Chaotropes & Kosmotropes and the Driving Force of the Salting Effect

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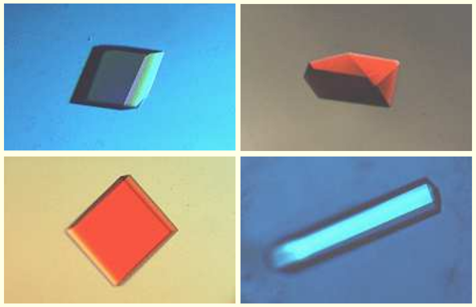
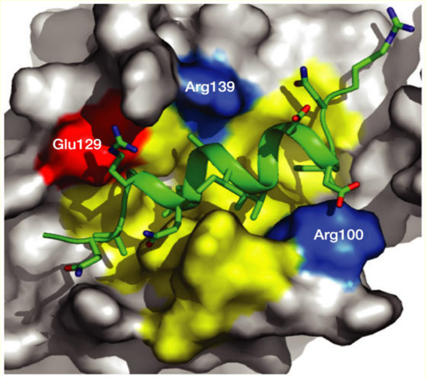
The Salting Problem and its Significance

How does the solvent induced interaction between non-polar solutes vary when salts of different types are dissolved in the aqueous solution?

- Protein solubility: crystallization and aggregation



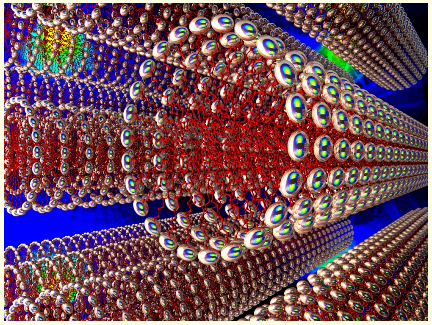
www.u.arizona.edu/weichsel



Nature Rev. Drug Disc. 3, 301 (2004)

- Recognition between proteins and multimerization
- Catalytic activity of enzymes
- Stability of secondary and tertiary structures

- Phase boundaries of micellar solutions and lipid bilayers
- Cloud point of non-ionic surfactants
- Polymer swelling



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Characteristics of the Salting Phenomenon

- It becomes important at moderate salt concentrations: 0.01–1.0 M
- Additive over all ions in solution; anions have larger effect than cations
- The dependence of solute solubility on salt concentration:

$$\log(S_0/S) = K_s C_s$$

Salting-Out: $K_s > 0$
stronger solute-solute interactions

Salting-In: $K_s < 0$
weaker solute-solute interactions

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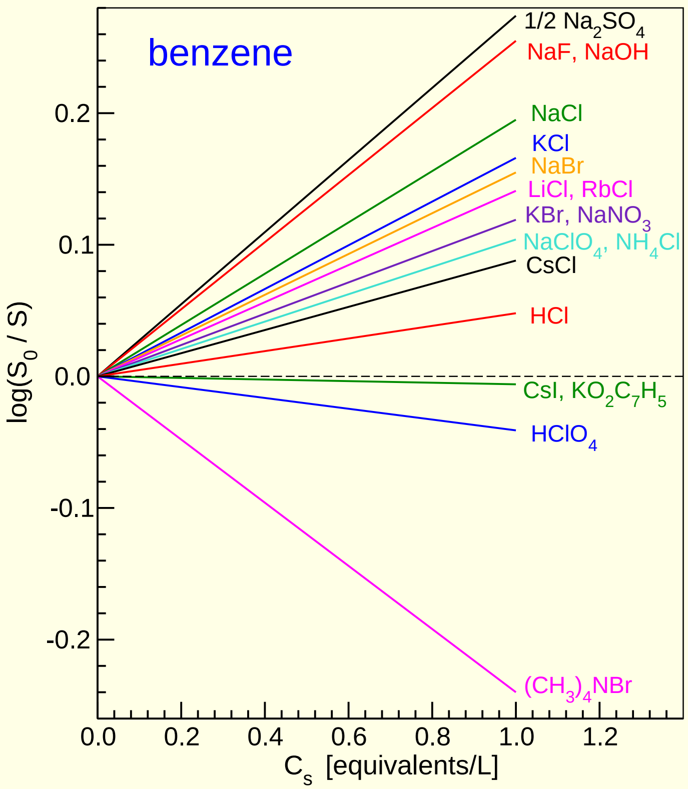

Long & McDevit, Chem. Rev. 51, 119 (1952)

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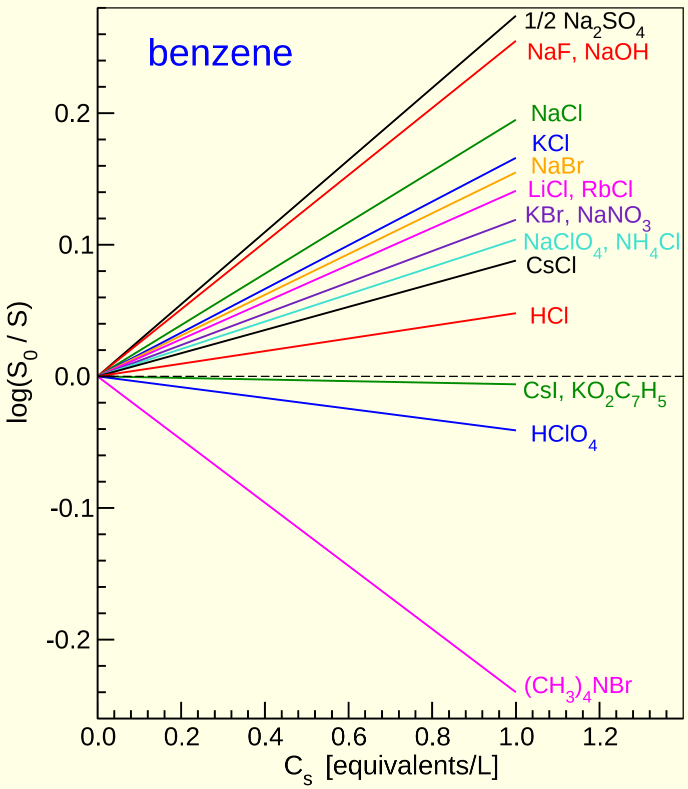
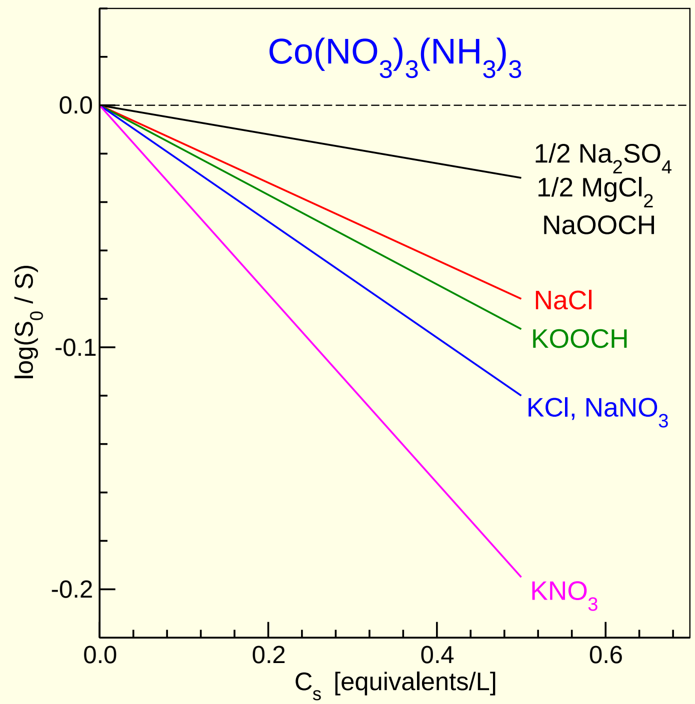




