Chemistry of Hofmeister Anions and Osmolytes

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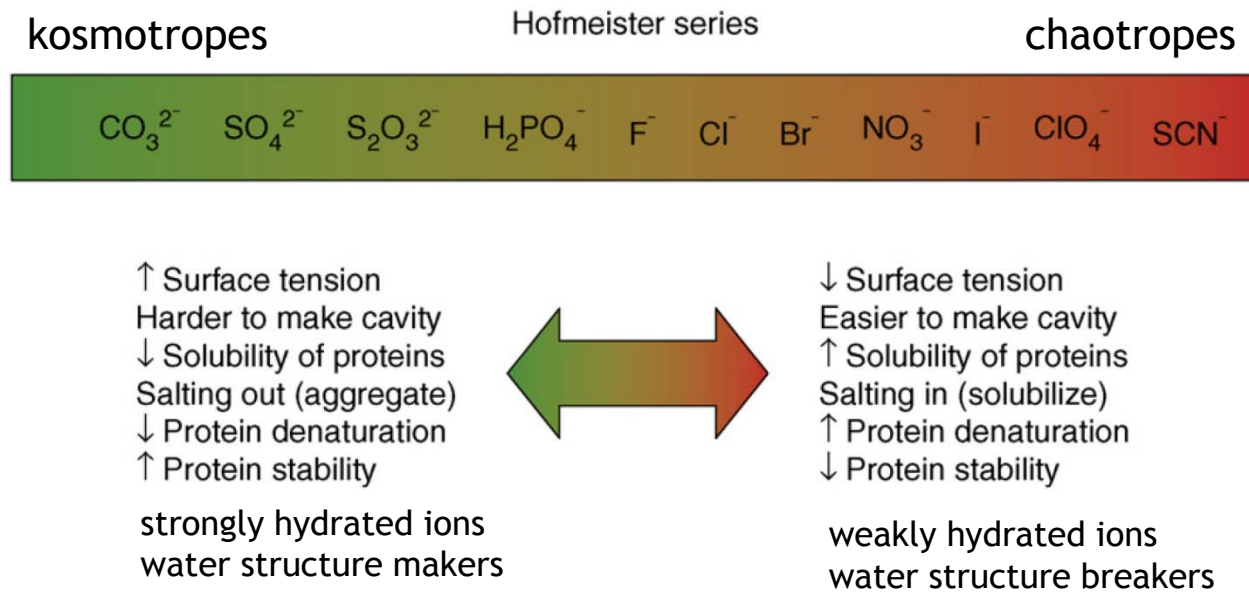
Hofmeister series: a ranking of the physical properties of ions in aqueous solutions discovered by Franz Hofmeister (1850–1922)

(enzyme activity, protein stability, protein–protein interactions, protein crystallization, optical rotation, bacterial growth)

kosmotropes   Hofmeister series   chaotropes

$$CO_3^{2-} \quad SO_4^{2-} \quad S_2O_3^{2-} \quad H_2PO_4^{-} \quad F^{-} \quad Cl^{-} \quad Br^{-} \quad NO_3^{-} \quad I^{-} \quad ClO_4^{-} \quad SCN^{-}$$

↑ Surface tension
Harder to make cavity
↓ Solubility of proteins
Salting out (aggregate)
↓ Protein denaturation
↑ Protein stability

↓ Surface tension
Easier to make cavity
↑ Solubility of proteins
Salting in (solubilize)
↑ Protein denaturation
↓ Protein stability

strongly hydrated ions
water structure makers

weakly hydrated ions
water structure breakers

recent studies

doubts about water structure making & breaking :

- Hydrogen-bonding network of the solution is not significantly changed by the ion's presence.-- Bakker

- The effects of different species on bulk water structure appeared to be uncorrelated with the Hofmeister series.-- Pielak

- Introduced a dispersion potential into DLVO(Derjaguin-Landau-Verwey-Overbeek) theory and employed their modified model to help interpret many ion-specific phenomena.-- Ninham

- The ions do not have long-range effects on bulk water structure.-- Saykally

understanding of the influence of salt at the protein/water and lipid/water interfaces :

- Molecular dynamic simulations at the protein/water interface-- Jungwirth

- Investigated lipid monolayer at the air/water interface and suggested that specific anion effects on this lipid model system were mostly related to ion size-- Leontidis

- Water structure and Langmuir monolayers by nonlinear optical spectroscopy-- Cremer

Propose alternative hypotheses

-bulk water structure making and breaking are not responsible for phenomena
 related to the Hofmeister series.

