour of electrolyte solutions is measured by the mean activity coefficient, $\gamma_{\pm} = (\gamma_+\gamma_-)^{1/2}$.[9] Its simplest expression is that derived *via* Debye–Hückel theory,[79]

$$\log \gamma_{\pm} = -\frac{Az_1z_2\sqrt{I}}{1 + Ba\sqrt{I}} \quad (3)$$

where z_1 and z_2 are the valences of the ions, I is the ionic strength, a is the ion diameter, and A and B are constants depending on the dielectric constant and temperature. This theory considers ions interacting with electrostatic forces only and treats water as a continuum. It cannot claim validity above 10^{-3}–10^{-2} M and does not take into account ion specificity.

2.4.1. Attempts to extend the Debye–Hückel law. Several attempts were made along the years to extend the range of validity of Debye–Hückel theory.[80,81] Robinson and Stokes added a linear term with an additional fitting parameter b to extend the range of validity:[9]

$$\log \gamma_{\pm} = -\frac{Az_1z_2\sqrt{I}}{1 + Ba\sqrt{I}} + bI \quad (4)$$

Decorations were made to allow short range ion hydration. The overlapping of such hydration shells gave an extra potential of interaction (Gurney potentials).[82,83] A further extension of eqn (4) gives an explicit form to this interaction term which can be obtained from equations of state for effective hard spheres,[84]

$$\log \gamma_{\pm} = -\frac{Az_1z_2\sqrt{I}}{1 + Ba\sqrt{I}} + Da^3I \quad (5)$$

In this expression the extra parameter, a, is the centre to centre distance of cation and anion on contact. From such an equation a set of apparently additive consistent ion size parameters could be found to predict the activities of alkali halides up to very high concentrations ($\sim$3 to 4 M).[43,84] The fitted effective ion sizes were reasonably consistent, except for some ions like Cs^+, and NO_3^-, SO_4^{2-}, PO_4^{3-}, AcO^-. For these the ion sizes that fit the data were less than the bare ion size. This suggests that extra attractive forces (dispersion forces) are operating. With multivalent and mixed electrolytes full nonlinear electrostatic theories give a good account, but only at low concentration.[85] For other experiments the effective ion size parameters that fit the data vary from experiment to experiment and are temperature dependent.

A review of the many attempts to come to grips with activities is due to Kunz and Neueder,[86] where they state: "There is not a single published work in which a prediction of these values can be found." Further "Today, it seems that the most physical model is one of the oldest: the Friedman–Gurney (FG) model".[87] This model uses sophisticated HNC calculations to treat the statistical mechanics, but still relies on 'Gurney potentials', with parameters adjusted for each salt.

An alternative approach focused on electrostatics and upon short ranged hydration anticipated Collins' rules. Hydration forces were calculated by the theory of Maxwell (1876) and revived a century later by Marcelja.[88,89] With the Marcelja theory of hydration fits to solubilities with a universal parameter

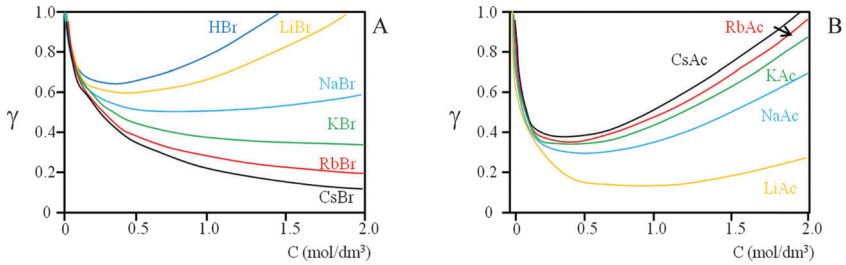

Fig. 2 Activity coefficients of alkali metals bromides (A) and acetates (B) as a function of concentration. The change of the anion results in a reversal of the cation series. Data from ref. 9.

'worked'. But it failed for few odd ions like silver and copper. So the theory had to be rejected.[90] The spectre of bulk water structure as the source of ion specificity loomed again!

2.4.2. Series reversal of activity coefficients. Let us emphasise the difficulties in predicting the behaviour of what in principle is a simple system (just salt in water!) with the following example. One of the most dramatic series reversal is that seen with the mean activity coefficients of alkali metal salts. They reverse with a change of anions.[9] At a given concentration, for bromide (or iodide) salts, the average activity coefficient decreases in the sequence: $Li^+ > Na^+ > K^+ > Rb^+ > Cs^+$ (Fig. 2).

Instead, if acetate or fluoride salts are considered, the activity coefficient decreases along an inverse series: $Cs^+ > Rb^+ > K^+ > Na^+ > Li^+$. These results imply that no consistent effective hard core interaction description between the ions is possible. We know that there are missing (quantum mechanical) dispersion forces between ions that are highly specific, and we do know that they also contribute specifically to hydration because of ion–water dispersion interactions. The specificity (in hydration) arises from differing ion sizes, static and dynamic (frequency dependent) ionic polarisabilities.

3. Insights from colloid and surfactant science

In colloid science generally, for a century or so, matters were assumed to be accommodated by using fitting parameters (inner and outer Helmholtz planes) that reflected ion size and hydration, specific (colloid) surface hydration, and forces due to overlapping hydration profiles of surface and ion. Again while the fitting parameters attempt to capture some of reality, there is even less predictability than for bulk electrolytes.

Matters were obscured (and still are) because most work in colloid science and in surfactant and polymer chemistry focuses on the easiest to use electrolytes like sodium chloride. That is, it ignores specific ion effects. Moreover, the idea that coions could adsorb at a surface of the same charge was seen as an absurdity. If electrostatic forces alone acted that would be so. But they are not the only forces as we shall see.

Extensive work in colloid and interface science has allowed the development of the new ideas, which will be explained in the next sections. We review some extensive research carried out since 1980s. They provide very different insights into our puzzles in bulk and protein systems. In particular, proteins, being macromolecules, are not colloids with smooth surfaces at a molecular level. They are not homogenous in charge, and are neither hydrophilic nor hydrophobic. We can draw more support for the modelling we are going to present in the next sections if we consider ion specificity in other systems in which ions interact with better defined surfaces. The highlight is on the behaviour of surfactant systems.

3.1. A paradox

Before we do so in detail, we discuss a paradox that shows quite starkly the dilemma faced by classical electrolyte solutions and the electrostatic double layer theory of forces between colloid particles. We consider two cases at first for illustration.

Consider direct force measurements between molecularly smooth surfaces of monolayers of an insoluble double chained cationic surfactant, dihexadecyldimethylammonium bromide.[91] These are either adsorbed or deposited on molecularly smooth mica and interact across an electrolyte solution. The quaternary ammonium head groups have two fixed water molecules of hydration. The forces between the surfaces fit to the classical Poisson–Boltzmann theory (DLVO) with and without an added electrolyte (KBr). To a very good approximation the measured forces fit theory with a (chemical) site binding model. It is assumed that 80% of the bromide counterion is actually bound. The same results emerge for osmotic force measurements on the corresponding lamellar phases. At very close distances hydration forces show up and are also measured.[91]

Next we consider micelles formed from the corresponding single chained surfactants hexadecyltrimethylammonium bromide.[92] The surfactant headgroup is essentially the same as those in the force measurements. The cmcs, aggregation numbers, and salt dependence can be measured and predicted by an electrostatic theory exactly equivalent to the Poisson–Boltzmann theory above including hydration forces. Counterion binding can be measured using NMR and comes out to be around 80% in apparent agreement with the force measurements. However, it can be shown that the phenomenological equation used to interpret NMR binding measurements is exactly equivalent to an electrostatic theory in which ion binding is connected to physisorption of the counterion.[93,94] There is no actual ion binding in the sense of a binding constant that has to be invoked to explain the force measurements. This theory

apparently agrees with experiment up to 130 °C.[92] So the force measurements ought to fit the Poisson–Boltzmann prediction but with no actual binding.

There is a paradox here that can only be resolved by admitting that we have to take into account the missing quantum dispersion forces which contribute directly and to hydration. These observations are reinforced if we consider the same situations but with acetate instead of the (strongly polarisable) bromide as the counterion.[91] Here the forces fit to Poisson–Boltzmann theory but with no binding of acetate ions. For the corresponding micelles too, there is no binding. (The NMR electrostatic ion binding model works only asymptotically in the limit of tight binding. Otherwise it is meaningless.[92–101])

These observations reflect quite dramatic differences. The forces between bilayers differ by more than an order of magnitude from one counterion (bromide) to another (acetate).[91] A careful study of such forces with Br^- *vs.* Cl^- as counterions shows that the forces cannot be explained without dispersion forces.[102] They are also extremely subtle. For the micelles of hexadecyltrimethylammonium surfactants, a change of counterion from bromide to the very similar chloride changes head group area so that one forms cylindrical micelles, the other spherical ones.[92]

3.2. The role of hydration

If we take the same systems and alter headgroup hydration *via* adsorption of alcohols[103] or by altering the headgroup, the forces again change dramatically.[104] In this case a change of headgroup from dimethyl-ammonium group to one with a methyl-hydroxyethyl-ammonium group changes the interbilayer forces with acetate counterion back to that observed with the dimethyl-ammonium headgroup and bromide. Clearly this is an effect of hydration. It implies obviously that binding of drugs to proteins, for example, can be highly dependent on a particular residue.

