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Hofmeister anion effects on thermodynamics of caffeine partition between aqueous and cyclohexane phases

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Hofmeister Anion Effects on Thermodynamics of Caffeine Partition between

Aqueous and Cyclohexane Phases

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A Project Presented to

the Faculty of the Undergraduate

College of Science and Mathematics

James Madison University

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in Partial Fulfillment of the Requirements

for the Degree of Bachelor of Science

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by Bradley Allen Rogers

May 2014

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Abstract

The Hofmeister series, discovered in 1888, originally ranked ions in correspondence to their relative effects on protein solubility. The series has shown stunning consistency for the relative effects of specific ions on physical phenomena that occur in aqueous solution. Protein denaturation, micelle formation, and surface tension comprise some of the aqueous processes of significance for Hofmeister ion discoveries. Despite significant research efforts confirming series' ranking, the mechanisms that explain the observed effects are not well understood. This research project herein investigates the specific anion effects on the thermodynamics of caffeine partition between aqueous and cyclohexane phases. The Gibbs free energy, enthalpy, and entropy for caffeine partition are determined in the presence of 11 sodium salts in the aqueous phase. Correlations between thermodynamic data and anion physical properties provide insights into the mechanisms through which anions interact with caffeine and further affect caffeine distribution between two phases. Application of the mechanisms describing the modulation of caffeine partition by anions may help explain Hofmeister anion effects on a variety of behaviors in aqueous solution.

<div align="center">**Introduction**</div>

Chemistry of Water

The chemical definition of a solution is a homogeneous mixture composed of a single phase. A solution is comprised of two components namely the solute and the solvent. Water is arguably the most important solvent in all of chemistry for its biological relevance and fascinating properties. The water molecule comprised of one oxygen and two hydrogen atoms, H_2O, results in an approximately tetrahedral configuration where two hydrogen atoms and two lone pairs of electrons spread about the central oxygen atom. The electrostatic repulsion between the lone pairs pushes the two hydrogen atoms closer together yielding an H-O-H bond angle of 104.5°. The polarity of water contributes to its fascinating properties. Polarity is brought about by the greater electronegativity, or affinity for electrons, of oxygen versus hydrogen atoms and ultimately results in a separation of charge throughout the molecule known as a dipole. The partial charges present on atoms are represented by greek symbol $\delta^{+/-}$. The vector summation of the two O-H bond dipoles and the two O (lone pair) dipoles of water yield a new vector known as the molecular dipole moment. Depictions of bond dipoles and dipole moments for water are summarized in Figure 1.

Given the discussed structural properties of a water molecule, the intermolecular forces present in solution can be addressed. Hydrogen bonding is an important intermolecular force
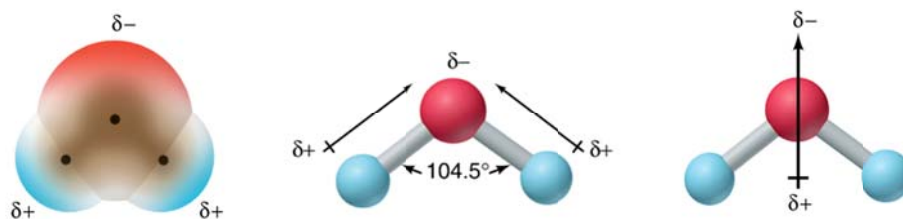
Figure 1. Electron distribution in H_2O molecule displaying partial charge, bond dipoles, and net dipole or dipole moment. This figure is obtained from ref.1.