-the physical properties of the monolayer may directly follow a Hofmeister series
 even when the adjacent water structure does not.

The choice of model systems

- the hydrophobic collapse of thermoresponsive Polymers and peptides
- the aggregation of proteins by temperature gradient microfluidics

Complementary data : vibrational sum frequency spectroscopy (VSFS) spectra

In this review

we focus on the chemical specificity of Hofmeister anions and the molecularlevel mechanism for urea denaturation.

we discuss the mechanisms for the Hofmeister series on the aggregation behavior of thermoresponsive polymers and peptides.

Finally, we briefly discuss the future prospects for this type of research.
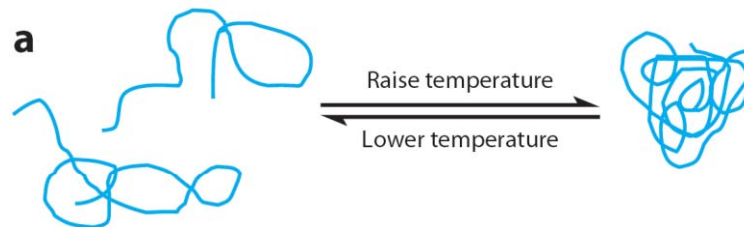
2. Hofmeister anions

2.1. Uncharged Model Systems: The Hydrophobic Collapse
of Thermoresponsive Macromolecules

employed poly(N-isopropylacrylamide) (PNIPAM)
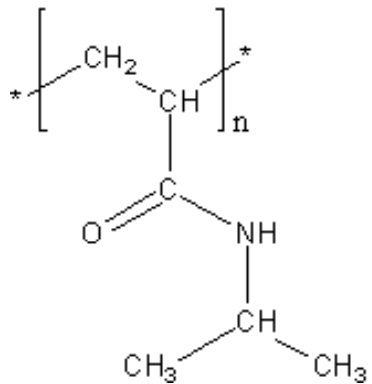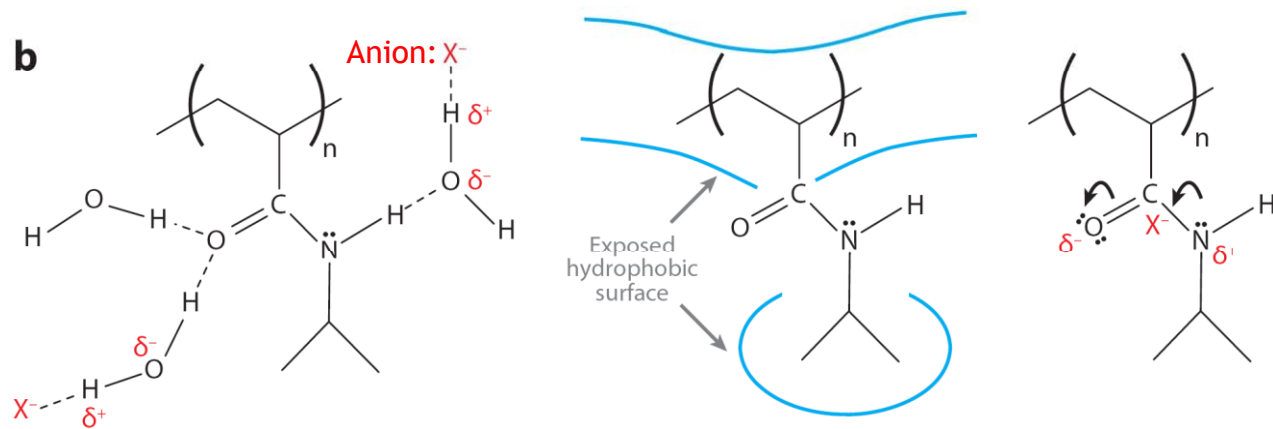
- hydrocarbon backbone with a pendant amide group

- temperature-responsive polymer

(a) The hydrophobic collapse of PNIPAM as a function of temperature.

- At temperatures below ~31°C: highly soluble in aqueous solution
- At temperatures over ~31°C : rapidly collapses, aggregates, precipitates

b

Anion: X−

Exposed
hydrophobic
surface

(b) Schematic diagrams of the interactions among anions, PNIPAM, and hydration waters.