- Salting-In enhances for larger and more polar solutes

Hofmeister Series

The ranking of the (Salting-Out and Salting-In) ions to precipitate proteins:

$$PO_4^{3-} > SO_4^{2-} > HPO_4^{2-} > OH^- > F^- > Cl^- > Br^- > NO_3^- > I^- > SCN^- > ClO_4^-$$

$$Al^{3+} > Mg^{2+} > Ca^{2+} > Ba^{2+} > Na^+ > K^+ > NH_4^+ > Rb^+ > Cs^+$$

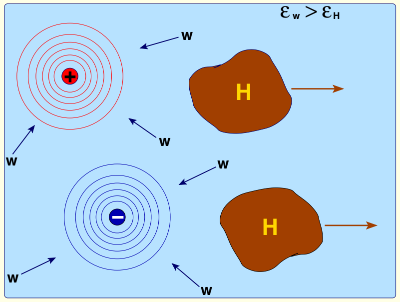
stronger solute-solute interactions $\Longleftarrow$ $\|$ $\Longrightarrow$ **weaker** solute-solute interactions

$\Longrightarrow$ Attraction between the proteins increases with ionic charge density

Proposed Explanations

$\nearrow$ Electrostatic theories

problems with predicting salting-in behavior

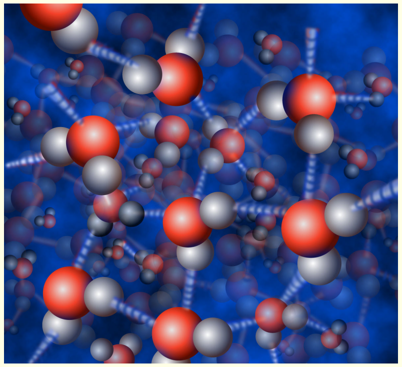


$\searrow$ Changes in the structure of water

⋆ Kosmotropic ions - order the structure of water $\Longrightarrow$ Salting-Out

⋆ Chaotropic ions - disorder the structure of water $\Longrightarrow$ Salting-In

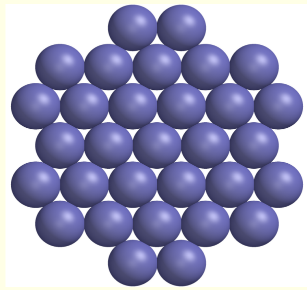
problems with accounting for different behavior of the same salt



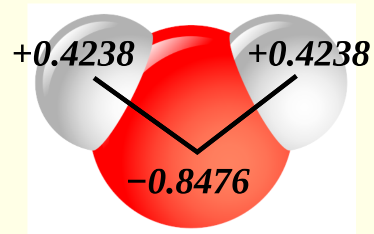
Molecular Dynamics Simulations

Two Hydrophobic Plates ($\varnothing \sim 2.1$ nm)
solvated in aqueous electrolyte solutions

$\sigma_{\text{plt}} = 0.40$ nm
$\epsilon_{\text{plt}} = 0.50$ kJ/mol



SPC/E water

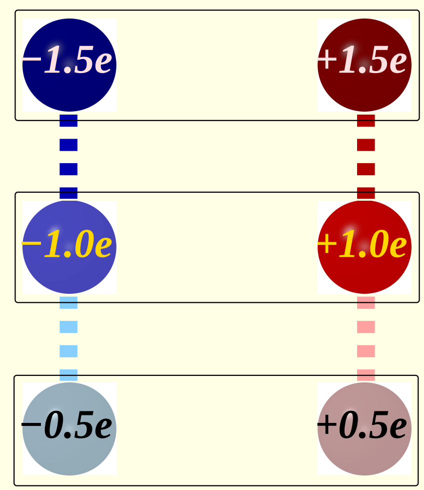


N = 1090 molecules

Salt : 30 anions & 30 cations

1.43 molal
(1.20–1.35 M)

$\sigma_{\text{ion}} = 0.50$ nm
$\epsilon_{\text{ion}} = 1.00$ kJ/mol



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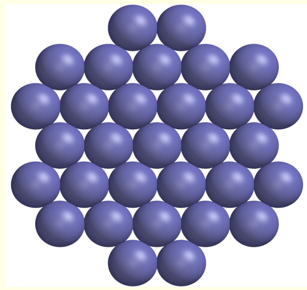

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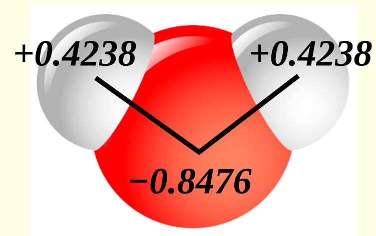

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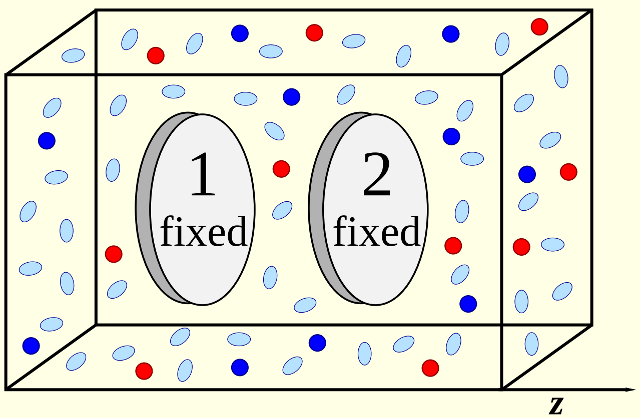
Potential of Mean Force