A great deal of work has been done on ion specificity of hydration forces between phospholipid bilayers. Most of the studies are associated with Parsegian and colleagues,[102] with very little on the effects of sugars that affect water structure. Similarly there is much available information on nonionic surfactants.[105] The inwardness of these data is that ions adsorb specifically at uncharged surfaces. Some other studies on ion specificity with micelles are those reported in ref. 96 and 106.

3.3. Specificity in microemulsions

Quite dramatic are effects of specificity on self-assembled vesicles, and ternary microemulsions formed from the cationic double chained surfactant didodecyldimethylammonium bromide (DDAB), oil (alkanes or alkenes) and water. The system is ideal in that it is very rich in phase behaviour.[98] The head group area is fixed, the interfacial forces due to headgroups on one side and oil adsorption on the other are fixed and the microstructure is determined by global packing alone.[97] The microstructure varies with a change of counterion Br^-, Cl^-, I^-.[107] The system is of biological interest because of the similarity of the dimethylammonium moiety and the terminal choline group of phosphatidyl choline.

Of more interest are microemulsions formed from the same surfactant, alkanes and water where the Br^- counterion is ion exchanged for SO_4^{2-}. Here instead of the usual reversed curvature structures (water-in-oil) that form with Br^-, the microemulsions have normal (oil-in-water) curvature.[108] This means that the divalent sulfate counterion is not adsorbed at a surfactant interface as strongly as Cl^-, Br^-, I^-. Remarkably, titration of only a very small amount of NaBr causes the microemulsion to reverse back to the Br^- only form. This is impossible if only electrostatic forces were operating, as the divalent sulfate ion would win out for the cationic interface against the univalent bromide.

At low water content, which can be as low as 1–2%, the microstructure of these systems is essentially connected cylinders of water in oil with the surfactant at the interface. Their diameters are typically as low as 10 Å. Water here is all 'hydration' water. The same is true for the force measurements above at small distances say 10 Å separation. And this certainly is a factor not understood.

A nice example is given in the work of Murgia *et al.*[14] If the microemulsions are formed successively with water containing low concentrations of NaBr, for that matter of all alkali metal bromide salts, nothing changes until the added salt reaches 10^{-3} M. At and beyond that point, the microemulsions collapse and phases separate. This is indeed remarkable. The counterion bromide is present at concentrations of at least 1 M. NMR measurements show the positively charged sodium ions adsorb onto the positively charged cationic dimethylammonium surfactant surfaces. Electrostatics can have no influence. Nor can the small amount of adsorbed sodium ions affect the curvature at the oil–water interface. At a certain point of sodium addition the adsorbed sodium is expelled from the connected cylinder microstructure to its junction nodes and collapses the structure.[15]

Especially notable is the fact that these cationic microemulsions do not form with buffers. At low water concentrations the water is all hydration water. Further the buffer anions adsorb at the surfactant headgroup as does sodium in the preceding example. This, the strange effects of buffers at very low concentrations compared to salt is a huge problem for classical theory.[10] It is as well known to biochemists as it is ignored by physical chemists.

3.4. Vesicles

The double chained cationic surfactants form lamellar phases in water with bromide counterions. With different counterions or salt addition they show Hofmeister effects, revealed by equilibrium spacing. Careful measurements show that it is impossible to account for the data using standard theories and dispersion forces have to be taken into account, and properly.[99]

An exhaustive analysis showed that was impossible to fit the data with classical theory (DLVO plus many parameters) so that again some extra forces were missing. At higher water content the lamellar phase swells to form univalent stable vesicles if the Br^- ion is exchanged with OH^-, AcO^-, NO_3^-, *etc.* The forces between lamellae change by orders of magnitude in agreement

with direct force measurements, and headgroup intra-surfactant interactions allow the required change in curvature.[109]

The same phenomenon occurs for anionic double chained surfactants.[110] The didodecylsulphosuccinates with sodium counterion form lamellar bilayer phases with only water of hydration. Upon ion exchange to lithium as counterions the surfactants swell to form stable vesicles. Addition of lithium salts in concentrations as high as 1 M does not affect their stability.

3.5. Hydrophobic interactions

A parenthetic consideration germane to this digression on ion specific forces is that of the role of interactions between hydrophobic surfaces. These are larger by an order of magnitude compared to the van der Waals forces expected from Lifshitz (Hamaker) theory.[6,111,112] The hydrophobic force is likely related to the effect of dissolved gas (see Section 4.3).[113] More recent work of Pashley[114] demonstrates convincingly that upon removal of atmospheric gas emulsions become stable. That is hydrophobic interactions are switched off upon removal of gas. In the model colloid system of Alfridsson *et al.*,[115] solid colloidal paraffin (hydrophobic) particles were functionalised with a long chained anionic surfactant. And the flocculation rates were studied as a function of the Hofmeister series, both in gassed and degassed states. The results bore no relation to the standard predicted rates of flocculation from DLVO theory. The Hofmeister series existed in both cases but was not recognisably related to the usual series, different again from gassed and degassed.

3.6. Summary of insights from colloid science and surfactants

Our attempts to come to grips with Hofmeister effects in Section 2 focussed on specificity in protein and bulk electrolyte solutions. In contrast, the results reviewed above focus on Hofmeister effects in, by and large, molecularly smooth homogenous particles or surfaces. Neither are good representations of Hofmeister's egg white proteins. These are certainly not smooth, or homogeneous. Nor are they made up of single ion pairs that act additively. Nevertheless, there are some common features among these systems. The specific interactions of counterions with surfactant (both charged and uncharged) headgroups affect their self-assembly properties through intra- and intermolecular forces. The first determine interfacial curvature, the second aggregation. A similar phenomenon occurs for charged and uncharged patches of proteins and for ion–ion interactions. We try to understand what is going on both at phenomenological and theoretical level in next sections. But first let us focus on some additional open problems, which are intimately connected to ion specificity.

4. Other open problems connected to ion specificity

The effects of buffers, of temperature and of dissolved gas are all, at this time, major fundamental challenges that are still open. We mention also some recent experiments on the electrochemistry of redox enzymes which might be important for applications[34] as well as experiments on the cloud points of phospholipids and lysozyme, which seem to provide new insights into the mechanisms of ion pumps.[30,116] We consider these effects that remain open problems as a memorandum for future research, and, more importantly, because the absence of their explanation flags a caveat on developments that we think represent progress.

4.1. Specific buffer effects

The list of salts used by Hofmeister also includes others that we term 'weak electrolytes'. They are indeed known to react with water by giving hydrolysis and so affecting pH,

$$A^- + H_2O \Leftrightarrow HA + OH^-$$

$$B^+ + H_2O \Leftrightarrow BOH + H^+$$

where A^- is the conjugate base of the weak acid HA and B^+ is the conjugate acid of the weak base BOH. This gives rise to an additional complication since there is an overlapping between two (ion and pH) effects. But this is not the main point. In fact, weak electrolytes are commonly used to set pH according to standard techniques.[117] The Henderson–Hasselbalch equation assigns buffer specificity to the pK_a of the undissociated weak electrolyte involved in the equilibrium.[118] One might reasonably think this should be a good approximation in chemical bulk systems. It has been shown that the addition of a strong electrolyte does affect the measured pH.[10] It follows a Hofmeister series. But somewhat startlingly, as already discussed above, the series reverses if the buffer changes from say phosphate to cacodylate at the same nominal pH. The series reverses again with the same buffer if in the background electrolyte sodium is replaced by potassium. The classical theory of buffers and pH is then missing something.[117,119] The assumptions that underlie our intuition have dramatic impact in biochemical systems[120,121] and most simply in the presence of a protein–enzyme,[122] or, *e.g.*, in the presence of colloidal limestone in barrier reefs. The evidence is that different buffers at the same (nominal) pH have a dramatic effect in influencing enzyme activities.[23,28] A further consequence is that the standard values of pK_as have to be questioned since they are arrived at by using the same classical theory.

Very recently, we performed a simple experiment which demonstrates explicitly the specific effects of buffers.[122] A solution of lysozyme was prepared at pH 7.15 by means of 5 different commonly used biological buffers, namely, TrisHCl, phosphate, carbonate, cacodylate, and citrate. The electrophoretic mobility of the lysozyme solution was measured through electrophoretic light scattering. The mobility depends on the effective charge Z carried by the protein. This can be calculated in a standard manner through:

$$Z = \sum_{i=\text{bases}} \frac{N_i}{1 + 10^{-pK_{ai}+pH_s}} - \sum_{j=\text{acids}} \frac{N_j}{1 + 10^{pK_{aj}-pH_s}} \qquad (6)$$

where N_i and N_j are the number of basic and acidic amino acid residues having the dissociation constants pK_{ai} and pK_{aj}

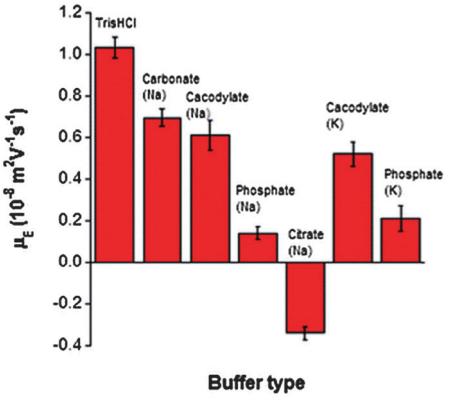

Fig. 3 Specific buffer (10 mM, pH 7.15) effects on lysozyme electrophoretic mobility. Reproduced from ref. 122.

respectively. The pH_s is the negative logarithm of the hydrogen ion activity at the protein surface, and can be calculated from:

$$10^{-pH_s} = 10^{-pH_s} e^{-\frac{\pm ze\psi(r)}{kT}} \quad (7)$$

where e is the elementary charge, $\psi(r)$ is the surface electrostatic potential, k is the Boltzmann constant and T the absolute temperature. This modelling requires that the effective charge, Z, and hence the electrophoretic mobility, depends on pH of the buffer used to fix it. The results in Fig. 3 show that this is not the case.