characterized by the attractive interaction between a hydrogen atom attached to an electronegative atom (nitrogen, oxygen, or fluorine). Water exhibits extensive hydrogen bonding network due to its ability to donate two hydrogen atoms as well as providing two lone pairs as H-bond acceptors resulting in four potential hydrogen bonds. Polarity and hydrogen bonding account for various physical properties including a high boiling point, high enthalpy of vaporization, and large heat capacity. An important concept for the scope of the project presented herein is water's ability to act as a solvent. Solvation is a factor largely attributed to the previously discussed properties of structure, polarity, and hydrogen-bonding capability. When solvation occurs in water, the polar or ionic solutes dissociate from each other and associate with the dipole moment of water molecules resulting in a solution. This concept is illustrated in Figure 2 for dissolution of a salt compound. The presence of ions in aqueous solution have been observed to affect an array of physical, chemical, and biochemical processes on the macroscopic scale. The project presented herein will include an overall discussion of the scientific communities' approach to elucidating a mechanism on the molecular scale and a model system to probe this phenomenon.
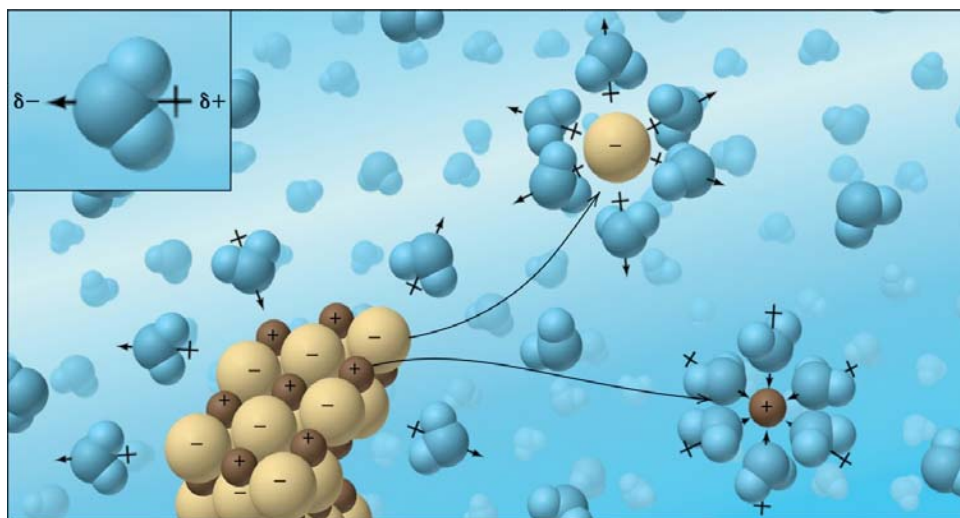
Figure 2. An ionic compound dissolving in water. This figure is obtained from ref. 1.

The Hofmeister Series

The Hofmeister series is comprised of an ion ranking in accordance to relative influence on aqueous processes. The series, discovered by Franz Hofmeister in 1888, ranked the ions by their relative effects on protein solubility.[2, 3, 4] Cationic and anionic series were developed with more pronounced effects observed for anions. Since its discovery, many research efforts have confirmed the Hofmeister series ranking for an expanse of aqueous phenomena including protein denaturation,[5, 6, 7] enzyme activity,[8, 9, 10, 11, 12] protein-protein interaction,[13, 14, 15] surface tension,[16, 17] polymer aggregation,[18] and micelle formation.[19, 20, 21] The anionic Hofmeister series is shown in Figure 3 by the relative specific ion's ability to affect processes in aqueous solution.[22] Well-hydrated anions on the left, known as Kosmotropes, tend to "salt-out", precipitate protein from solution and stabilize the folded structure of protein. Weakly hydrated chaotropic anions on the right behave in opposite ways. The central chloride ion is serves as the dividing line between these two types of behaviors. Despite the significant ranking confirmations, the mechanisms explaining the observed effects remain ambiguous.

The original mechanistic propositions for Hofmeister effects concern specific ion

Hofmeister Series

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

↑↑↑ 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

Figure 3. Anionic Hofmeister series. This figure is reproduced from ref. 22.

contribution to hydrogen-bonding network of bulk water. These bulk water mechanisms coined the terms chaotropes and kosmotropes describing the destabilization, "structure breakers" or stabilization, "structure makers" of the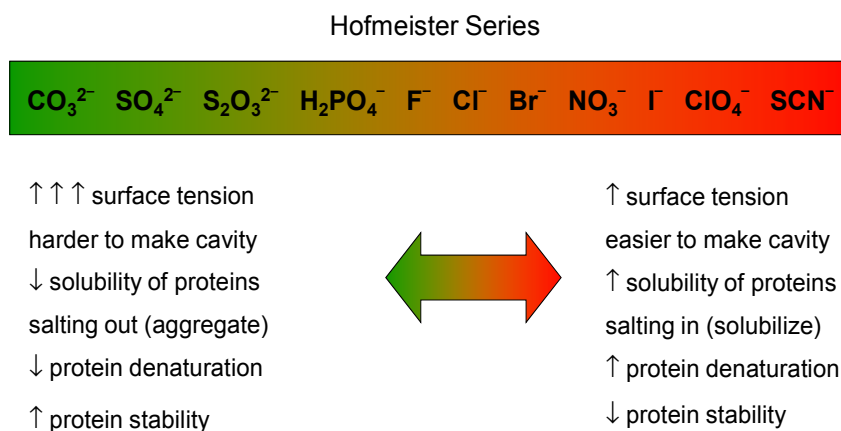 solution's hydrogen bonding, respectively.[23] This mechanism was widely accepted and used to rationalize observed effects in aqueous solutions throughout the last century. However, recent studies have cast doubt upon the notion that ions can alter hydrogen-bonding networks outside of the first solvation shell.[24, 25, 26, 27] Despite the shortcomings of the bulk water mechanism the terms chaotropes and kosmotropes have endured to describe ions' generalized effects on aqueous processes.

