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 solute particles vary when salts of different types are dissolved in the aqueous solution?
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How does the solvent induced interaction between solute particles vary when salts of different types are dissolved in the aqueous solution?

- Protein solubility: crystallization and aggregation

- 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
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:

\[
\log\left(\frac{S_0}{S}\right) = K_s C_s
\]

Salting-Out: \( K_s > 0 \)  
Stronger solute-solute interactions

Salting-In: \( K_s < 0 \)  
Weaker solute-solute interactions
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[Graph showing solubility changes with salt concentration for various solvents and solutes.]

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Salting-In: \(K_s < 0\)

- Salting-In enhances for larger and more polar solutes

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Hofmeister Series

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

\[
\text{PO}_4^{3-} > \text{SO}_4^{2-} > \text{HPO}_4^{2-} > \text{OH}^- > \text{F}^- > \text{Cl}^- > \text{Br}^- > \text{NO}_3^- > \text{I}^- > \text{SCN}^- > \text{ClO}_4^- \\
\text{Al}^{3+} > \text{Mg}^{2+} > \text{Ca}^{2+} > \text{Ba}^{2+} > \text{Na}^+ > \text{K}^+ > \text{NH}_4^+ > \text{Rb}^+ > \text{Cs}^+
\]

\[\text{stronger solute-solute interactions} \quad \Rightarrow \quad \text{weaker solute-solute interactions}\]

\[\Rightarrow \text{Attraction between the proteins increases with ionic charge density}\]

Electrostatic theories

problems with predicting salting-in behavior

Proposed Explanations

Changes in the structure of water

\* Kosmotropic ions - order the structure of water \[\Rightarrow \text{Salting-Out}\]

\* Chaototropic ions - disorder the structure of water \[\Rightarrow \text{Salting-In}\]

problems with accounting for different behavior of the same salt
Molecular Dynamics Simulations

Two Hydrophobic Plates ($\sim 2.1$ 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)

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Potential of Mean Force

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

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

Salt: 30 anions & 30 cations

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

$T = 300$ K
$P = 1$ atm
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:

\[ P(aq) + P(aq) \rightleftharpoons P_2(aq) \]

\( w(r) \) [kJ/mol]

\( q = 0.50 \)

\( q = 0.60 \)

\( q = 0.70 \)

\( q = 1.00 \)

\( q = 1.20 \)

\( q = 1.40 \)

\( d \) [nm]

Salting-In ions: \( q < 0.90 \ e \)

\textbf{weaker} effective interaction between plates

Salting-Out ions: \( q > 0.90 \ e \)

\textbf{stronger} effective interaction between plates

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

The Corresponding Changes in Water Structure

Water-Water RDF

Interactions Between Water Molecules

The Corresponding Changes in Water Dynamics

Salting-out ions induce an increase in the viscosity, and a decrease in the rotational decay rate of water. Vise versa for salting-in ions.

It is the strength of the ion-water interactions, and not the ion-induced structural changes of water, that affect the dynamics of water.
A Thermodynamic View: Preferential Binding

Linked Functions: J. Wyman, Adv. Protein Chem. 19, 224 (1964)

Consider the reaction: \[ \text{A(aq)} + \text{B(aq)} \rightleftharpoons \text{C(aq)} \]

Now, add a ligand (salt) \( X \) that can (in addition to water) interact with A, B and C.
A Thermodynamic View: Preferential Binding

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Consider the reaction: \[ A(aq) + B(aq) \rightleftharpoons C(aq) \]

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

\[ A + iX + jW \rightleftharpoons AX_iW_j \quad i = 0, 1, \ldots, p \quad ; \quad j = p - i \]
\[ B + kX + lW \rightleftharpoons BX_kW_l \quad k = 0, 1, \ldots, q \quad ; \quad l = q - k \]
\[ C + mX + nW \rightleftharpoons CX_mW_n \quad m = 0, 1, \ldots, r \quad ; \quad n = r - m \]

How does the addition of \( X \) affect the equilibrium constant of the reaction?

In the limit of infinite dilution of A, B and C \[ \implies \]

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

\( \nu_{Y,M} = \) 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

$q = 0.50 \text{ e}$

$q = 0.90 \text{ e}$

$q = 1.40 \text{ e}$
Relation between $\Delta \nu_{\text{pref}}$ and $\Delta G$

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

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

P(aq) + P(aq) ⇌ P_2(aq)

binding of the ions $\implies$ salting-in
exclusion of the ions $\implies$ salting-out
Mechanism of Salting-In and Salting-Out

What is the driving force for: \[ \text{P(aq)} + \text{P(aq)} \rightleftharpoons \text{P}_2\text{(aq)} \] in pure water?

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

- \( \Delta H < 0 \) = enthalpic penalty for solvating a hydrophobic surface due to loss of hydrogen bonds at the interface
- \( \Delta S > 0 \) = 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 \( \Delta H \) and \( \Delta S \) in salt solutions relative to pure water

\[
\Delta\Delta G(q) = \Delta G_{\text{salt}}(q) - \Delta G_{\text{water}}
\]

\( \implies \) Salting-Out \( \Delta\Delta G < 0 \) \( \implies \) Salting-In \( \Delta\Delta G > 0 \)

\[
\Delta\Delta H(q) = \Delta H_{\text{salt}}(q) - \Delta H_{\text{water}}
\]

\[
\Delta\Delta S(q) = \Delta S_{\text{salt}}(q) - \Delta S_{\text{water}}
\]
Mechanism of Salting-Out

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

\[ \Delta \Delta G = \Delta \Delta H - T \Delta \Delta S \]

negative  positive  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 ($0.65 < |q| < 0.90 \text{ e}$): \[ \Delta \Delta G = \Delta \Delta H - T \Delta \Delta S \]

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

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

\[ \Delta \Delta G = \Delta \Delta H - T \Delta \Delta S \]

\[ \text{positive} \quad \text{positive} \quad \text{negative} \]

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 \( \Delta G \) 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.
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