An anion(X−) can polarize a water molecule that is directly involved in hydrogen bonding with the amide

the polarization of hydration shell water molecules related with the hydration entropy(ΔS_{hydr}) of each anion.

Hydration entropy of an ion:
the degree of order or disorder created
by adding an ion to an aqueous solution

c
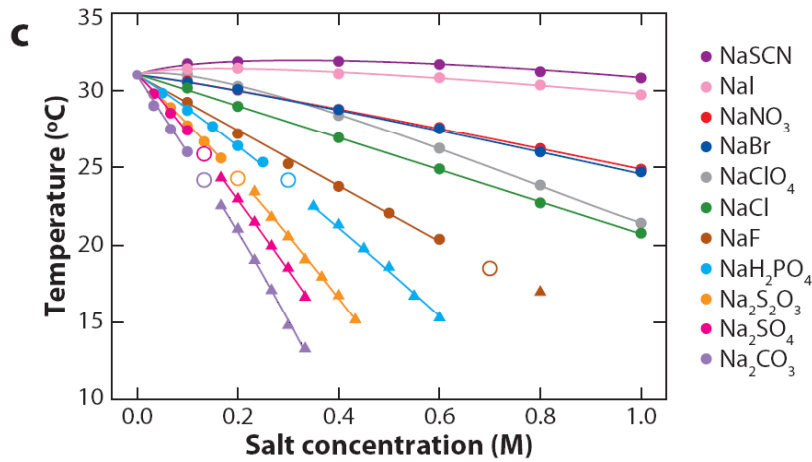
c) Plot of the lower critical solution temperature values for PNIPAM as a function of salt concentration between 0.0 and 1.0 M for a series of 11 Hofmeister salts. The triangular symbols for the kosmotropes are for the lower-temperature phase transition of a two-step phase transition. The higher-temperature phase transition for kosmotropes is not shown. The order of the curves (from top to bottom) corresponds to the color legend at the right of the figure. The solid lines are fits to the experimental data points.

The perturbation of PNIAPM's LCST by chaotropic anions was modeled :

$$T = T_0 + c\,[M] + \frac{B_{\max} K_A [M]}{1 + K_A [M]} \qquad \text{--(1)}$$

constant, a linear term, and a Langmuir isotherm

The perturbation of PNIAPM's LCST by kosmotropic anions was modeled :

$$T = T_0 + c\,[M] \qquad \text{--(2)}$$

T_0 : the LCST of PNIPAM in pure water
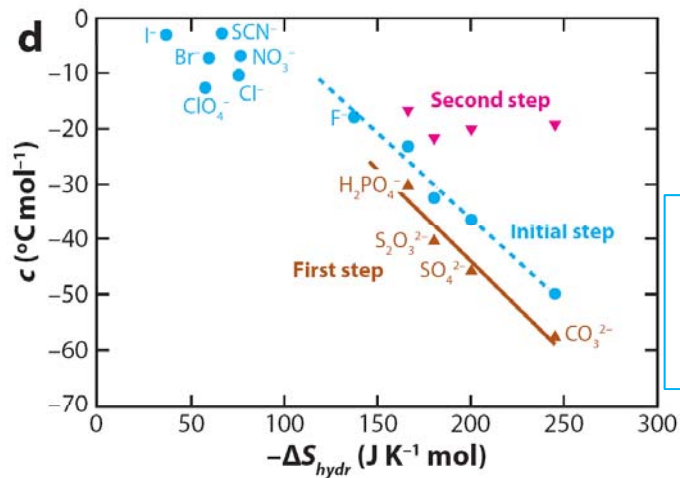[M] : the molar concentration of salt.
C: units of temperature/molarity
K_A : the apparent binding constant of the anion to the polymer
$B_{\max}$: the maximum LCST increase at saturation ion binding