Important investigations concerning the notion of ion influence on the bulk hydrogen-bonding network of water have been conducted by Bakker and co-workers.[24, 28, 29, 30, 31, 32] The methods of these experiments concern orientational correlation times for water molecules in various salt solutions by measurement using femtosecond two-color pump-probe spectroscopy. Through sodium anion solutions analyses, it was discovered that the relaxation correlation time for water molecules was indeed slower in the first hydration shell; however, this effect was not observed in bulk solutions farther from the ions even at high salt concentrations.[24] In addition to spectroscopic methods, thermodynamic studies have investigated the Hofmeister ion effects on water's structural characteristics. A study was performed by Pielak and co-workers using pressure perturbation calorimetry, which measures the heat transfer resulting from a pressure change above sample.[33] Seventeen solutes known for stabilizing or denaturing effects were chosen for the analysis. The results of the experimentation afforded poor correlation between the known effects on protein stability and the bulk water structure.[33] The recent surge of publications discrediting the previously accepted bulk water theory has served to rekindle the mystery concerning mechanisms behind Hofmeister effects. This driving force has spawned significant

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research efforts with an ultimate goal to elucidate the mechanisms through which ions interact with macromolecules. The concepts of bulk water structural effects and direct interactions between ions and macromolecules are illustrated in Figure 4 below.
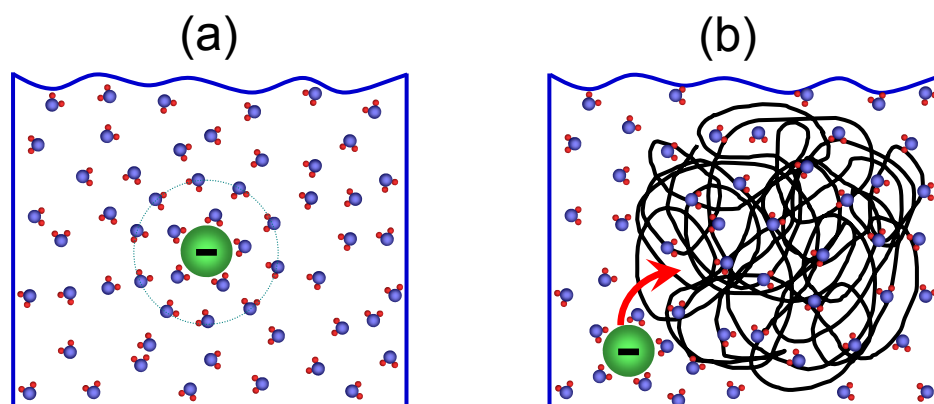
Figure 4. Anions and water structure. (a) Organized or structured water beyond an anion's first hydration shell necessary for structure making and breaking effects of bulk water mechanism. (b) The direct interaction of an anion with a macromolecule in aqueous solution, where the macromolecule is represented by the black lines. Size of the anion is representative of sulfate SO_4^{2-} ion relative to the water molecules. The macromolecule is not drawn to a general scale. This figure is reproduced from ref. 22.

Our Model System

Herein, we use a simple model as illustrated in Figure 5a, the partition of caffeine between aqueous and cyclohexane phase in the presence of salts, to probe the mechanisms of the Hofmeister series. The density of cyclohexane and water at 25 °C are 0.7781 and 0.997 g/mL, respectively, resulting in a system where the organic layer resides above the aqueous. Caffeine, the transfer molecule, is a highly polar molecule and thus soluble in water, specifically 16 mg/mL at room temperature.[34] The structure of caffeine displayed below as a bond-line structure representation in Figure 5b. Caffeine's structure is classified as a methylated xanthine. The xanthine core contains a two fused ring structure consisting of a 6-membered pyrimidinedione and 5-membered imidazole. The pyrimidinedione contains two amide functional groups that

primarily exhibits zwitterionic character, as demonstrated by significant resonance contributions where the nitrogen carbon bond exhibits significant double bonded character. Thus, each of the six atoms within the pyrimidinedione ring system are sp^2 hybridized and correspondingly planar. This characteristic, in combination with the planar characteristics of the imidazole, affords an aromatic structure containing 10 π-electrons according to Huckel's rule. [35] A bond-line representation of caffeine with the common atom numbering system is provided in Figure 5c. Caffeine exhibits both polar and hydrophobic characteristics, which affords significant solubility in the aqueous and cyclohexane phases. Caffeine's characteristic absorbance at 273 nm allows the detection of its concentration by UV-Visible spectroscopy. In addition to its use as a transfer molecule in the partition coefficient model, caffeine has significant biological relevance due to its well-known pharmaceutical application as a mild stimulant. [36, 37, 38] It has been observed that caffeine, as well as the di and mono methylated xanthines, distribute between aqueous-organic phases as a function of Hofmeister salt presence.[39]