T=300 K
P=1 atm

$$\frac{1}{2}\left\langle \hat{r}_{12}\cdot(\vec{F}_1-\vec{F}_2)\right\rangle_{\vec{r}_1,\vec{r}_2} = -\partial w(r_{12})/\partial r_{12}$$

$$\left\langle \hat{r}_{\perp}\cdot(\vec{F}_1-\vec{F}_2)\right\rangle_{\vec{r}_1,\vec{r}_2} = 0$$

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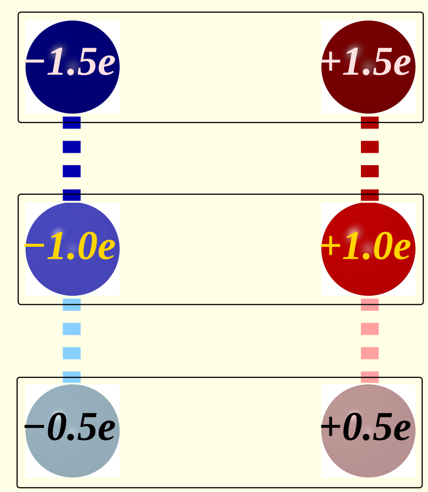
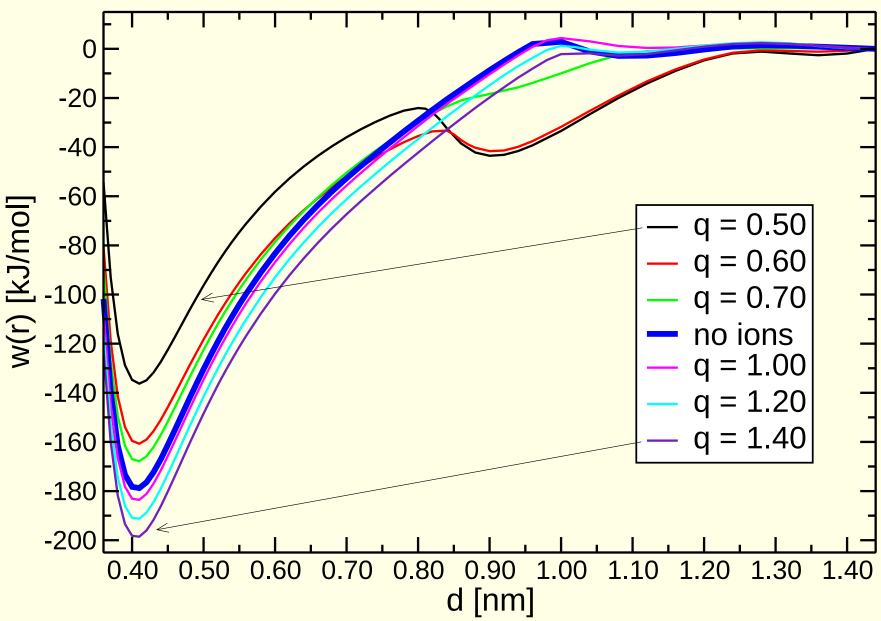
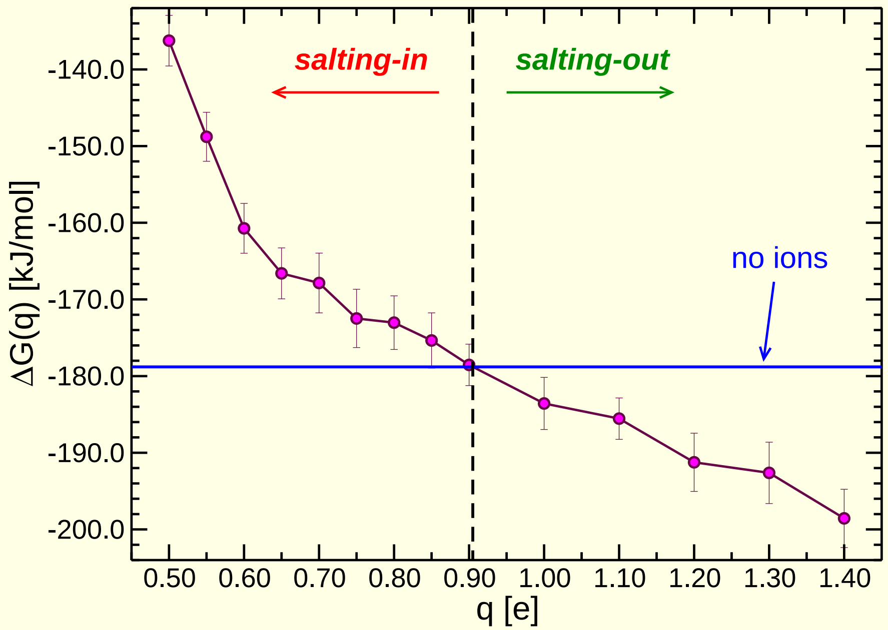


Changes in the Hydrophobic Interaction as a Function of the Type of Salt in Solution

Free energy profile of bringing the plates from far apart to contact



Free energy difference for association process: $P(aq) + P(aq) \rightleftharpoons P_2(aq)$