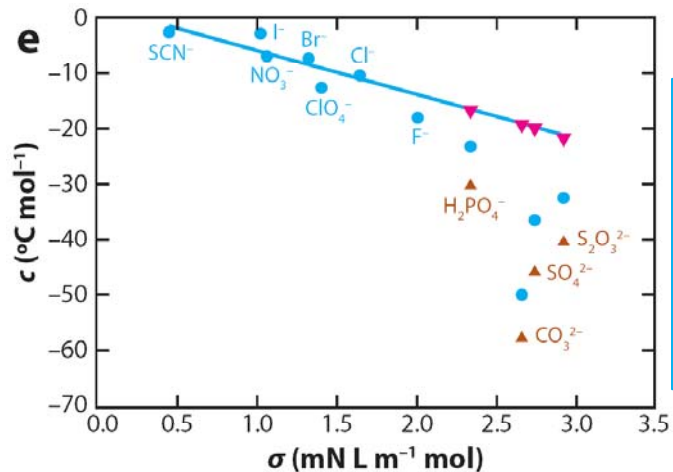lightscattering data show both a low and high temperature change

Beyond a certain concentration, however, a two-step transition is observed for the kosmotropic anions (CO_3^{2-}, SO_4^{2-}, $S_2O_3^{2-}$, $H_2PO_4^-$, and F^-),

The first step in the two-step phase transition has a steeper slope than that initially observed, whereas the second step has a shallower dependency on salt concentration.

d

(axes: c (°C mol^{-1}) vs $-\Delta S_{hydr}$ (J K^{-1} mol))

Labels: I⁻, SCN⁻, Br⁻, NO₃⁻, ClO₄⁻, Cl⁻, F⁻, H₂PO₄⁻, S₂O₃²⁻, SO₄²⁻, CO₃²⁻

Second step, Initial step, First step

the initial slope and the slope from the first step of the two-step phase transition correlate well with hydration entropy(ΔS_{hydr}) for kosmotropes.

Hydration entropy of anion: the degree of order or disorder created by adding an ion to an aqueous solution

e

(axes: c (°C mol^{-1}) vs σ (mN L m^{-1} mol))

Labels: SCN⁻, I⁻, Br⁻, NO₃⁻, Cl⁻, ClO₄⁻, F⁻, H₂PO₄⁻, S₂O₃²⁻, SO₄²⁻, CO₃²⁻

when the same c values are plotted against the surface tension increments of anions(σ)

the data for chaotropes and the second step of the two step phase transition are correlated,

(d) Plot of hydration entropy of the 11 anions versus the fitted c values from Equations 1 and 2. (e) Plot of surface tension increment of the 11 anions versus c values obtained from Equations 1 and 2. Hydration entropy and surface tension increment values were obtained from References 2, 79, 133, and 134.

strongly and weakly hydrated anions affect the LCST of PNIPAM by different mechanisms

- The chaotropes decrease the LCST via a surface-tension effect

- The kosmotropes decrease the LCST via the polarization of hydration shell water molecules and surface-tension effects

To measure the binding constants of chaotropic anions to the macromolecule in an isothermal fashion, Cremer and coworkers studied specific ion effects on interfacial water structure next to PNIPAM by VSFS
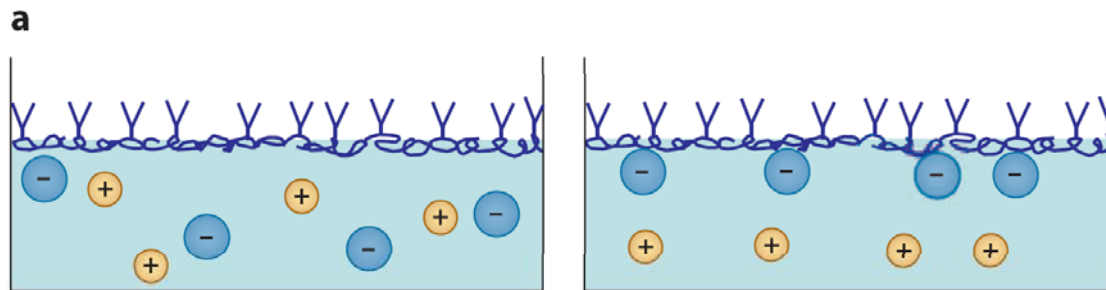
(a) Schematic diagram of anion adsorption onto a PNIPAM monolayer adsorbed at the air/water interface.
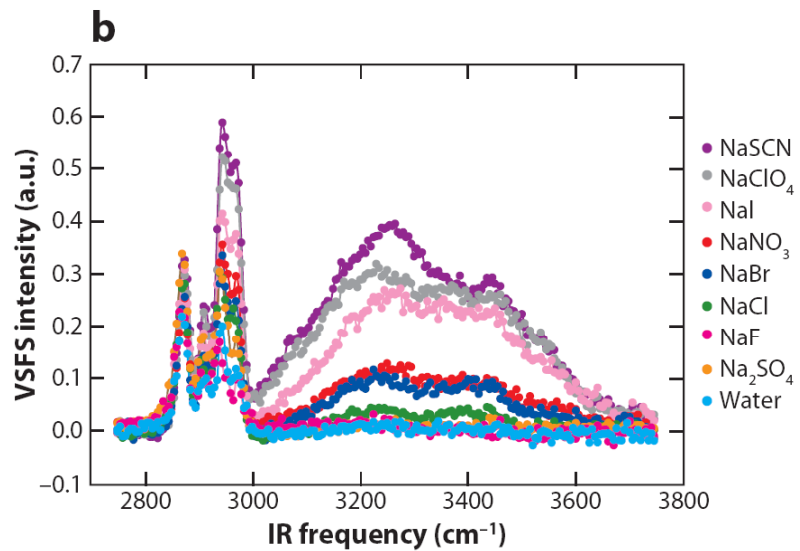
(b) Vibrational sum frequency spectroscopy spectra showing specific anion effects on PNIPAM adsorbed at the air/water interface. Each subphase contained 1 M of a given salt as indicated in the legend except for NaF and Na2SO4, which are measured with saturated solutions (~0.8 M forboth salts).