In fact, at fixed pH (7.15) mobility decreases along the series Tris/$TrisH^+$ > carbonic acid/hydrogen carbonate ~ cacodylic acid/cacodylate > dihydrogen phosphate/hydrogen phosphate > hydrogen citrate/citrate. It is particularly significant that the sign of mobility is reversed when citrate buffer is used. This means that the net charge has become negative although it should be positive (lysozyme isoelectric point ~11). This might drastically influence interactions in biological systems. Moreover, if salts are added the commonly observed ion specificity is observed.[122] But the type of buffer has a strong influence on the measured electrophoretic mobility and plays a fundamental role on affecting ion specific effects. Indeed, ion specific effects seem to be superimposed on a more important buffer specific effect.

A possible explanation is that, as well as strong electrolytes, weak electrolytes (buffers) specifically interact with the protein–enzyme surface. The measured mobility is the outcome of the (ion specific) simultaneous equilibria established by the buffer species in the bulk and at the protein surface. A similar reasoning holds for the measurement of pH in such systems with the additional complication that specific adsorption at the glass electrode surface contribute to the final outcome of the electrochemical potential that we call pH.[10,123]

The inference is that the buffer moiety, even at very dilute concentrations compared with background salt, can have a much stronger ion binding capacity than the counterion (or coion) for a surface.

4.2. The effects of temperature

Temperature has a drastic effect in biological systems. The human body has an optimal temperature of 37 °C (normothermia). Temperatures in the range 38–41 °C are associated with infectious diseases, and for T > 42 °C death can result. Proteins–enzymes can lose their functions and often denature due to an increase of temperature. This is due to the modification of secondary/ternary/quaternary structure of proteins caused by heat. These effects are widely acknowledged and undisputed.

But at a simpler level temperature also affects electrolyte solutions and related precipitation equilibria. This was first observed by Berthollet[124] in 1798 when he was part of the scientific team accompanying Napoleon's expedition that invaded Egypt. Visiting the 'El Natron' Lakes in the Nile flood plane west of Cairo, he observed sodium carbonate deposits on the surrounding limestone (calcium carbonate) hills.[125] This unexpected finding was explained as due to a reverse precipitation reaction between NaCl and $CaCO_3$. Berthollet related this counterintuitive reaction to the high temperatures reached during summer in that area. This was possibly the first observation of the effect of temperature on chemical equilibria. Such observations really led to the development of physical chemistry and remain unexplained.

Increased temperature, salts, and solutes like different isomers of sugars all affect nucleation and precipitation of particles from solution, their size, polydispersity and shape, a veritable gallimaufry of supra Hofmeister behaviours that await systematic exploitation. This, *terra incognita*, is presumably how biology is able to manufacture magnetic nanoparticles for navigation in the brains of fish and birds, and how in lactose rich early mammalian mothers milk, nanoparticles of calcium phosphate form.

The only thing that is clear is that whatever water structure and hydration means, it changes with temperature and solutes. By 90 °C water has lost any hydrogen bonding and behaves exactly like hydrazine N_2H_4 in all its thermodynamic parameters. Similarly for low temperatures.[126] Specific ion effects at high temperatures can have nothing to do with water structure.

4.3. The effects of dissolved gas

No theory or simulation experiments take account of effects of dissolved gas, which water in the real world of biology contains. This complicates matters more. Atmospheric dissolved gas, essential for the existence of most life (*i.e.* oxygen), plays a key role in affecting interactions.[13,113–115] This is known, but its consequences are unknown. The effects on interaction forces and on water structure are large.[6,127]

Gas solubility changes with salt concentration and is also ion specific.[128] Moreover, extensive studies of Craig *et al.*[129] have been made on salt dependence and specificity of bubble coalescence. Some empirical rules to take into account the phenomenon have been proposed.[13] But the reason for the occurrence of the phenomena is still not understood. It probably depends on dissolved gas that affects water structure. That is suggested by numerous studies of gas dependence of hydrophobic interactions.[127,130,131]

4.4. Ion specificity in bioelectrochemistry

Very recently a new door has been opened onto an already unexplored field of Hofmeister phenomena. Electrochemical

studies of redox proteins and enzymes require the use of salts as supporting electrolytes. The choice of the salt relies on the assumption that the electrolyte used does not affect the electrochemical properties of the proteins and enzymes under investigation. Recently Magner and coworkers[34] found that the electrochemical properties of the redox protein cytochrome *c* at a 4,4′-bipyridyl modified gold electrode are ion specific. Both the redox potential ($E^{o\prime}$) and the Faradaic current are influenced by the nature of the electrolyte used according to a Hofmeister series (Fig. 4). It is very likely that the nature of the ion may affect the kinetics of the redox process, although this last phenomenon has not been explored yet. But the importance of these studies is from an applications point of view. Indeed, it is very likely that the response observed with the model redox protein cytochrome *c*,[34] is in fact general for other redox proteins and enzymes. This may ultimately be displayed as changes in sensitivity or response for such enzymes when utilized in applications such as biosensors and biofuel cells.

4.5. New inputs into the mechanism of ion pumps

The physiological salt concentration is about 150 mM. At such a concentration electrostatics and electrostatic forces lose their dominance. The Debye screening length is lower than 1 nm so that biology belongs to the domain of ion specificity. There is a constant movement of ions carrying the same valence inside and outside cells. For human erythrocytes (red blood cells), transmembrane enzymes (*e.g.* Na^+,K^+-ATPase) are acknowledged to act as 'ion pumps' catalysing the transfer of ions across the membrane.[132] The reaction steps involve cycling between two different enzyme conformations in which either Na^+ or K^+ are selectively bound on one side of the plasma membrane or the other. Na^+,K^+-ATPase transports three Na^+ ions out of the cell for every two K^+ carried in, hydrolysing one ATP molecule in each turn of the reaction cycle.[133] This mechanism in turn maintains an electrochemical gradient that drives the otherwise energetically unfavourable secondary active transport of L-amino acids *via* integral membrane proteins (*e.g.* Na^+-symporters) and contributes to the regulation of cell volume.[133] Nevertheless, as recognized by Skou (the discoverer of ion pumps) in his Nobel lecture, the proposed model is just a '*working hypothesis which explains a good deal of the experimental observations*'.[134] There are still unanswered questions at the molecular level, that is: (i) where are the binding sites for the cations, (ii) what is their nature, (iii) how does the system discriminate between Na^+ and K^+?[134]

A contribution to these questions on the mechanism of ion pumps and more generally, can come from the specific ion partitioning that occurs between two phases in equilibrium at a finite volume. In red cells a concentrated phase of haemoglobin is separated from a finite volume of overall physiological salt solution by a cell membrane. Haemoglobin molecules are tightly packed and express a high surface area available for specific ion adsorption.

We remark on some recent studies of Lo Nostro and coworkers[30,116,135] to illustrate this mechanism. An aqueous dispersion of dioctanoyl-phosphatidylcholine (diC_8PC) phase separates upon cooling. Upon phase separation, two phases coexist. The upper phase consists of a diluted micellar solution of the lipid, while the bottom phase is a gel-like highly viscous phase and contains very large entangled wormlike aggregates. The addition of different sodium salts results in a consistent shift of the coexistence curve and in a variation of its skewness (Fig. 5).

These changes follow a Hofmeister series and are particularly relevant in the presence of chaotropic anions. The concentrations of the anions in the two coexisting phases show that Br^- and NO_3^- accumulate in the lipid rich bottom phase, resulting in an asymmetric partition between the two coexisting phases, while F^- ions distributes almost evenly. Specific ion binding to micelle surfaces in the two-phase system provides a reasonable mechanism for the observed asymmetric ion partitioning. Similarly, an aqueous dispersion of lysozyme and SDS phase separates below the cloud point.[30] Anions partition asymmetrically between the two phases and cloud point temperatures change according to a reversed Hofmeister series. In a system of finite volume, a concentrated dispersion of a protein acts as an ion 'sponge'. The difference in ion concentration between the concentrated and dilute dispersion is maintained without the need for an ion pump.