R. Zangi, M. Hagen & B. J. Berne, J. Am. Chem. Soc. 129, 4678 (2007)

Salting-In ions: q $< 0.90\ e$

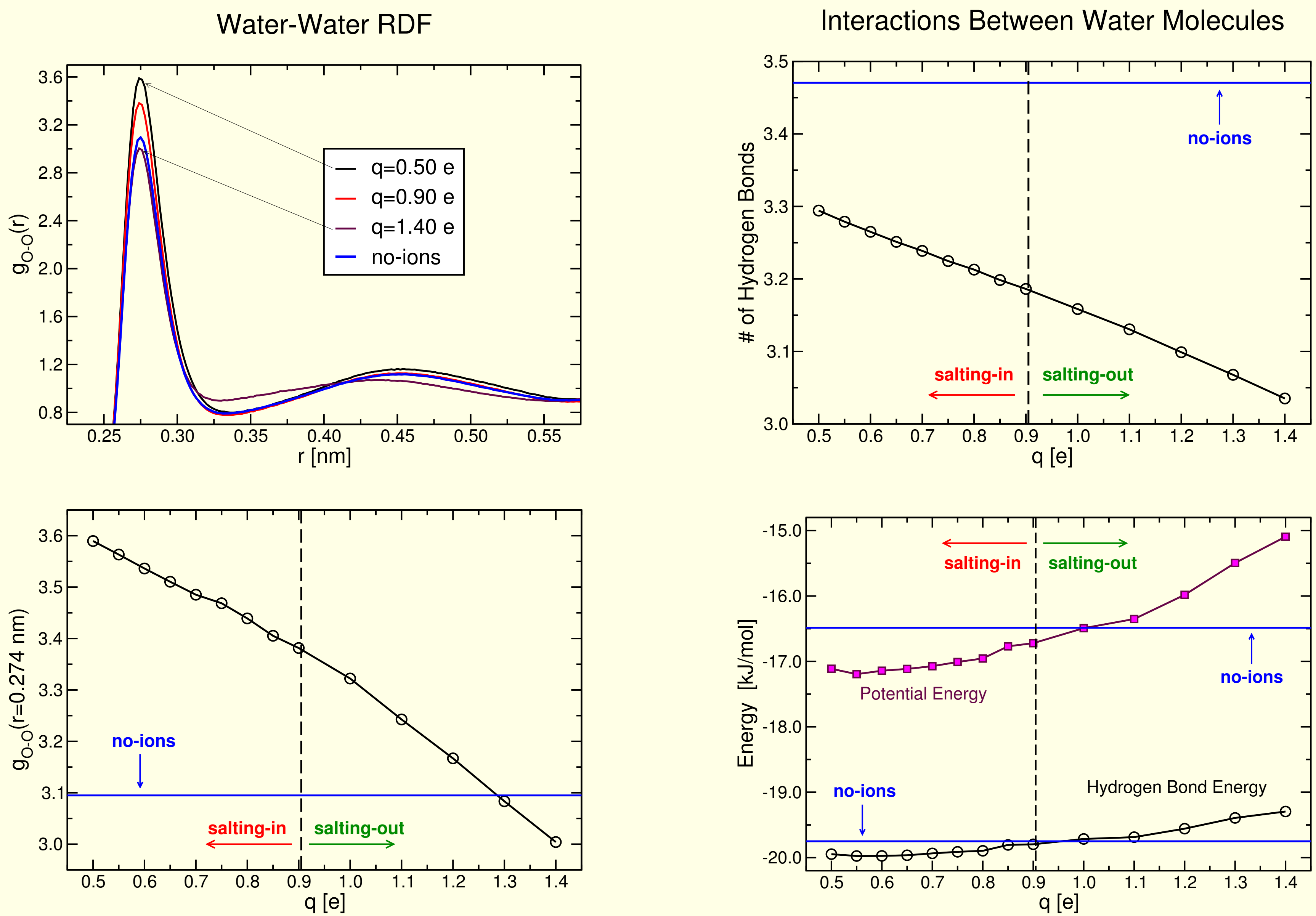
weaker effective interaction between plates

Salting-Out ions: q $> 0.90\ e$

stronger effective interaction between plates

- Why did the effective interaction change?
- Can the variation be predicted?

The Corresponding Changes in Water Structure



R. Zangi, J. Phys. Chem B. 114, 643 (2010)

The Corresponding Changes in Water Viscosity

Experiments:

Salting-out ions *increase* viscosity $(B > 0)$
Salting-in ions *decrease* viscosity $(B < 0)$

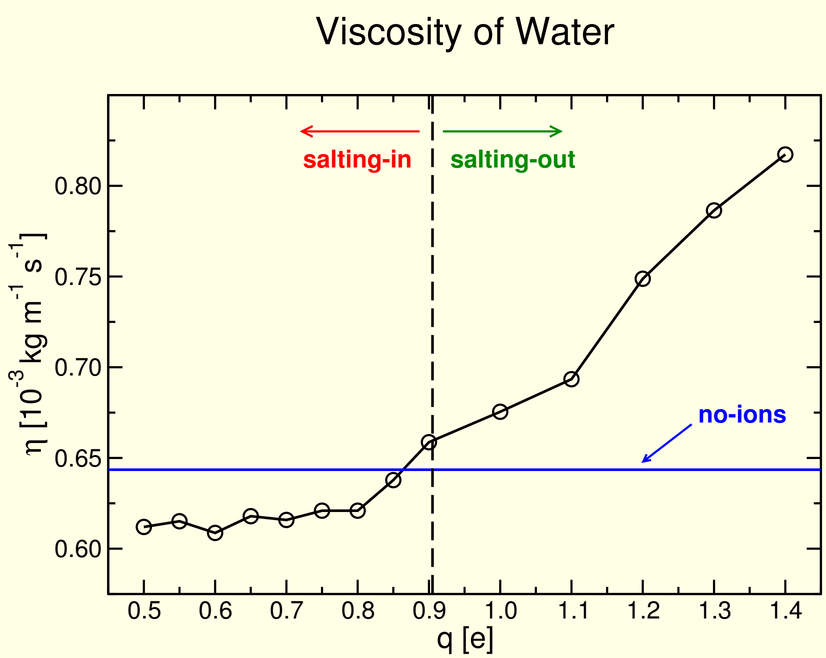
For dilute aqueous salt solutions:

$$\eta/\eta_0 = 1 + A\sqrt{c} + Bc + \ldots$$

Cations	**B** [1/M]	**Anions**	**B** [1/M]
Mg^{2+}	0.385	CO_3^{2-}	0.294
Ca^{2+}	0.284	SO_4^{2-}	0.206
Sr^{2+}	0.261	OH^-	0.122
Ba^{2+}	0.216	F^-	0.107
Na^+	0.085	Cl^-	-0.005
K^+	-0.009	Br^-	-0.033
NH_4^+	-0.008	NO_3^-	-0.043
Rb^+	-0.033	I^-	-0.073
Cs^+	-0.047	SCN^-	-0.022
Me_4N^+	0.123	ClO_4^-	-0.058

Y. Marcus, Chem. Rev. 109, 1346 (2009)

Simulations:



It is the strength of the ion-water interactions that that affect the viscosity water.