The intensities of both OH peaks (3200 ,3400 cm−1) followed the Hofmeister series:

$$SCN^- > ClO_4^- > I^- > NO_3^- \approx Br^- > Cl^- > pure\,water \approx F^- \approx SO_4^{2-}$$
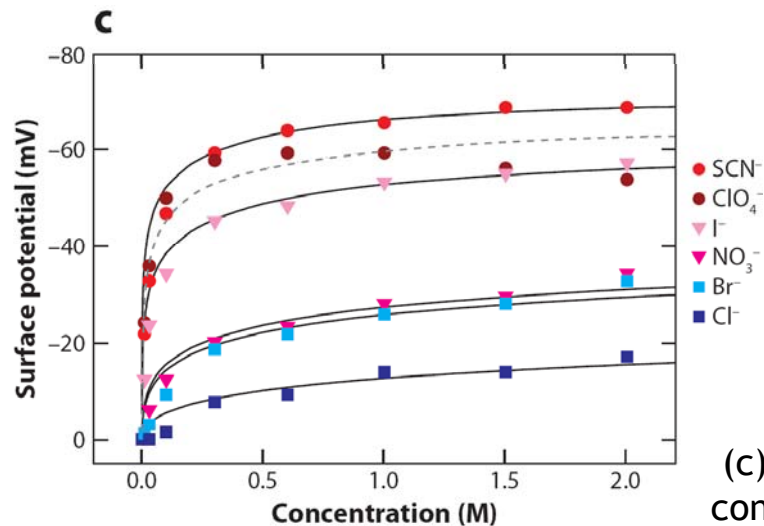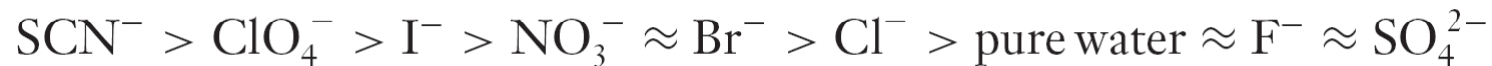
except for perchlorate, because of its larger size compared with other anions.

(c) Change in the surface potential as a function of salt concentration in the subphase. The curves represent fits using the Gouy-Chapman-Stern model.

2.2. Positively Charged Systems: Liquid/Liquid Phase Separation of Proteins

study the liquid-liquid phase separation of lysozyme
in the presence of chaotropic salts

below the phase-transition temperature:
→ formation micrometer-sized droplets of aggregated proteins.

a liquid-liquid phase separation:
→ the solution separates into two-coexisting liquid phases
(one rich in protein and one poor in protein)