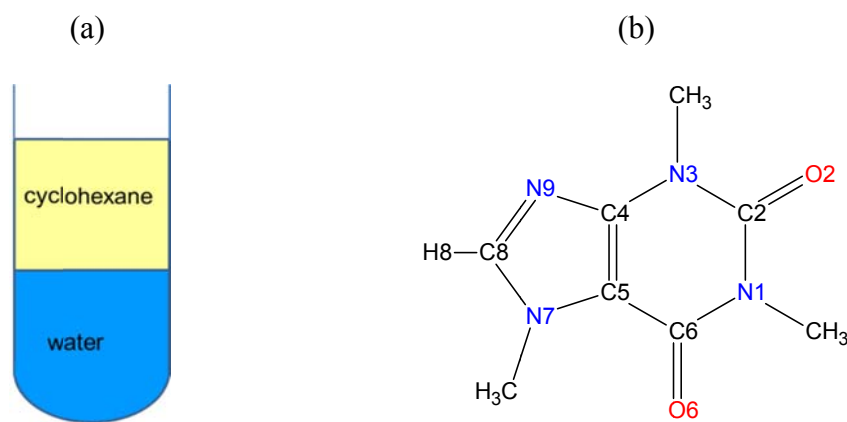**Figure 5.** (a) Illustration of the cyclohexane-aqueous system used in the caffeine partition in the presence of Hofmeister anions. (b) Structure of caffeine, the transfer molecule, in the experimental partition coefficient model exhibiting labeled atoms, except the three methyl substituents. Highly electronegative atoms oxygen and nitrogen are provided in red and blue, respectively, which contribute to caffeine's high polarity.

When assessing the partition of caffeine it is necessary to consider its hydration environment in the aqueous phase as well as the cyclohexane phase. Interactions between solvating water molecules and caffeine in the aqueous phase are considered to highly complex as has been observed for many other large, polyatomic solutes. Molecular dynamic simulations suggest that the carbonyl oxygen atoms O2 and O6 as well as the lone pair baring nitrogen atom N9 provide highly polar atoms, which may participate in hydrogen bonds with hydrating water molecules.[40] It should be noted that the pK_a of caffieine, 0.6, indicates caffeine's ability to act as a weak base and acquire a proton. [34] Weak basicity can be attributed to the unfavorable electrostatic repulsion resulting from proton acquisition. Under the experimental conditions employed herein, caffeine will exist in its basic form. In short, lone pairs of the two carbonyl oxygen atoms and N9 nitrogen should participate in significant hydrogen bonding interactions. Computational data has provided evidence for pseudo hydrogen bonding character in the proton H8 attached to the sp^2 hybridized carbon C8.[40] Similar proton hydrogen bonding behavior between that of an aliphatic hydrogen and true hydrogen bonding proton has been observed for topologically and chemically similar protons of nucleic acid purines.[39] These polar atoms serve to increase caffeine solubility in the aqueous phase.

A partition coefficient, P, is an equilibrium constant representing the extent to which a target molecule is distributed between two phases. [41] In the partition model, the transfer of caffeine, is an equilibrium process in which the molecule seeks the distribution of lowest energy between the two phases. The partition coefficient is governed by the equilibrium represented as below:

$$Caffeine\ (aq) \rightleftharpoons Caffeine\ (org) \qquad\qquad \text{Equation 1}$$
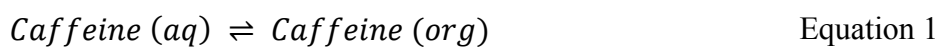
The partition coefficient, like other equilibrium constants, is calculated by a ratio of products to reactants, specifically caffeine concentrations in the organic to the aqueous phases shown in Equation 2.