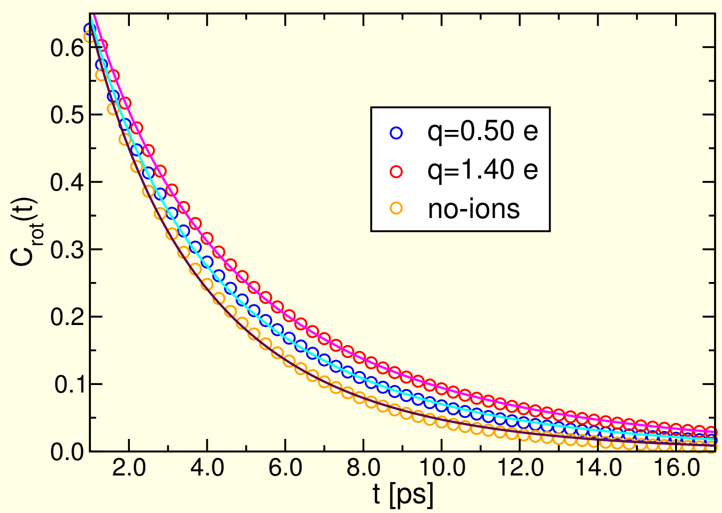
The Corresponding Changes in Water Reorientation

Reorientation auto-correlation function of waters

- of normal to the molecular plane vector
- of dipole moment vector

$$C_{\text{rot}}(t) = A \cdot \exp\left[-(k_{\text{rot}} \cdot t)^{\beta}\right]$$

Fitting β and k_{rot}

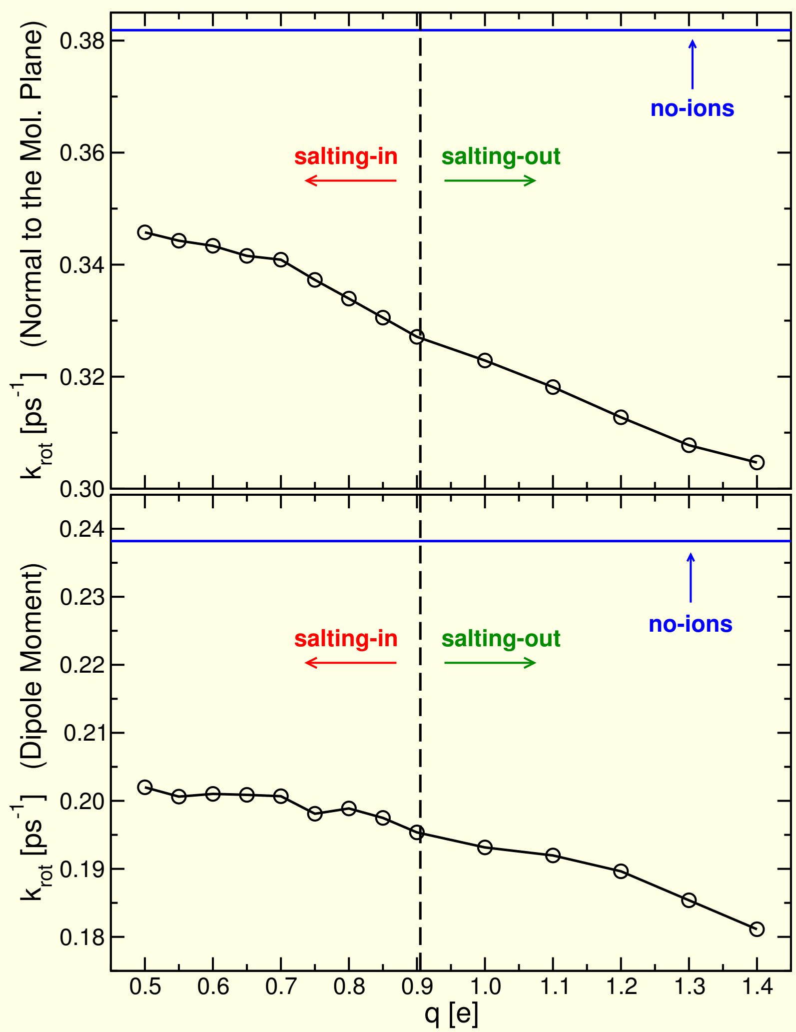


$C_{\text{rot}}(t=0) = 1 \implies A = 1$

β for normal to the plane: 0.77–0.79

β for dipole moment: 0.78–0.70

Rotational Decay Rate



A Thermodynamic View: Preferential Binding

Linked Functions: *J. Wyman, Adv. Protein Chem. 19, 224 (1964)*
C. Tanford, J. Mol. Biol. 39, 539 (1969)

Consider the reaction: $\mathsf{A(aq)} + \mathsf{B(aq)} \rightleftharpoons \mathsf{C(aq)}$

Now, add a ligand (salt) X that can (in addition to water) interact with A, B and C

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$$A + iX + jW \rightleftharpoons AX_iW_j \qquad i = 0, 1, \ldots, p \quad ; \quad j = p - i$$

$$B + kX + lW \rightleftharpoons BX_kW_l \qquad k = 0, 1, \ldots, q \quad ; \quad l = q - k$$

$$C + mX + nW \rightleftharpoons CX_mW_n \qquad m = 0, 1, \ldots, r \quad ; \quad n = r - m$$

How does the addition of X affect the equilibrium constant of the reaction?