If a similar mechanism is at work to maintain a fixed Na^+/K^+ concentration ratio between inside and outside the cell, this can either assist or counteract the action of Na^+,K^+-ATPase. That is, specific ion binding can be part of the whole

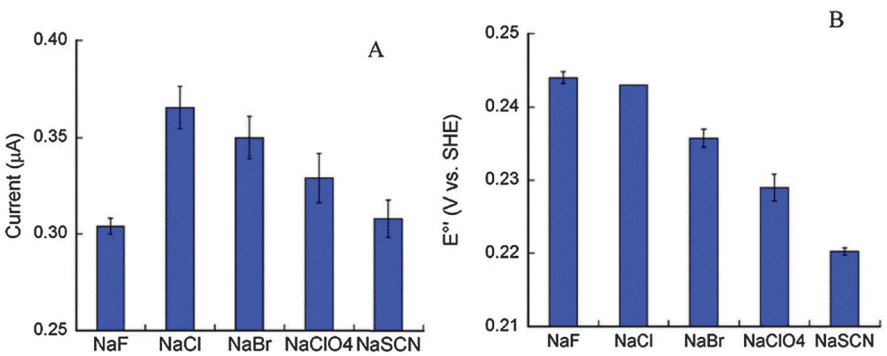

Fig. 4 Ion specificity in bioelectrochemistry. (A) Plot of peak current of cytochrome *c* at 298 K in the presence of a range of anions (200 mM). (B) Redox potential, $E^{o\prime}$, of cytchrome *c* for a range of anions at 298 K (200 mM). Reproduced from ref. 34 with permission from the PCCP Owner Societies.

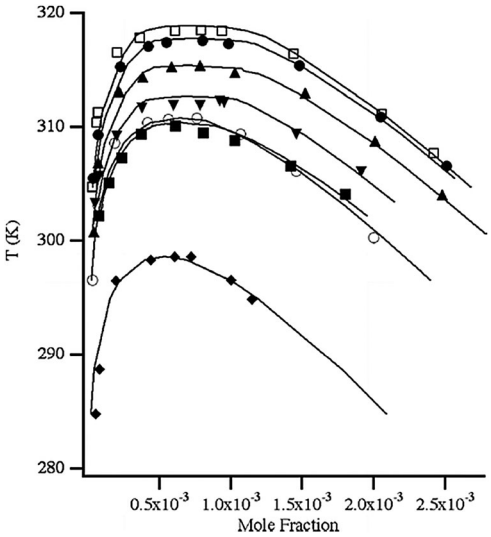

Fig. 5 Coexistence curves for dioctanoylphosphatidylcholine–H_2O dispersions in the presence of different 0.05 M sodium salts: fluoride (□), acetate (●), chloride (▲), bromide (▼), nitrate (■), azide (○) and iodide (◆). Reprinted with permission from ref. 116. Copyright (2007) American Chemical Society.

mechanism of 'ion pumps'. The source and the mechanisms behind this specific ion binding are the subject of the next sections.

5. Recent approaches to Hofmeister phenomena. Ion–ion and ion–surface interactions

The sections above dealt with insights gleaned from solution chemistry, colloid science and protein chemistry and the difficulties which we still have to take on with ion specificity. But whatever the ion specific phenomenon being investigated (electrolyte activities, colloid phase transition, protein aggregation, enzyme activities, *etc.*), it is necessary to disentangle specific ion–ion and ion–surface interactions first. In other words, we need to understand which laws, or at least empirical rules, we can invoke to put order into what will remain otherwise an incomprehensible mess. The two most popular approaches which aim to solve the puzzle will be reviewed in the next paragraphs. We will discuss both their strength and weak points and finally how they could be reconciled.

5.1. The law of matching water affinities

A very useful rule, the *law of matching water affinities* (LMWA) was formulated by Collins.[44] It brought a systematic framework to ion–ion and ion-charged site interactions that had previously been absent. The starting point of this LMWA is the old classification of ions as either kosmotropes or chaotropes depending on the sign of Jones–Dole viscosity *B* coefficient.[44,69,136,137] This classification is still used. But the meaning of the words 'kosmotrope' and 'chaotrope' is no longer taken as related to 'long range water structure'. Rather it is understood as a characterisation of the 'degree of hydration'. Loosely speaking this is high for kosmotropes and low for chaotropic ions. Then, it is recognised that ions of opposite charge tend to associate to form ion pairs.[138]

Collins deduced his rules of cation–anion pairing (LMWA) by the observation of the 'volcano plot' (Fig. 6(A)).[139] The 'volcano plot' correlates the standard heat of solution of a crystalline salt at infinite dilution with the difference between the absolute heats of hydration of the corresponding individual gaseous anion and cation.

The LMWA asserts that: '*Cations and anions form stable ion pairs if their respective hydration enthalpies* (considered to be a measure of 'water affinities') *match*'. That is, the lower the difference between the hydration enthalpies of the anion and of the cation then, the higher is the tendency of the ions to form a contact ion pair.

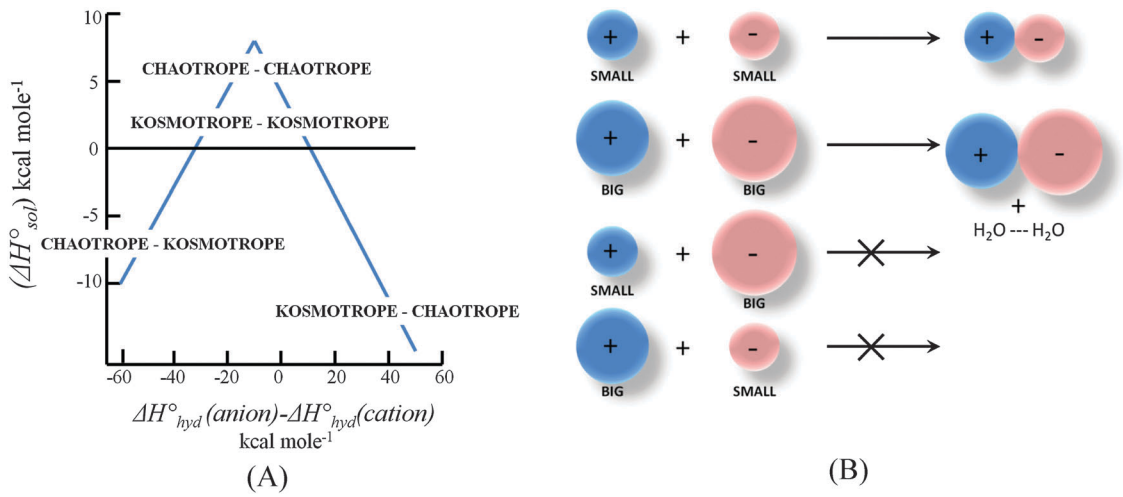

Fig. 6 The Law of Matching water affinities (LMWA). (A) Volcano plot. Adapted with permission from ref. 69. Copyright (2004) Elsevier. (B) Schematics of LMWA: a kosmotropic (chaotropic) cation would form a contact ion pair with a kosmotropic (chaotropic) anion, whereas a kosmotropic (chaotropic) cation would not form a contact ion pair with a chaotropic (kosmotropic) anion. Adapted with permission from ref. 69. Copyright (2004) Elsevier.

This will be less probable if the difference between the hydration enthalpies is large. In simple terms, a kosmotropic (small) cation likes kosmotropic a (small) anion and a chaotropic (big) cation likes a chaotropic (big) anion.[44] Collins' rule, schematised in Fig. 6(B), is successful in putting order into a series of phenomenon as shown in the next paragraphs.

5.2. The reversal of activity coefficients of alkali metal salts accommodated *via* LMWA

A strong reinforcement for the validity of the LMWA was given by Kunz.[38] He proposed a qualitative explanation for the affinity of charged surfactant head groups for different counterions (see next paragraph) and why the specific order of the mean activity coefficients of alkali metal salts reverses by changing the anion (*e.g.* bromide with acetate). At a fixed high concentration, say 0.5 M, when electrostatic interactions are screened, a lower activity coefficient is a sign of a stronger anion–cation interaction (in Collins' language a contact ion pair is formed). For the kosmotropic acetate (B = 0.236), the mean activity coefficient decreases in the sequence $Cs^+ > Rb^+ > K^+ > Na^+ > Li^+$ (see Fig. 2 above). This means a stronger interaction of acetate with the kosmotropic Li^+ (B = 0.147), rather than with the chaotropic Cs^+ (B = −0.045), according to LMWA. Instead, if the salts of the chaotropic Br^- (B = −0.032) are considered, the average activity coefficients decrease along an inverse series $Li^+ > Na^+ > K^+ > Rb^+ > Cs^+$. Again, in agreement with LMWA, it is the chaotropic Cs^+ which interacts more strongly with the Br^-.

5.3. Counterion binding to surfactant head groups

We have shown above (Section 3) that the self-assembly of surfactants is strongly affected by ion specificity. Many possible explanations for the observed phenomenon were given. Recently, Kunz and coworkers investigated the micelle-to-vesicle transition of a catanionic surfactant system induced by specific cation effect.[140,141] The series reverses if dodecylsulfate is used instead of dodecylcarboxylate. On the basis of these results and of molecular dynamics simulations, Kunz, Jungwirth and coworkers[142] tried to apply LMWA to rationalise counterion binding to surfactant headgroups. In order to do that they first classified anionic surfactant headgroups as chaotropic (soft) or kosmotropic (hard). According to this classification the chaotropicity (softness) of surfactant charged headgroups increases along the series: carboxylate < phosphate < sulfate < sulfonate (Fig. 7).