$$P = \frac{[X(organic)]}{[X(aqueous)]} = \frac{c_{OR}}{c_{AQ}}$$

Equation 2

The partition coefficient can thus serve as a model for thermodynamic studies, where a transfer of caffeine molecules into the organic layer at a specific temperature yields free energy value. Free energy, formally known as Gibb's Free Energy, is a thermodynamic value representing spontaneity or equilibrium shifts for a process of interest. At equilibrium, Gibbs free energy for caffeine transfer is equal to zero. Gibbs free energy for caffeine transfer under standard condition, $\Delta_{transfer}G^o$, is calculated by Equation 3:

$$\Delta G^o_{transfer} = -RTln(P)$$

Equation 3

where R is the gas constant (8.314 J mol^{-1} K^{-1}), T is the temperature (K), and P of the partition coefficient of caffeine between the aqueous and cyclohexane phases. Enthalpy, $\Delta_{transfer}H^o$, a measure of heat transfer, and entropy, $\Delta_{transfer}S^o$, a measure of changes to system, are related to $\Delta_{transfer}G^o$ Equation 4.

$$\Delta G^o_{transfer} = \Delta H^o_{transfer} - T\Delta S^o_{transfer}$$

Equation 4

This linear relationship provides an experimental means to determine enthalpy and entropy by extracting the y-intercept and negative slope respectively from a plot of Gibbs free energy versus temperature. Heat transfer corresponding to enthalpy data bare interpretations where negative values represent heat release, exothermic, and positive values represent heat consumption, endothermic. Entropy provides a measure of system order where positive values correlate to increased disorder of a system and negative values for order.

Mechanistic inferences are then explored by correlation of thermodynamic quantities to various physical properties of ions in solution. Polarizability and hydration shell characteristics exhibiting correlation with ion binding as well as studies for the partitioning of poorly hydrated ions at the air-aqueous interfaces.[16, 17] Many anion and cation physical properties are reversed for observed Hofmeister effects suggesting that oppositely charged species may operate through different mechanisms.[42] Additionally, different physical properties are believed to have varying degrees of significance for the mechanisms of chaotropic and kosmotropic ions.[42] The caffeine partition model provides a system in which correlations may be applied to probe the ever elusive mechanisms of the Hofmeister series.

Experimental

UV-Visible Spectroscopy Analysis

Method development for determining caffeine concentration in solution was achieved by preparation of a calibration curve, Beer's Law plot. Caffeine concentrations were prepared ranging from 0 to 0.2 mM in deionized water, followed by subsequent absorbance measurement using an Agilent 8453 UV-VIS diode array spectrophotometer. Wavelength of maximum absorbance, λ_{max}, at 273 nm, were plotted as a function of caffeine concentration affording a linear regression known as a Beer's Law plot. The molar extinction coefficient, slope of the described plot, was obtained and used for conversion of absorbance values to units of caffeine concentration.

Partition Coefficient Preparation

Caffeine partition experiments begin with preparation of the aqueous phase. Aqueous phases were prepared with 10 mM caffeine and the desired salt concentration using gravimetric

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methods. It should be noted that several hygroscopic salts known to absorb moisture from the atmosphere were baked in an oven at 100 °C and subsequently weighed for solution preparation (i.e. $NaNO_3$, NaBr, NaI, NaSCN, and $NaClO_4$). Biphasic systems were created by combining 3 mL of the caffeine-salt solution and 3 mL of cyclohexane in a centrifuge tube. The system was agitated using the shake-flask method for 1 minute followed by an equilibration period of 20 minutes. Analysis of the equilibrated caffeine partition was carried out by organic layer extraction, involving the careful acquisition of the top-most 2.5 mL of the cyclohexane phase. Subsequent UV-VIS analysis, using quartz cuvettes, was performed on the extracted organic phase to determine absorbance values at a wavelength of 273 nm.

Procedural Development

Two extraction procedures were assessed in an effort to maximize precision of the partition coefficient measurements. All extractions were performed using disposable glass pipettes. The dual phase analysis technique employed two separate extractions. The first extraction, followed by transfer to a clean centrifuge tube, obtained 2.5 mL of the cyclohexane phase. The remaining organic phase was then removed from the system. The aqueous phase extraction obtained 2.5 mL of the aqueous layer. Aqueous extract was transferred into a separate centrifuge tube and a 1/50 dilution was performed. Extractions were subject to UV-Vis analysis and ultimately free energies were obtained from the determined partition coefficient. A second procedure, single-phase analysis, only used the determined organic phase concentration from the first extraction. This value was used for an aqueous phase concentration determination by difference calculation from the initially prepared 10 mM aqueous concentration. The two procedures were assessed by comparison of R^2 values corresponding to the slopes of free energy vs. salt concentration plots using the two described calculations. The second procedure was

employed in this study. Equilibration time was assessed by 1 M of three sodium anion aqueous phases used in preparation of the biphasic systems. Single-phase extractions were performed at a range of equilibration times, between 0 and 60 minutes followed by UV-Vis spectral analysis. The anions chosen for equilibration determination included Sulfate, Chloride, and Perchlorate, providing an expansive range over kosmotropic to chaotropic ions respectively within the anionic Hofmeister series. It was found that 20 min equilibration periods yielded consistent absorbance values in the presence of all Hofmeister sodium salts.