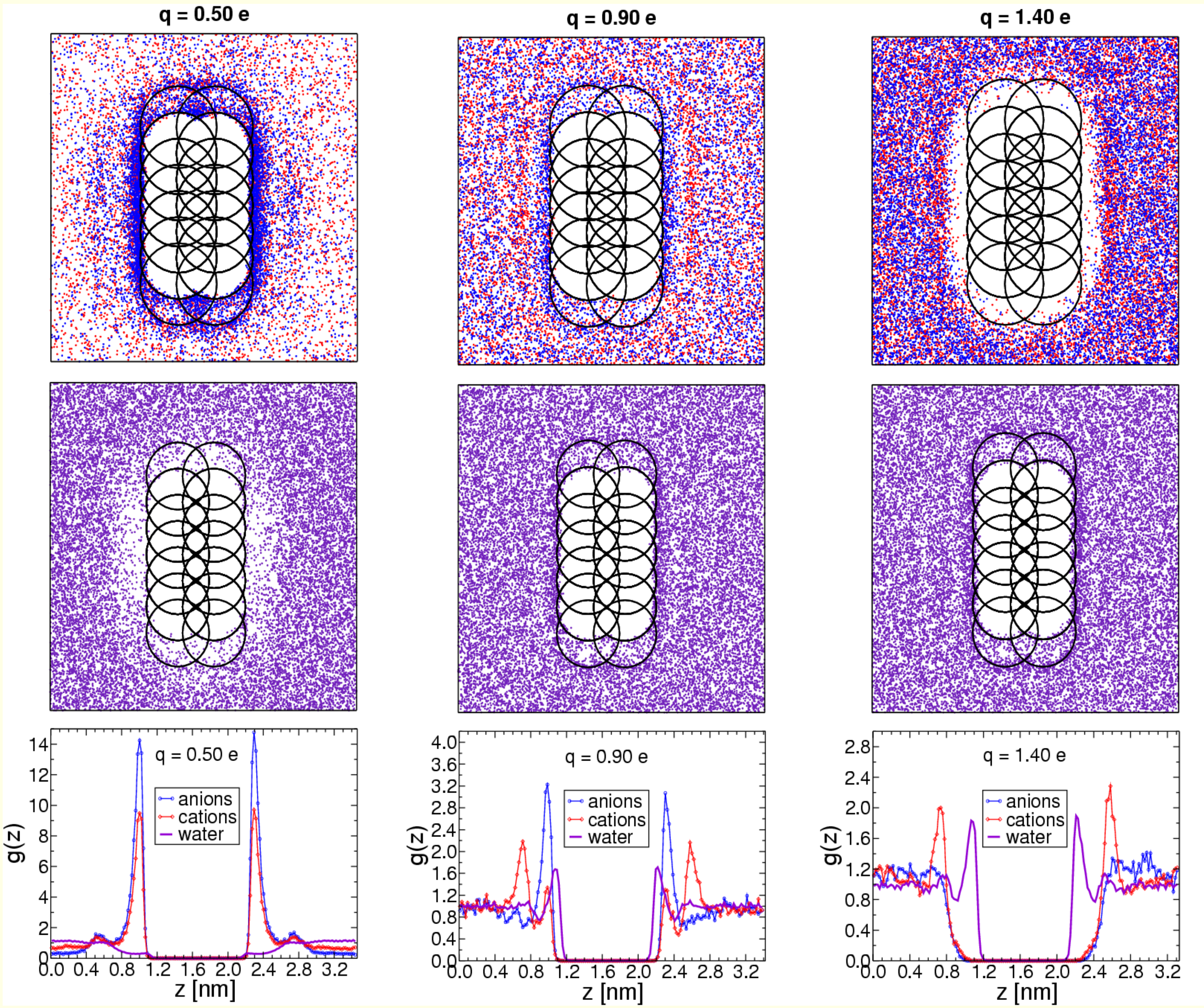
In the limit of infinite dilution of A, B and C $\Longrightarrow$

$$\frac{d \ln K}{d \ln a_X} = \nu_{X,C} - \nu_{X,A} - \nu_{X,B} - \frac{n_X}{n_W}(\nu_{W,C} - \nu_{W,A} - \nu_{W,B}) \equiv \Delta\nu_{X,\ \mathrm{pref}}$$

$\nu_{Y,M}$ = number of Y molecules bound to M macromolecule

a_X = chemical activity of X

Binding/Exclusion of the Ions and Water



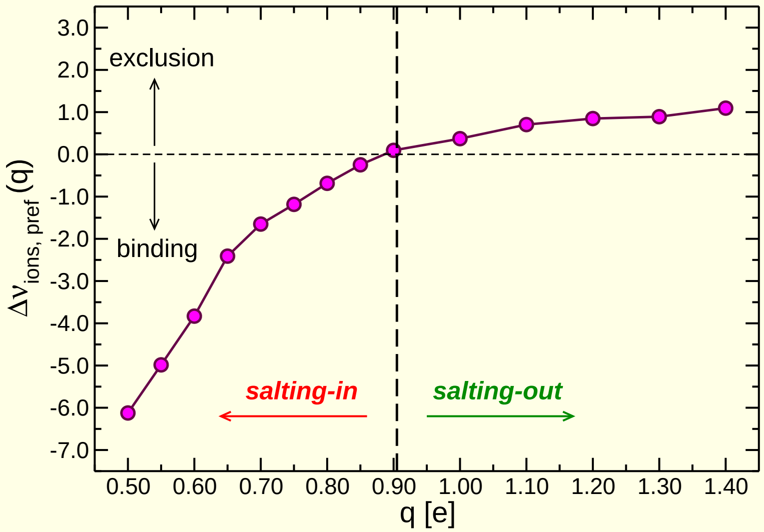
Anions & Cations

Water

Density Profiles

Relation between $\Delta\nu_{pref}$ and ΔG

$$\Delta\nu_{\text{ions, pref}} = (\Delta\nu_{\text{cations}} + \Delta\nu_{\text{anions}})/2 - \frac{n_{\text{salt}}}{n_{\text{water}}}\Delta\nu_{\text{water}}$$

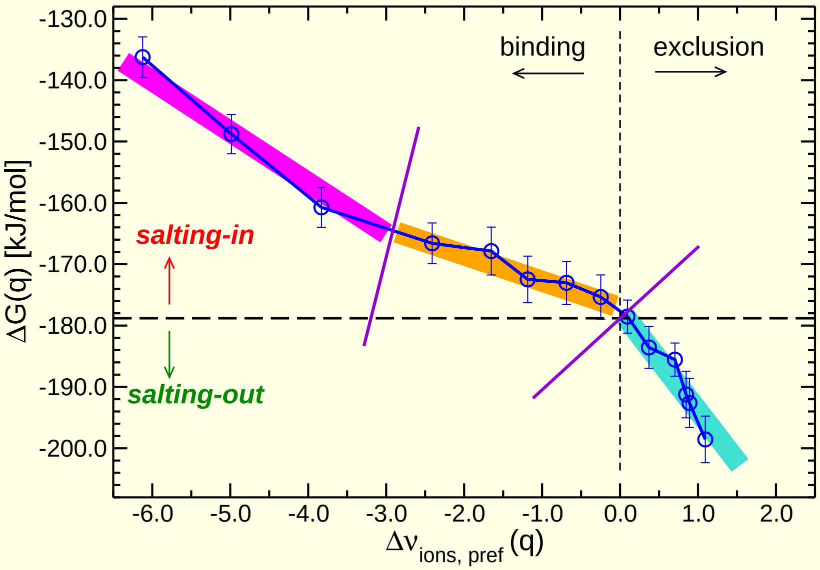


$$P(aq) + P(aq) \rightleftharpoons P_2(aq)$$

binding of the ions $\Longrightarrow$ salting-in

exclusion of the ions $\Longrightarrow$ salting-out

$$d(\Delta G) = -RT\Delta\nu_{\text{ions, pref}} \cdot d\ln a_{\text{ions}}$$



Mechanism of Salting-In and Salting-Out

What is the driving force for: P(aq) + P(aq) $\rightleftharpoons$ P_2(aq) in pure water?