The anion effects on the cloud-point temperature can be modeled

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

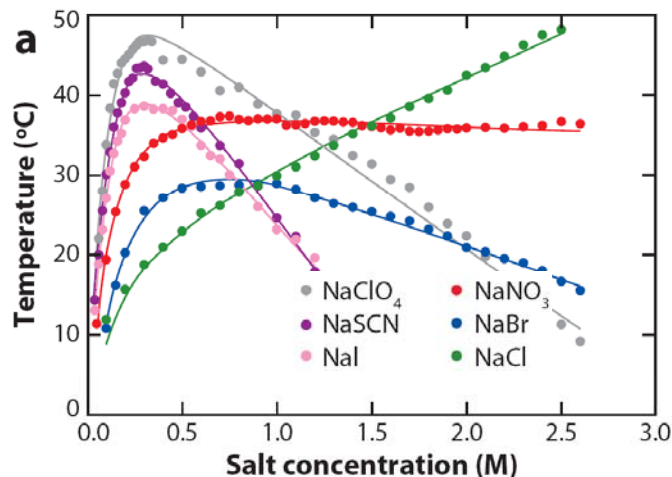T_0 is: the cloud-point temperature of lysozyme in the absence of salt
$[M]$: the molar concentration of salt
b : an electrostatic interaction factor that is related to the surface potential of lysozyme
$B_{\max}$: the maximum increase in the cloud-point temperature under saturation conditions.
Both $B_{\max}$ and b measure the effectiveness of a specific anion to screen the electrostatic repulsion between the charged macromolecules.
c : specific anion effects on the interfacial tension at the protein/water interface.

the system follows

- an inverse Hofmeister series at low salt concentration

- a direct Hofmeister series at high salt concentrations

(a) Cloud-point temperature data for the liquid-liquid phase transition of lysozyme as a function of anion type and concentration.
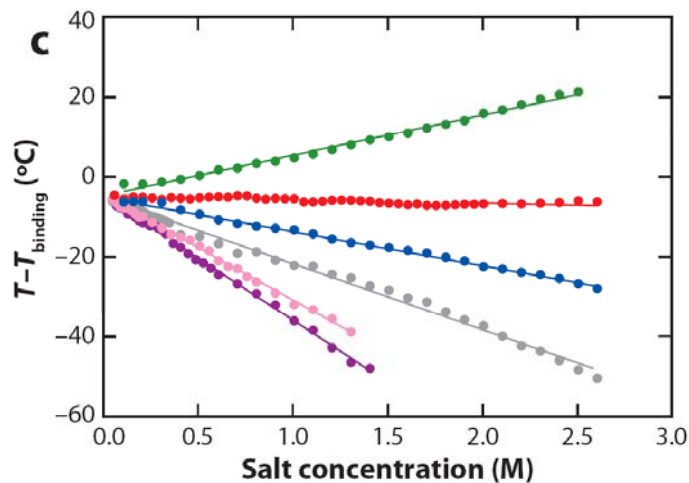All experiments were performed with 90.4 mg ml−1 lysozyme in 20 mM tris buffer at pH 9.4.
The solid lines are curve fits to Equation 3.
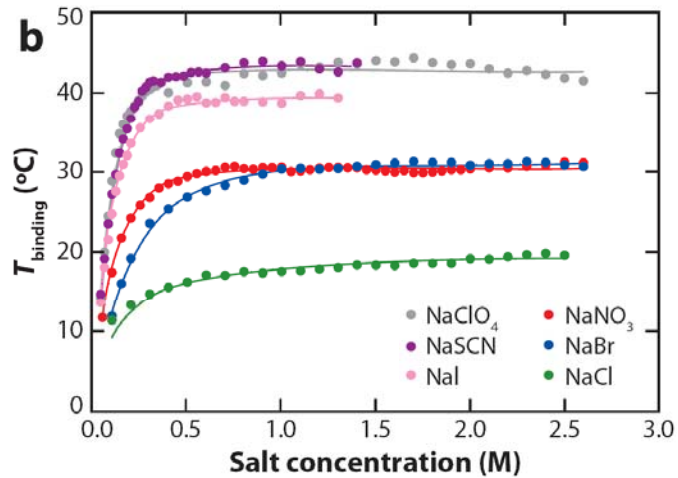
These residuals follow an inverse Hofmeister series from the most effective to least effective salting-out anion:
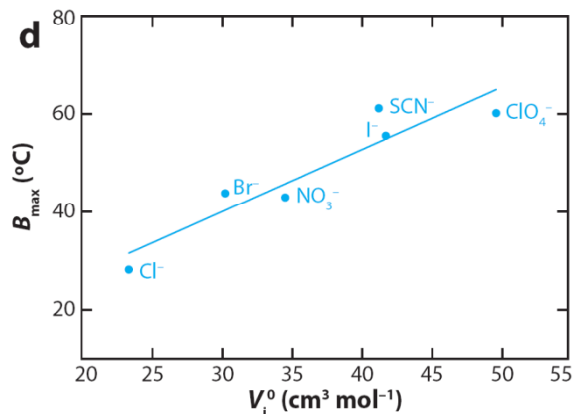
$ClO_4^- > SCN^- > I^- > NO_3^- > Br^- > Cl^-$
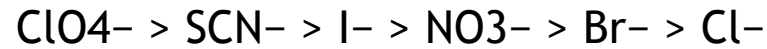
(b) The residual data after subtracting the linear portion contribution from Equation 3.