Concentration Dependence

Caffeine partition as a function of anion concentration was assessed with the biphasic system containing aqueous phases of 10 mM caffeine and variable salt concentrations ranging from 0 to 2 M. Sodium salts concentration variations were prepared for each of the eleven Hofmeister series anions. Free energy calculations were plotted as a function of anion concentration to yield thermodynamic coefficients describing the extent of ion concentration on caffeine distribution.

Temperature Dependence

Temperature dependence of caffeine partitioning was also determined. Biphasic system with aqueous phases containing 10 mM caffeine concentrations and 0.5 M or 1.0 M sodium salt concentrations were prepared. Partition coefficients were calculated from the prepared systems in water bath temperatures ranging from 298 to 319 K. Free energy calculations were plotted vs. the corresponding temperature yielding enthalpy and entropy for the caffeine partition.

Results and Discussion

UV-vis Analysis

The wavelength of maximum absorbance, λ_{max}, was found at 273 nm for aqueous

solutions of caffeine. A plot of absorbance vs. wavelength for 10 mM caffeine in water is shown

in Figure 6a. The molar extinction coefficient of caffeine, *a*, was determined to be 9725 $M^{-1}cm^{-1}$

from the slope of the absorbance vs. caffeine concentration plot shown in Figure 6b.

(a)   (b)
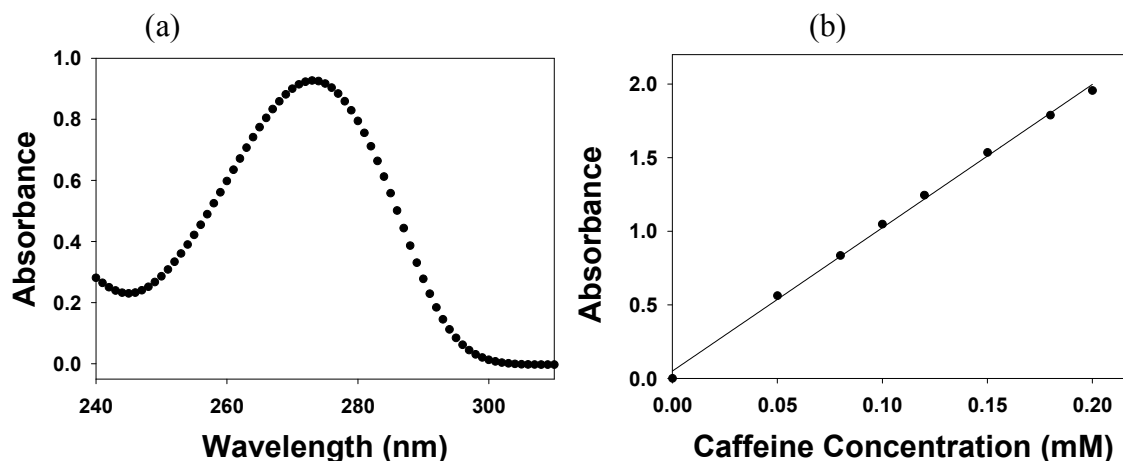
Figure 6. (a) UV-Visible spectrum for the analysis of 10 mM caffeine in water. (b) Absorbance of caffeine at 273 nm as a function of concentration, exhibiting a slope of 9725 $M^{-1}cm^{-1}$.

The concentration of caffeine in the organic phase (c_{OR}) is determined by using the

absorbance at 273 nm according to Beer's Law shown in Equation 5.

$$c_{OR} = \frac{A}{ab} \hspace{4cm} \text{Equation 5}$$

where *A* is the absorbance of caffeine and *b* is the cuvette cell path length (*b* = 1 cm). Aqueous

caffeine concentration was determined by subtracting the determined organic phase

concentration, c_{OR}, from the original 10 mM concentration, Equation 6, based off the assumption

that total caffeine within the system should be equal to the initial concentration in the aqueous

phase.

$$c_{AQ} = [10\ mM] - c_{OR} \qquad\qquad \text{Equation 6}$$

Using the caffeine concentration of each phase the partition coefficient, *P*, can be calculated

from a ratio of caffeine concentration in the organic to aqueous phase, represented in Equation 2.

Determining the partition coefficient, describing the extent of caffeine distribution into the

organic phase, allowed for the calculation of Gibbs Free Energy for caffeine transfer, $\Delta_{trs}G^o$, by

using Equation 3.