Hence, for carboxylate surfactants the tendency to form ion pairs would decrease along the series $Li^+ > Na^+ > K^+ > Rb^+ > Cs^+$. A reversed cation series would be expected for sulfonate surfactants. The same concept can be used to understand and predict the binding of ions to cationic surfactant headgroups and to protein charged groups. Let us focus on this last issue.

5.4. Counterion binding to protein surface charged groups

Proteins are zwitterionic macromolecules, that is, their surfaces carry both acidic and basic amino acids residues. These become charged by exchanging protons with water. Collins has classified the charged residues as kosmotropic or chaotropic on the basis

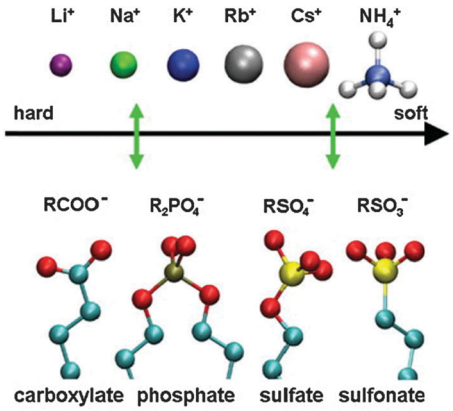

Fig. 7 Ordering of anionic surfactant headgroups and the respective counterions regarding their capabilities to form close pairs. The green arrows mean strong interactions (close ion pairs). Reproduced with permission from ref. 140. Copyright (2008) Elsevier.

of their chemical similarity with kosmotropic or chaotropic ions.[44] That is, the positively charged groups (due to Lys, His, Arg residues) are classified as chaotropic since they are similar to NH_4^+ (B = −0.007). The negatively charged groups (due to Asp and Glu residues) are classified as kosmotropic due to their similarity with CH_3COO^- (B = 0.236).

On the basis of these assumptions, and by applying LMWA (*cf.* Section 5.1), the order of anion binding to positively charged surface group would be: $SCN^- > I^- > NO_3^- > Br^- > Cl^-$ and, that of cation binding to negatively charged groups would be $Li^+ > Na^+ > K^+ > Rb^+ > Cs^+$.

Support for this prediction has been given by Cremer and coworkers.[143] For example, they determined the change of cloud point temperatures of a negatively charged polypeptide in the presence of different chloride salts. The cation specific cloud point temperature, T, as a function of concentration, $[M]$, was fitted with the following equation:

$$T = T_0 + c[M] + \frac{B_{max}[M]e^{-b[M]^2}}{K_d + [M]e^{-b[M]^2}} \quad (8)$$

where T_0 is the phase transition temperature of the polypeptide at $[M]$ = 0, B_{max} is the maximum decrease in the cloud point temperature when all the negative sites are paired with cations, the constant b is related to the strength of electrostatic (and we also argue dispersion) interactions between the charged group and the cations, and K_d is the apparent dissociation constant for the specific interaction of the cations to the negative surface sites.

The lower the value of K_d the stronger the binding affinity should be. The estimated dissociation constants, K_d, of cations with the negative carboxylate groups of their model anionic polypeptide was correlated with the difference in the hydration enthalpies ($\Delta H_{hyd(Acetate\text{-}Cation)}$) of acetate and that of different monovalent cations (Fig. 8). They found an acceptable correlation for monovalent cations (but no correlation for divalents).

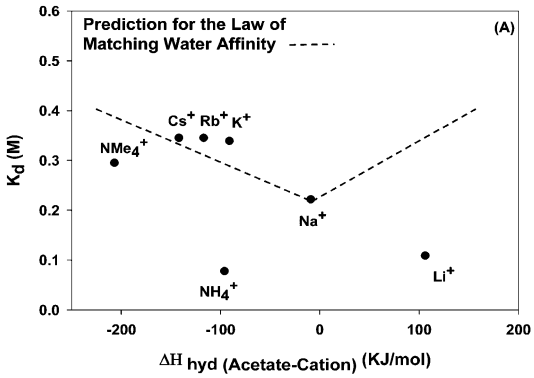

Fig. 8 Correlation of observed dissociation constant (K_d) values for the cations with the hydration enthalpy difference between the acetate ion and the cationic species for monovalent metal chlorides. Reprinted with permission from ref. 143. Copyright (2012) American Chemical Society.

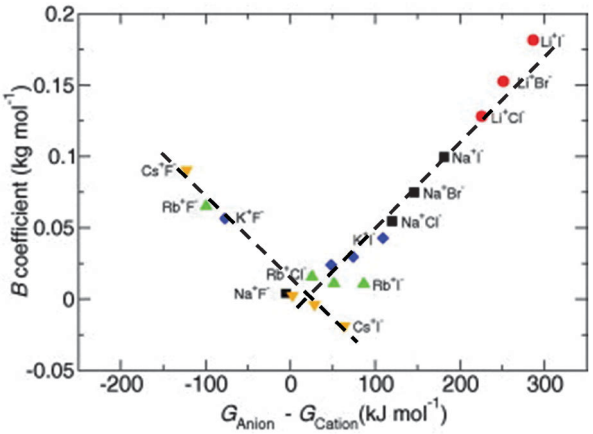

Fig. 9 The 'inverted volcano plot' proposed by Duignan *et al.*[55] It reports Bromley's experimentally determined *B* coefficients[144] as a function of the difference in anion and cation solvation energies. *B* empirically represents the ion–ion interactions that determine activity coefficients. Copyright (2014) Elsevier.

5.5. Limitations of the LMWA

It has to be remarked that LMWA is not a 'theory' but rather an empirical rule based on phenomenological observations. Its development comes from a correlation of thermodynamic properties of salts and single ions at infinite dilution. Recently, some criticism to this correlation has been raised.[5] In fact it is difficult to understand why properties of single ions at infinite dilution have anything to do with ion–ion or ion–protein interactions. Nevertheless, it should be recognised that LMWA can be also inferred from the viscosity *B* coefficients at finite concentrations or, as very recently proposed by Duignan *et al.*,[55] by Bromley's *B* coefficients. Indeed, Kunz[38] has argued that the electrolyte properties that most clearly exhibit the law of matching water affinity are the activity coefficients because they give a measure of the strength of the ion–ion interactions. Bromley[144] estimated the activity coefficients, up to reasonably high concentrations and with good accuracy, using only one experimental parameter *B*. A low *B* value means a small activity coefficient and, hence, a more attractive ion–ion interaction. Fig. 9 shows a plot of Bromley *B* coefficient against the difference in cation and anion solvation energies.[55] The figure looks like an 'inverted volcano plot' and has a clear physical interpretation.

Another limitation of the LMWA comes from its application to the case of ion–protein interactions which do not involve only charged amino acid residues. Experiments carried out at Cremer's lab showed that ions can also bind to uncharged amide groups of polypeptides and proteins.[145–148] Moreover, simulations carried out by Lund *et al.*[149] showed the importance of specific ion interactions with nonpolar surface patches of proteins (see Section 7).

6. Ion quantum (dispersion) interactions

The LMWA is an inference from thermodynamic observations. Its justification ultimately has to rely on a proper statistical mechanical molecular theory of electrolyte solutions. Such a justification has to explain specific interactions of ions and also has to predict hydration and hydration shell interactions. That is in fact available to us and this is a more detailed approach we now explore. This approach to ion specificity recognises that the classical electrostatic (plus hydration) theories omit any explicit account of quantum mechanical interactions between ions and quantum contributions to self-energies. These are indeed ion specific.[46] The inclusion of these additional interactions presents some difficulties which need to be explained.

6.1. Difficulties in including quantum interactions

6.1.1. The first difficulty. The inclusion of quantum interactions might be considered implicit, but is certainly unquantified, in classical theories. It is implicit in notions like adjustable ion size, hydration and hydration shell interactions (Gurney potentials). In the double layer theory, they are implicitly included in core notions like inner and outer Helmholtz planes and dielectric constants. A difficulty is that different parameters – even for the same ion pair electrolyte – apply to each experiment or situation. The parameters are ion specific – including those that ought to be constant. Ionic radii that fit activities *e.g.*, are sometimes required to be less than crystallographic radii.[84] The parameterisation requires multiple fitting parameters, and the theory then loses predictability.