In the large scale regime it is **enthalpic** and **entropic**:

- $\Delta H < 0 \Longleftarrow$ enthalpic penalty for solvating a hydrophobic surface due to loss of hydrogen bonds at the interface

- $\Delta S > 0 \Longleftarrow$ entropic penalty for solvating a hydrophobic surface due to ordering of interfacial waters

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In salt solutions:

The mechanism for Salting-In and Salting-Out can be inferred from changes of ΔH and ΔS in salt solutions relative to pure water

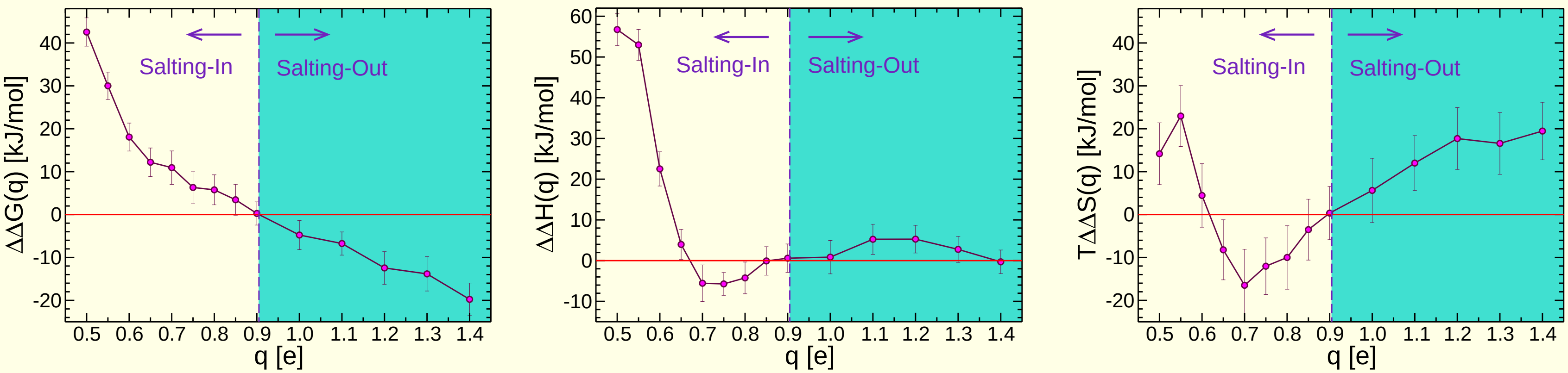
$$\Delta\Delta G(q) = \Delta G_{salt}(q) - \Delta G_{water}$$

$$\Longrightarrow \quad \text{Salting-Out} \quad \Delta\Delta G < 0 \qquad \text{Salting-In} \quad \Delta\Delta G > 0$$

$$\Delta\Delta H(q) = \Delta H_{salt}(q) - \Delta H_{water}$$

$$\Delta\Delta S(q) = \Delta S_{salt}(q) - \Delta S_{water}$$

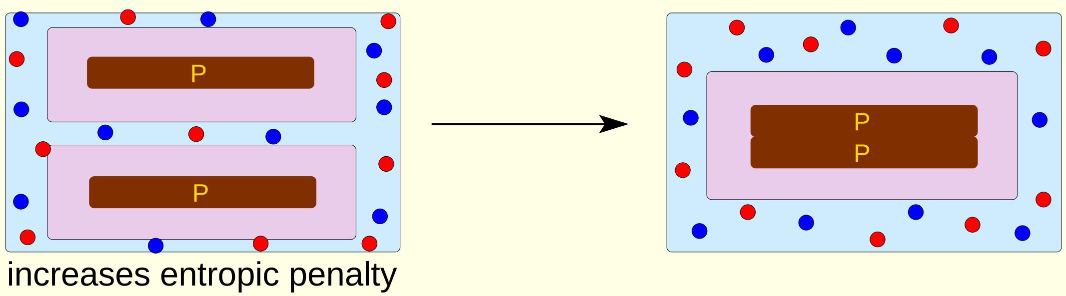
Mechanism of Salting-Out



For Salting-Out (high charge-density ions):

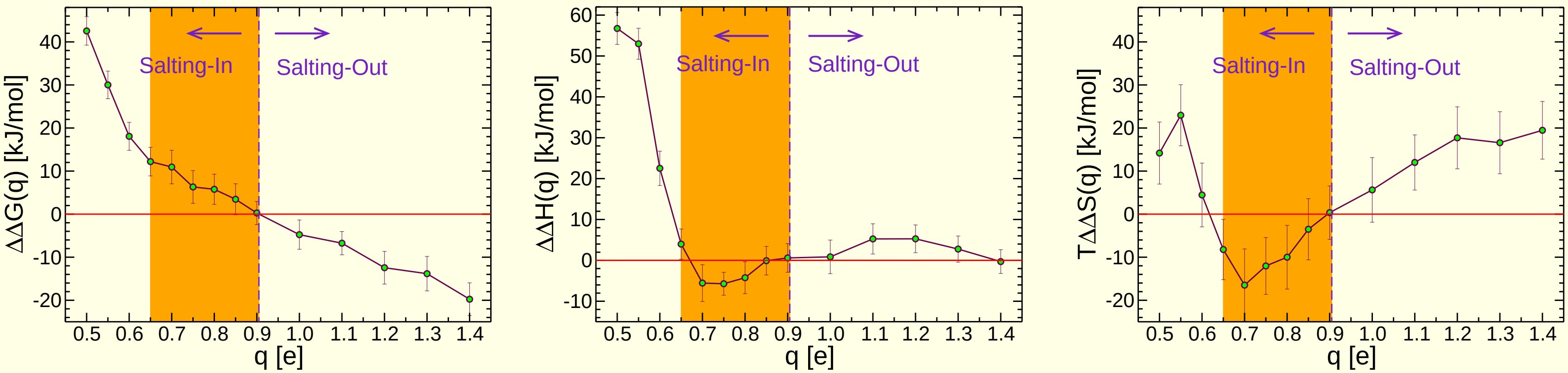
$$\underbrace{\Delta\Delta G}_{\text{negative}} = \underbrace{\Delta\Delta H}_{\text{positive}} \underbrace{- \; T\Delta\Delta S}_{\text{negative}}$$