a direct Hofmeister series can be revealed by subtracting off the binding curve portion of the data in Figure 4a and plotting the linear residuals:

$Cl^- > NO_3^- > Br^- > ClO_4^- > SCN^- > I^-$.
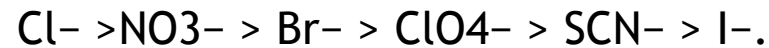
(c) The residual data after subtracting the binding isotherm contribution from Equation 3.
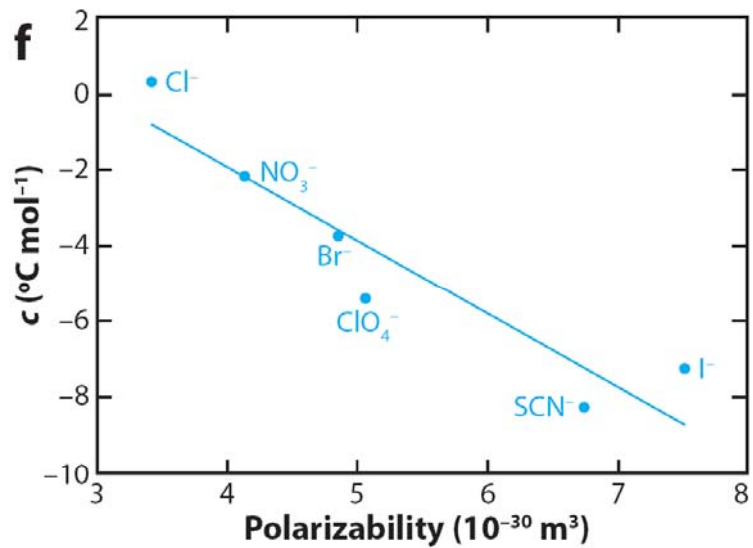
This series results from the differing abilities of the anions to associate with the positively charged lysozyme surface, and it is correlated with the size of the hydrated anions,
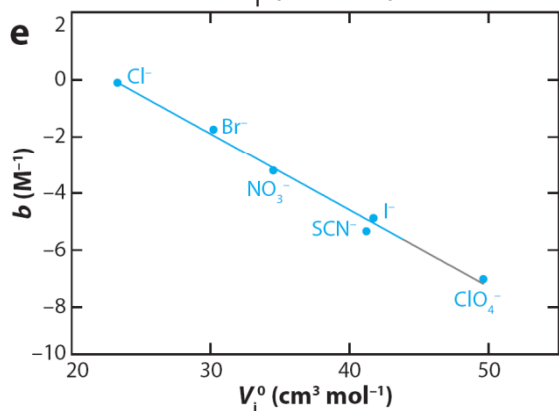
(d) Correlation of standard partial molar volumes of the anions versus theconstant B_{max}.
(e) Correlation of standard partial molar volumes for the anions versus the constant b.

(f) Plot of the polarizability of the anions versus the constant c.

an excellent correlation is found to the polarizability of the anions

SUMMARY POINTS

1. In uncharged systems, the anionic Hofmeister series can be explained on the basis of the direct interactions of anions with macromolecules and their immediately adjacent hydration shells. The series is related to the anions' hydration entropy, surface tension increment, and ability to bind to the macromolecules. Kosmotropic and chaotropic anions typically work through separate mechanisms.

2. Positively charged systems follow both inverse and direct Hofmeister series depending on salt concentration. At low salt concentrations, electrostatic interactions follow an inverse Hofmeister series, which is correlated with the size and hydration of the anions.
After the positive charges are neutralized, the systems obey a direct Hofmeister series,which is affected by interfacial tension at the protein/aqueous interface in the presence of chaotropic anions.