In colloid science quantum interactions are also explicit in the DLVO theory of stability that includes attractive dispersion forces to oppose electrostatic (double layer) forces but only partially, and in fact erroneously. The quantum mechanical attractive forces include all many body forces *via* Lifshitz theory, which relies (in principle) on all measured frequency fluctuations in the dielectric susceptibilities.[6,150,151] But it ignores hydration at interfaces. It treats a liquid across which two particles interact as a bulk liquid. This is only half the problem with developing a consistent theory. (This is not quite such a difficulty as it appears. A theorem of statistical mechanics shows that in order to get free energies to the

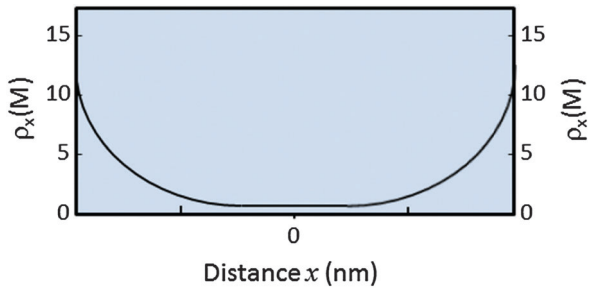

Fig. 10 The Poisson Boltzmann distribution of counterions from two charged surfaces. Counterion concentration at a distance x (ρ_x) from the charged surface decreases exponentially according to: $\rho_x = \rho_0 e^{-ze\psi_x/kT}$. Here ρ_0 is the counterion concentration in the bulk, z is the valence, e is the elemental charge, ψ_x is the electrostatic potential, k the Boltzmann constant and T the absolute temperature. DLVO theory is inconsistent since it treats ion–surface electrostatic interactions as varying exponentially and van der Waals quantum forces (Lifshitz theory) as varying linearly.

second order one needs the profile of order at an interface hydration only to zeroth order).[152]

6.1.2. The second difficulty. It can be proved[46] that even if dispersion forces are dealt with accurately, the assumption of additivity of electrostatic forces and dispersion forces is not just incorrect, but badly so. This is so even if water is treated as a continuum solvent. The additivity ansatz occurs in all theories of electrolytes. For electrolyte solutions the dispersion forces are either ignored or subsumed in additive hydration parameters. In colloid science (DLVO theory) electrostatic double layer forces are treated in non-linear theory (Fig. 10), the quantum forces in a linear theory (Lifshitz theory). This violates some fundamental laws of physics.[46]

In a consistent theory the dispersion (and hard core and other) forces have to be treated at the same nonlinear level as will be explained in the next paragraph.

It can also be shown that the additivity approximation ignores ion specificity. The same remarks hold for bulk electrolytes, activities and all other properties. They hold whether or not the solvent for an electrolyte is treated in a continuum approximation, (primitive model), or if it is treated at a molecular level (civilised model).[6]

6.2. Inclusion of quantum interactions: formalism

There are two ways in which this can be done. The first is the high road *via* statistical mechanics. Electrostatic and dispersion forces between ions are incorporated into the partition function for the electrolyte solution from the beginning.[153,154] A program to incorporate these dispersion forces, missing from classical electrolyte theory has been embarked upon by Kjellander in an elegant series of recent papers.[155–157] But this high road is very complex even though some useful asymptotic results can be extracted. For example when ionic dispersion forces are included, the pair distribution function in an electrolyte decays as a power law, not with an exponentially screened Debye length decay. It rapidly becomes so complex that the insight tends to be obscured, and practically, computation of thermodynamic properties becomes very difficult.

A second approach cuts through those difficulties using a bootstrapping procedure. We illustrate for the example of colloid particle interacting across an electrolyte. Bear in mind that the dispersion forces need to be treated consistently with those due to electrostatics. Then this can be done by including in the mean field Poisson–Boltzmann equation an additional (mean field) term, $U_x^{\text{dispersion}}$, which is added to the conventional electrostatic potential ($ze\psi_x$),

$$\rho_x = \rho_0 e^{-\left(ze\psi_x + U_x^{\text{dispersion}}\right)/kT} \tag{9}$$

The approximations required and formal derivation from statistical mechanics are done in ref. 52, 53 and 158.

Electrostatic interactions alone cannot explain ion specific results. This is not *a priori* obvious. When ionic charge and the concentration are the same for all 1 : 1 electrolyte ions, ionic radii and consequent hydration will be different. But as remarked above the difficulty is that radii are fitting parameters and vary with the experimental situation. And worse, sometimes these fitted radii are less than bare ion radii.

We are forced to include the missing dispersion forces. In fact, at any substrate/water interface, ions experience, besides an image charge interaction, a quantum mechanical fluctuation (dispersion potential) given by Lifshitz theory. The image charges effects are included in the formalism and cannot be separated out. The potential includes image forces and many body dipole–dipole, dipole–induced-dipole and induced-dipole–induced-dipole forces. This potential $U_{\pm}(x)$ is given schematically as

$$U_{\pm}(x) = \frac{1}{x^3}\int_0^{\infty} \frac{\alpha(i\omega)}{\varepsilon_w(i\omega)}\left(\frac{\varepsilon_w(i\omega) - \varepsilon_s(i\omega)}{\varepsilon_w(i\omega) + \varepsilon_s(i\omega)}\right) d\omega \tag{10}$$

where $\alpha_{\pm}(i\omega)$ is the excess polarisability of the ions as a function of frequency, x is the distance between the ion and the interface, and $\varepsilon_w(i\omega)$ and $\varepsilon_s(i\omega)$ are the dielectric functions of water and of the substrate. In general, the integral is a sum over frequencies and includes temperature explicitly. These forces that drive ionic adsorption appear to be a major player in several Hofmeister phenomena and depend strictly on the nature of the participating entities. The potential can be positive or negative depending on frequency-dependent dielectric susceptibilities of the substrate.

Physically, in this modification of the standard treatment of electrostatic interactions, besides an electrostatic interaction with its neighbours and with a surface, any ion will also experience, an additional dispersion potential. This can either enhance or diminish electrostatic interactions in ways that are specific and counterintuitive as illustrated in Fig. 11.

For example, in this extension of classical Born, Debye–Hückel, DLVO, Onsager–Samaras theories, ions with charge of the same sign can attract, coions can adsorb at surfaces of the same charge.

6.3. Inclusion of quantum interactions: implementation

The first attempts to apply this theory to some specific examples estimated the dispersion potential, $U_x^{\text{dispersion}}$, from the static

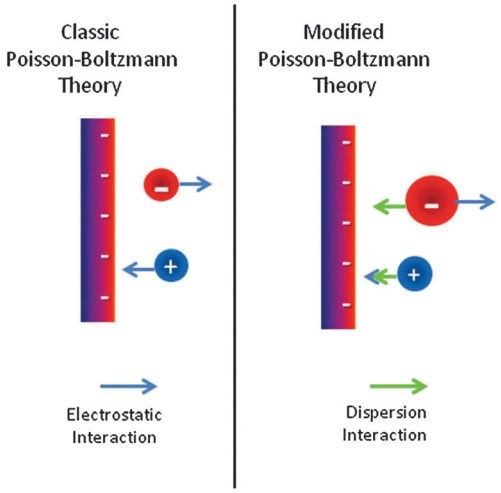

Fig. 11 Schematic representation of the classic Poisson–Boltzmann theory and its modification that includes ion dispersion forces.

polarisability of the ions and a single adsorption frequency ω estimated from ionisation potentials and electron affinities of ions. The dispersion potential at a distance x from an interface is approximately,

$$U_x^{\text{dispersion}} = \frac{B}{x^3} \tag{11}$$

Where the dispersion coefficient, B, is roughly

$$B = \frac{\alpha^*(0)h\omega}{16\pi}(n_w^2 - n_s^2) \tag{12}$$

where, n_w and n_s represent the refractive index for water and the substrate (the dispersion potential changes sign according to whether the refractive index of the substrate is larger or smaller than that of water), $h\omega/2\pi$ is the ionisation potential of the ion, $\alpha^*(0)$ is the static excess polarisability (that is the difference in polarisability of an ion compared to an equivalent volume of water). In general, the higher the polarisability (Table 1) the higher the dispersion force the ion would experience when interacting with another ion or with an interface. With this approach ion specificity emerged naturally thanks to an ion specific molecular parameter. But this modelling considered all ions having the same unknown radii and moreover ion hydration was neglected.[45] This is plainly far too crude and over-simplified. Since *cf.* eqn (11) and (12) polarisability scales as radius cubed, any crudity here is subsumed in the unknown polarisability and does not affect the proof of concept. But something came out right, and at least confirmed the necessity for the explicit inclusion of dispersion forces.[45] But it led to the idea that there was a conflict with Collins' rules. As the situation has been outlined so far, there is indeed a conflict.

One approach considers interactions correctly including quantum forces, but only in a continuum solvent approximation. The other (Collins) does the job through embracing empirical hydration effects. The resolution is to include hydration in *ab initio* calculations of polarisabilities and size.