Gibbs Energy of Caffeine Partition vs. Salt Concentration

Caffeine, 10 mM, partitioning between the aqueous-cyclohexane system was investigated

as a function of sodium salt concentrations, between 0 and 2 M, for 11 anions in the Hofmeister

series. Exceptions for this range exist for $NaSO_4$, $NaCO_3$, and NaF due to their low solubility.

Free energy of caffeine transfer, $\Delta_{trs}G^o$, as a function of ion identity and concentration were fitted

with a linear regression curve as shown in Figure 7. The slopes, termed as *c* in kJ mol^{-1} M^{-1},

provide a quantitative description for caffeine distribution as a function of specific anion

concentration. The abstracted *c* values together with the physical properties of anions are

compiled in Table 1. Fitted *c* values contain important information describing an ion's effect on

caffeine distribution as a function of concentration. Positive values correspond to an ion's ability

to increase caffeine solubility in the aqueous phase of the system. Negative values correspond to

decreased aqueous solubility and the ability to push caffeine molecules into the cyclohexane

phase. These results are consistent with previously determined aqueous effects of chaotropic and

kosmotropic anions to solubilize (salt-in) or precipitate (salt-out) moieties from aqueous solution,

respectively. The determined values follow a direct Homeister series exhibiting increasingly

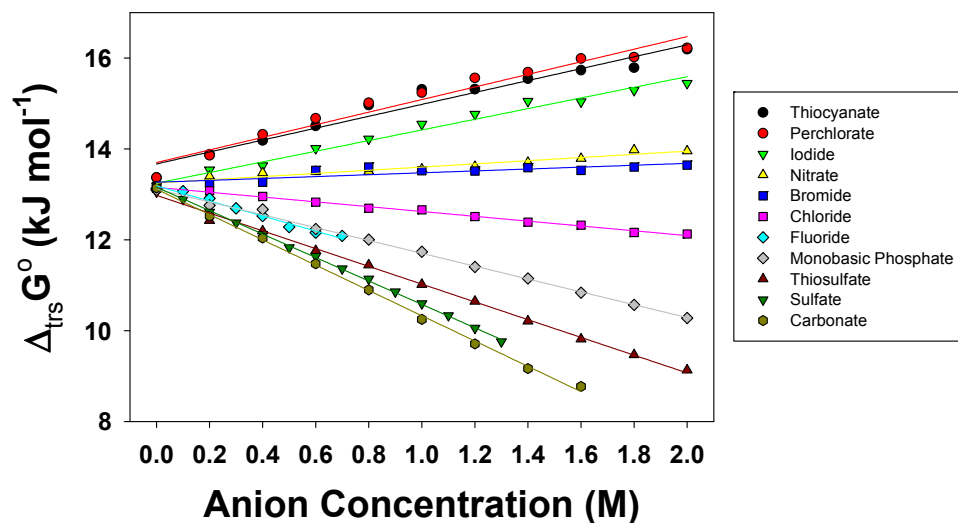negative slopes from chaotropic to kosmotropic anions. Visualizing the described trend across

Figure 7. Gibbs free energy of caffeine transfer between cyclohexane-aqueous phases versus sodium salt anion concentration. The plot summarizes the trends for each anion of the Hofmeister series.

Table 1. Fitted c values and physical properties of anions. Units for physical properties include c (kJ mol^{-1} M^{-1}), V_i^o (cm^3 mol^{-1}), *Polarizability* (Å^3), $\Delta_{hydr}G^o$ (kJ mol^{-1}), $\Delta_{hydr}S^o$ (J mol^{-1} K^{-1}), $\Delta_{hydr}H^o$ (kJ mol^{-1}), *Water structure* (ΔH-Bonds),*Viscosity B-coefficient* (dm^3 mol^{-1}), $\sigma_{air-water}$ (mN m^{-1} mol^{-1}), *Hydration Number* (Stokes Radius, pm). Values not found in the literature were noted by the symbol, N/A.