Thus, Salting-Out is purely an entropic effect



Salting-Out: is driven by elimination of an exclusion zone for the ions

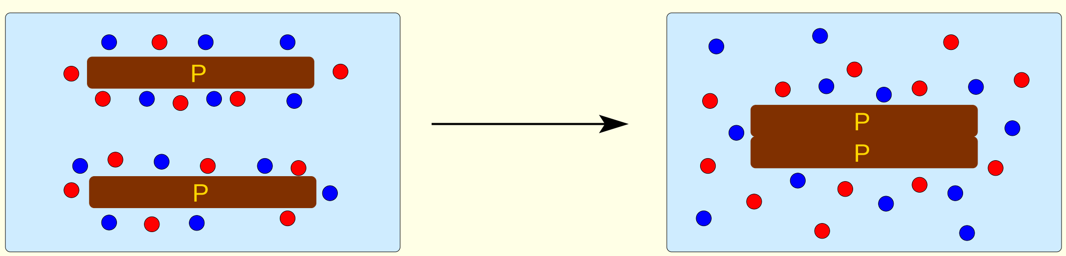
Mechanism of Salting-In (region-I)



For Salting-In ($0.65 < |q| < 0.90\ e$):

$$\underbrace{\Delta\Delta G}_{\text{positive}} = \underbrace{\Delta\Delta H}_{\text{negative}} \underbrace{-\ T\Delta\Delta S}_{\text{positive}}$$

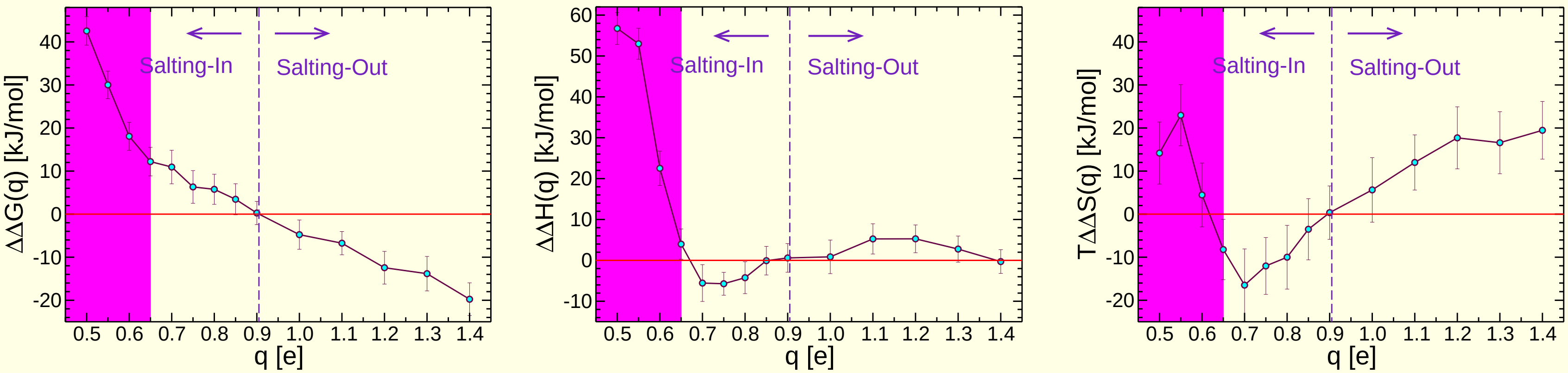
Thus, Salting-In in this regime is an entropic effect



reduces entropic penalty

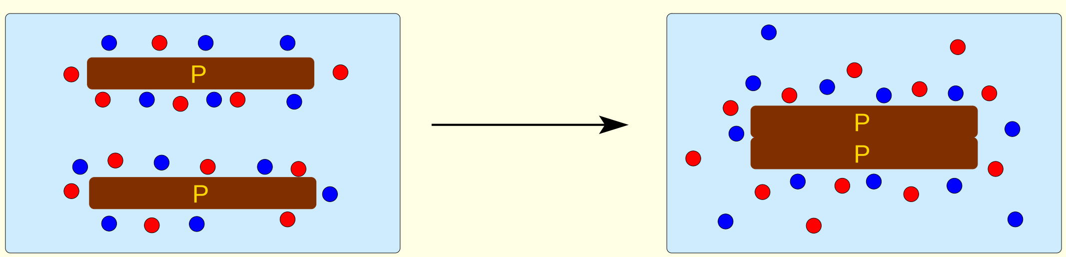
Salting-In: the binding of ions reduces the ordering of the interfacial water (entropic penalty) and, therefore, stabilizes the monomeric state.

Mechanism of Salting-In (region-II)



For Salting-In (low charge-density ions): $\underbrace{\Delta\Delta G}_{\text{positive}} = \underbrace{\Delta\Delta H}_{\text{positive}} \underbrace{- \ T\Delta\Delta S}_{\text{negative}}$

Thus, Salting-In in this regime is an enthalpic effect

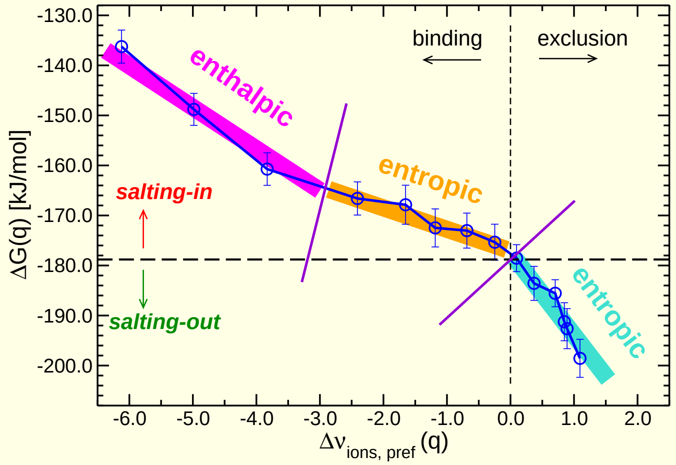


Salting-In: the binding of ions reduces the enthalpic penalty when the plates are solveted in water (acting as 'surfactants').

Conclusions

- We did not find a correlation between the ion-induced changes of the structure (and dynamics) between water molecules and the ability of these ions to alter the magnitude of the hydrophobic interactions.

- However, we did observe that ΔG correlates with $\Delta\nu_{ions,\ pref}$ (depends on both ions and solute) with 3 different slopes. From $\Delta\Delta H$ and $\Delta\Delta S$ we find the 3 slopes match 3 different mechanisms for the salting effect.



- For a given charge density, anions bind stronger than cations.

- As the polarity of the solute increases the ion-water attractive interactions will increase (dipole–dipole interactions) and the transition from salting-out to salting-in will occur at higher ionic charge density (i.e., more salting-in).

Acknowledgments

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Morten Hagen

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