Later developments did the job correctly. The frequency dependent dynamic polarisabilities were calculated by Parsons *et al.*[41,159] from *ab initio* quantum mechanics (QM), as ion size and hydration were equally necessary to quantify ion specificity. The dispersion potential was then calculated according to,

$$U_x^{\text{dispersion}} = \frac{B}{x^3} f(x) \tag{13}$$

where $f(x)$ is a form factor which accounts for the finite size of the ion (including hydration), and the B dispersion coefficient was now calculated by,[160]

$$B = \frac{kT}{2}\sum_n \frac{\alpha^*(i\omega_n)}{\varepsilon_w(i\omega_n)}\left[\frac{\varepsilon_w(i\omega) - \varepsilon_s(i\omega)}{\varepsilon_w(i\omega) + \varepsilon_s(i\omega)}\right] \tag{14}$$

where $\omega_n = 2\pi kTn/\hbar$ and k and T are the Boltzmann constant and the temperature. $\varepsilon_w(i\omega)$ and $\varepsilon_s(i\omega)$ are the dielectric functions of water and the substrate, respectively. $\alpha^*(i\omega)$ is the excess dynamic polarisability of the ion. The magnitudes, and even the signs, of the dispersion potentials near the two interfaces depend in a sensitive way on these frequency-dependent entities. It is important to note that by bringing to bear *ab initio* QM, ion size is no longer a parameter. It is the same for electrostatics and quantum forces for the first time. It is not an adjustable parameter. The QM interaction is not a parameter either. It should be explained that ion size and ion polarisability have contrasting effects. Polarisability generally increases with size, hence strengthening the dispersion interaction while, at the same time, the increased size diminishes the interaction. In addition, hydration water molecules change the effective size of the ion. The final outcome is a subtle balance between all these effects which become much more complicated for some non-spherical ions (*e.g.* NO_3^-, SCN^-) due to the anisotropy of polarisability. The testing of these developments has been and is being accomplished successfully now in a series of papers on electrolyte properties.[20,52,53,161–163]

6.4. Recent developments: free energy of ionic hydration

The ion dispersion forces theory is currently being applied to explain a series of phenomena in different systems.[164,165] For example, very recently it has been shown how the solvation energy of some ions can be predicted with a good level of agreement with the experimental data even in the approximation of the continuum solvent model (Fig. 12). Solvation energies measure the change in free energy of a solute in a vacuum compared to that of the solute immersed in water.[53]

This needs to consider, besides the conventional electrostatic energy (Born energy), also the energy required to create a cavity to accommodate the ion, as well as the dispersion energy.[52,53] The reason why the Born model gives in general a good estimation of solvation energies is because the cavity and the dispersion contributions cancel in most – but not all – cases. Nevertheless, the inclusion of the dispersion term is fundamental to get a very good agreement with the experimental values.[53] This is at the basis for anticipated developments like the calculations of osmotic and activity coefficients, as well as of surface tensions of electrolyte solutions.

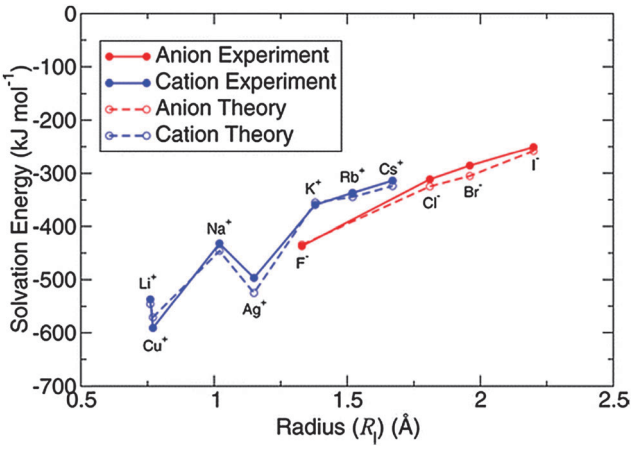

Fig. 12 Calculated solvation energies compared with experiment for some ions. Reprinted with permission from ref. 53. Copyright (2013) American Chemical Society.

7. Towards reconciliation between the two approaches

7.1. What went wrong?

Although progress in the theory includes quantum dispersion force correctly and explicitly, the reconciliation and equivalence with the LMWA has not been recognised.

LMWA considers the interaction of ions with other ions and with discrete surface charged sites of opposite charge. The first approach is successful in qualitatively ordering electrolyte behavior, like for the series reversal observed for the activity coefficients of alkali metals salts, and for counter-ion binding to surfactant charged headgroups.[38] (There is a difference between an empirical characterisation and a testable theory). In contrast to the case of ions interacting with (both colloidal and protein) surfaces the modelling so far that includes ionic dispersion forces has assumed that interacting surfaces carry a uniformly smeared charge.[162] But even with such simple modelling, Boström *et al.*[45] provided an elegant explanation of anion Hofmeister series reversal by changing pH (below and above the isoelectric point). The same approach has been used in giving some possible explanations of series reversal observed with changing salt concentration for lysozyme systems,[162] the shift in isoelectric point of BSA,[161] or the surface charge of mesoporous silica.[20] But it does not explicitly explain the specificity of ion pairing for surface sites as LMWA does. This may lead to the prediction of discordant cation binding sequences to anionic sites of proteins[143,166] or surfactant headgroups.[142] The necessity of a modelling improvement will be better explained by means of a practical example. We now consider a recent work where specific ion binding is invoked to explain protein aggregation.[77]

7.2. Protein aggregation explained by specific ion binding

In the previous paragraphs we have explained two apparently opposing approaches to deal with ion specificity. We focused our attention on specific ion–ion and ion–surface interactions. We now show how such kind of interactions may affect macroscopic phenomena as protein aggregation. We take as an example a recent work based on turbidimetric pH titrations of haemoglobin.[77] Turbidimetric titrations can be used to study the effect of pH on the aggregation/disaggregation of protein molecules. The effect is important at the salt concentration of $\leq$150 mM. We illustrate the differences between the two approaches.

Fig. 13 shows the ion specific turbidimetric titration of haemoglobin as a function of pH. An estimation of the extent of aggregation is given by the ratio of transmittance T/T_0 at different pH values (T_0 is the transmittance of the optically clear protein solution). The haemoglobin suspension is optically clear below pH 5 (T/T_0 = 1), and then becomes cloudy as pH is increased due to the aggregation of protein molecules. T/T_0 reaches a minimum at about pH 7.4, then it increases, due to the re-dissolution of protein aggregates, reaching a value close to that at the beginning of the titration.

The effect of pH on protein aggregation can be explained to first approximation by invoking DLVO theory of colloid science[167–169] based on the balance of attractive (van der Waals) and repulsive (Coulomb) interactions. This can only provide a rough guide since ion specificity is not included. For proteins, repulsive forces are pH-dependent since the electric charge on the protein surface is produced by the dissociation of weak acidic (R-COOH) and basic (R-NH$_2$ or similar nitrogen-based) groups carried by surface amino acids. The repulsive force is minimal at the isoelectric point (IEP, zero net charge) and maximal at pH $\gg$ IEP or pH $\ll$ IEP. The attractive force, instead, should not be affected by pH.

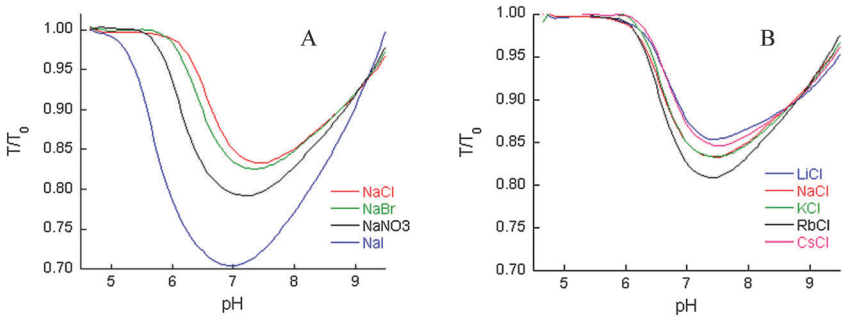

Fig. 13 Specific ion effects on turbidimetric pH titration (T/T_0 *vs.* pH) of haemoglobin dispersions at salt concentration = 50 mM and temperature = 25 °C. (A) Specific anion effects; (B) specific cation effects. Reprinted with permission from ref. 77. Copyright (2013) American Chemical Society.

But, as always, DLVO fails to predict ion specific effects. Salts formed by ions having the same charge would behave in the same way. But this does not occur if NaCl is substituted by another monovalent salt at the same concentration (Fig. 13).

Here in almost the whole investigated pH range, anions promote aggregation according to an inverse Hofmeister series: $I^- > NO_3^- > Br^- > Cl^-$. Our interpretation is that specific anion binding decreases the net positive surface charge of protein molecules, and hence decreases the repulsion among them, thus allowing for protein molecules aggregation. Cation specific effects were similarly observed in the presence of different 50 mM chloride salts. At the starting pH 4.5 haemoglobin carries a positive net charge, so that cations behave as coions. The T/T_0 values show a less marked variation along the investigated pH range for cations than in the case of anions.[32] Nonetheless, the effect is quite marked. Cations promote hemoglobin aggregation in the order $Rb^+ > K^+ \sim Na^+ > Cs^+ > Li^+$.

LMWA and dispersion forces approaches would predict the same sequence of anion binding, in one case (LMWA) because the chaotropic positive amino groups would prefer to form contact ion pairs with more chaotropic anions ($I^- > Cl^-$). In the other case (dispersion forces), the higher the anion polarisability the higher the attractive dispersion potential to the protein surface will be ($I^- > Cl^-$).

Things become more complicated for cations. Differently from anions, a higher cation binding produces a more positive charge which results in a lower aggregation. Here we observe that the aggregation decreases in the series $Rb^+ > Li^+$ (if we do not consider Cs^+) that is, Li^+ binds more than Rb^+. This is exactly what is predicted by LMWA. The kosmotropic carboxylate group will prefer to form a contact ion pair with the kosmotropic Li^+ rather than the chaotropic Rb^+. But, the LMWA mechanism is only part of the story for protein systems. Cremer and coworkers have clearly shown that besides charged groups, uncharged polar groups have also been found to be binding sites for anions.[145,147] This kind of mechanism might also apply to Cs^+ and so explains the 'strange' sequence ($Rb^+ > K^+ \sim Na^+ > Cs^+ > Li^+$) observed for hemoglobin aggregation That is, besides ion pair formation (according to LMWA) the interaction of the highly polarizable Cs^+ with uncharged sites is also likely at work.[77] This type of mechanism was in fact proposed by Lund *et al.*[149]

7.3. How could we reconcile the two approaches?

In the early attempts to include dispersion forces the $U_{dispersion}$ was estimated from ion static polarisabilities. No ion size or ion hydration was considered. Since polarizability increases upon going from Li^+ to Cs^+, a stronger adsorption for Cs^+ rather than Li^+ at a protein surface is expected.[166] But if we consider LMWA the formation of ion pairs between a cation and a negatively charged kosmotropic carboxylate would follow the order $Li^+ > Na^+ > K^+ > Rb^+ > Cs^+$.[143] That is, the two approaches would predict exactly the opposite sequences (Fig. 14). Even the most recent developments (although they quantify ion specific interactions features from *ab initio* dynamic ion polarisabilities and ion radii) fail. In fact, up to now, the specificity of the discrete surface site has not been considered. Indeed the dispersion potential has been calculated by modelling the surface just in terms of its dielectric function $\varepsilon_s(i\omega)$ (eqn (8)). But in fact it should also consider the chemical nature (that is kosmotropic or chaotropic, soft or hard) of the charged site. This is in fact considered by LMWA, which for proteins classifies the negative and positive protein surface sites as kosmotropic and chaotropic respectively.

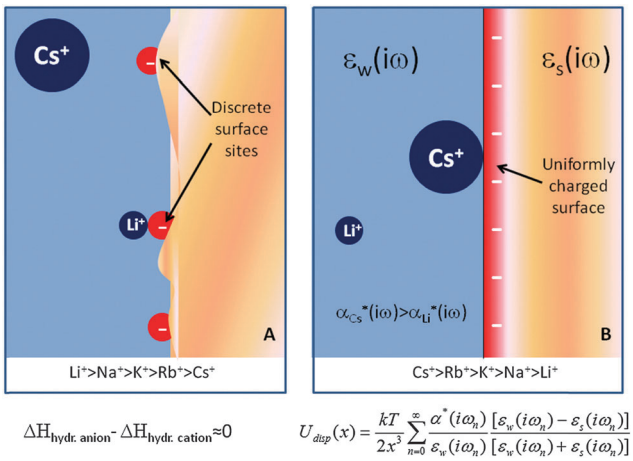

Fig. 14 A schematic comparison between (A) the law of matching water affinities and (B) the theory of ion dispersion forces, to explain the specific interactions of cations with a negatively charged surface. Depending on the nature of the surface (*i.e.* a protein), the two approaches may predict opposite cation series.

The consideration of a protein surface to be uniformly charged with a dielectric function $\varepsilon_s(i\omega)$ without taking into account the occurrence of a discrete (kosmotropic/chaotropic) charged site corresponds to a model of the solvent as a continuum instead of taking into account its granularity at a molecular level and the consequent accompanying hydration. That is, it captures some basic issues but might give wrong results in very specific cases.

The goal of LMWA is to explain ion specificity in the case where two ions of opposite charge or a charged surface group and different counterions interact. An ion pair is formed only when their sizes – or their water affinities – match. The concept is simple and generally valid.

The inclusion of ion dispersion forces is in principle able to give a theoretical framework to the LMWA but, as exhaustively explained in the previous paragraphs, this has not been reached yet. The goal is to recognise that all the interactions which the LMWA invoke as the driving forces of the formation of ion pairs (that is ion–water, ion–ion and ion-charged site interactions) are in fact due to the cooperation of electrostatic and quantum mechanical dispersion forces.

But the final goal will be the improvement of the modelling to predict specific ion binding to charged surface sites. This cannot be done by using the dielectric function of the interface as the sole parameter. Although surface hydration has been included to model mica surfaces,[160] this method has not been applied for more complicated surfaces (*e.g.* surfactants, proteins, polymers).

A way to solve this problem might be to include in the model the discrete surface site in a way similar to what has already been done by Parsons for the interacting ions.[159] That is, the polarisability, the size, and the hydration of the surface site should be calculated *ab initio*.

8. Concluding remarks

The only conclusion to any discussion involving water is that it cannot be concluded. When solutes are thrown into the mix, and temperature and dissolved gas are factors, any attempts to capture its essence are bound to be elusive and or illusory. The venerable Hofmeister specific ion effect with colloids and proteins that we have reviewed is an example of a more general challenge. Hofmeister effects have escaped explanation for almost 130 years now. Every time an 'explanation' emerges, a counterexample seems to pop out to invalidate it. Any progress in systematising the phenomena, we are grateful for.

The barriers to progress are large. Berthollet observed that in a solution comprised of a mixture of $CaCO_3$ and NaCl, calcium carbonate precipitates at low temperatures, and sodium carbonate at high temperatures (50–60 °C) and the results of such (inorganic) precipitation and nanoparticle nucleation experiments depend strongly on the perturbations of water structure by solutes like sugars. However we think of 'water structure' it clearly affects nucleation, crystal growth and interactions and specific 'hydration' as a function of temperature. Further, we know that dissolved gas looms always in the background as an unspoken elephant in the living room, which affects 'hydrophobic' interactions. Moreover, there is the existence of gels, jellyfish with 95–98% water[59] being perfectly functional, seemingly providing an unarguable, and certainly not understood case for 'very long ranged water structure', shades of polywater. Given that, it takes a certain amount of chutzpah or naivete to tackle the problem. With this in mind we have tried to put order in at least some phenomena, which are certainly at work, although they are not the full story, in ion specific experiments.

We have shown how Collins' Law of Matching Water Affinities,[44] can be useful in describing specific ion/ion and ion/charged site binding sequences. They are important because they characterise and bring to order properties like activity coefficients,[38] surface charge,[34] electrophoretic mobilities,[33] interaction of ions with surfactant charged headgroups,[142] and ultimately, protein aggregation.[77] Collins' rules, the LMWA, are derived for correlations with experimental observations on single ions (volcano plot).[44] They are likely related to Born free energies of transfer, which have been shown to depend on previously neglected dispersion Born energies.[53] Although the basis of the Volcano plot is questionable, the ion binding sequence given by the rule is usually correct as confirmed by wide experimental evidence. However, the rules are not the whole story as they neglect ion–neutral site interactions.[149] They do exist and are part of ion–protein surface interactions.[31,77,145] These types of interactions together with ion-charged site both originate in previously neglected dispersion forces.[46] This is emerging in the properties of electrolyte solutions.[52,53,55]

But the inclusion of these additional interactions presents some technical difficulties that are still extant. The modelling used to include ion dispersion interactions appeared to predict in some cases opposite ion binding sequences to what was predicted by LMWA.[143,166] The reason for this is clear. The disagreement is because while on the one hand the polarisability (and later more recent developments, even the size and the hydration[54]) of the ion was considered, on the other hand the charged surfactant or protein interface was modelled (besides having a smeared out charge) only in terms of its dielectric function. That is, the chemical nature of the surface sites was not considered.

The way to reconcile the correct sequence, given by Collins' rules, with the correct theory (which includes ion dispersion interactions) is to consider that charged sites can be either chaotropic (soft) or kosmotropic (hard). That is, the polarisability, size, and hydration of the charged site need to be included in the modelling. Otherwise wrong or partially correct sequences are sometimes obtained. With the problems now identified, better quantitative modelling is coming into sight.

Here, we have faced what in principle is an easy form of a more general problem. We have attempted to seek a theoretical basis for the phenomenology of the Law of Matching Water Affinities. Further work is still needed but these two apparently opposing approaches are in fact one and the same. We have indicated here how they are reconcilable, the LMWA being derivable from a more complete theory of electrolytes.[53]

But on the way to that resolution, we have necessarily to consider what seem to be still open challenges. The interpretations of all of the standard measurements on which our arguments are based depend on and rely on a theory. In most part this underlying, classical, theory is based on electrostatics alone, be they measurements of pH, or buffers, molecular forces, electrophoresis, ion binding, pK_as, and so on. That, as we have discovered, is inadequate and erroneous, and has been swept under the carpet. The unrecognised problem of dissolved gas and its connection to 'hydrophobic' interactions takes us into another realm, as does the problem of water at different temperatures and 'water structure' in the presence of solutes. Henry[59,68] has argued cogently that zoomorphic water, water in cells, is very different. And in this he is very probably correct. Phenomena like the reversal of the series observed for buffer solutions in enzyme activities,[23] pH measurements,[10] or buffer specificity in electrophoretic mobilities[122] still await explanation. They have implications for matters as fundamental as membrane potentials in physiology. In real systems things are complicated further by the presence of mixed electrolytes, as Na^+ and K^+ in red cells. The necessity for rebuilding theoretical foundations to include specific dispersion forces consistently with electrostatics and consequent hydration is obvious.

We live in interesting times.

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