Anion	c	V_i^o	Polarizability	$\Delta_{hydr}G^o$	$\Delta_{hydr}S^o$	$\Delta_{hydr}H^o$	ΔG_{HB}	B-coefficient	σ	Hydration Number
SCN$^-$	1.31	41.2	6.739	-287	-66	-311	-0.82	-0.022	0.45	-0.8200
ClO$_4^-$	1.39	49.6	5.062	-214	-57	-246	-1.01	-0.058	1.4	-1.0100
I$^-$	1.17	41.7	7.512	-283	-36	-291	-1.09	-0.073	1.02	-1.0900
NO$_3^-$	0.35	34.5	4.134	-306	-76	-312	-0.68	-0.045	1.06	-0.6800
Br$^-$	0.21	30.2	4.852	-321	-59	-336	-0.80	-0.033	1.32	-0.8000
Cl$^-$	-0.53	23.3	3.421	-347	-75	-367	-0.61	-0.005	1.64	-0.6100
F$^-$	-1.66	4.3	0.876	-472	-137	-510	0.08	0.127	2.00	0.0800
H$_2$PO$_4^-$	-1.41	34.6	5.787	-473	-166	-522	-0.10	0.34	2.33	-0.1000
S$_2$O$_3^{2-}$	-1.95	38.2	9.196	N/A	-180	N/A	-0.43	N/A	2.90	-0.4300
SO$_4^{2-}$	-2.58	25.0	5.466	-1090	-200	-1035	-0.21	0.206	2.73	-0.2100
CO$_3^{2-}$	-2.79	6.7	4.539	-479	-245	-1397	0.28	0.294	2.60	0.2800

the series is assisted through correlation to an equal spacing of kosmotropic and chaotropic characteristics as shown in Figure 8.

Physical Property Correlations and Mechanistic Inference

Previous work on aggregation of polymers has suggested that chaotropes and kosmotropes produce observable Hofmeister effects through different mechanisms.[18] An effective technique for mechanistic exploration involves the correlations of observable
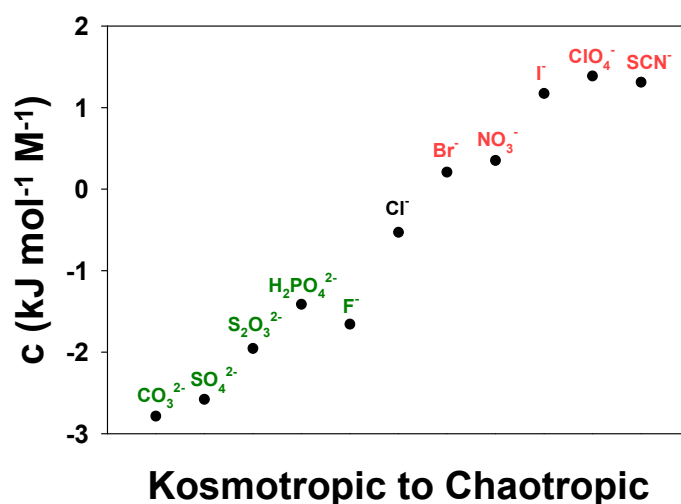
Figure 8. Relative c coefficient trend across the kosmotropic to chaotropic spectrum of the Hofmeister series.

thermodynamics to the physical properties of ions. Chaotropic anions are usually large and exhibit soft characteristics. Partial molar volume, V_i^o, is a physical property of anions that is interpreted as the volume of a hydrated ion. Extrapolation of partial molar volume involves changes in apparent volume as function of solute addition. Chaotropic softness is grounded by a physical constant known as polarizability. Polarizability is a characteristic describing the extent to which an ion may experience electron cloud distortion by the presence of an external electric field. This distortion of an ion's normal charge distribution effectively

induces temporary dipoles. Ion size and polarizability are related to each other due to the increasingly weak nature of electron-nucleus attraction in orbitals of large ions. Together, large and soft qualities of chaotropic ions afford interesting solvation effects in which the extent of hydration is inversely proportional to size and polarizability. In other words, low charge densities present in large, soft ions bring about weaker interactions with solvating water molecules. Gibbs free energy of hydration of a particular ion, $\Delta_{hydr}G^o$, represents the extent to which the ion is hydrated. Another parameter describing an ion's solvation is hydration number, which denotes the number of water molecules associated in its hydration shell by correlation to ion radius. The large, soft, and poorly hydrated nature of chaotropic ions exhibited correlation to the c values. In contrast, the c values for kosmotropic anions showed poor correlation to size, softness, and hydration properties. Correlating properties, which directly and indirectly describe poor hydration of chaotropic ions, are summarized in Figure 9. The correlations shown in Figure 9. support the ideology in which chaotropic anions produce 'salting-in" effect through a different mechanism than kosmotropic "salting-out". Polarizability and hydration number display similar characteristics with a thiocyanate and perchlorate outlier in the respective plots. Significant research efforts have suggested that large, soft chaotropic anions show an increased affinity to partition at the air-water and aqueous-hydrophobic interfaces. [17] This affinity is proportional to the energetic investment of partial dehydration of an ion's hydration sphere. Ions with small free energy of hydration should possess the ability to partially dehydrate. Partial dehydration allows chaotropic ions to equilibrate between bulk solution and interfacial regions within solution. Combination of partitioning affinity and poor hydration correlations suggest an ion's ability to shed the hydration shell and interact directly with caffeine producing the observed solubility
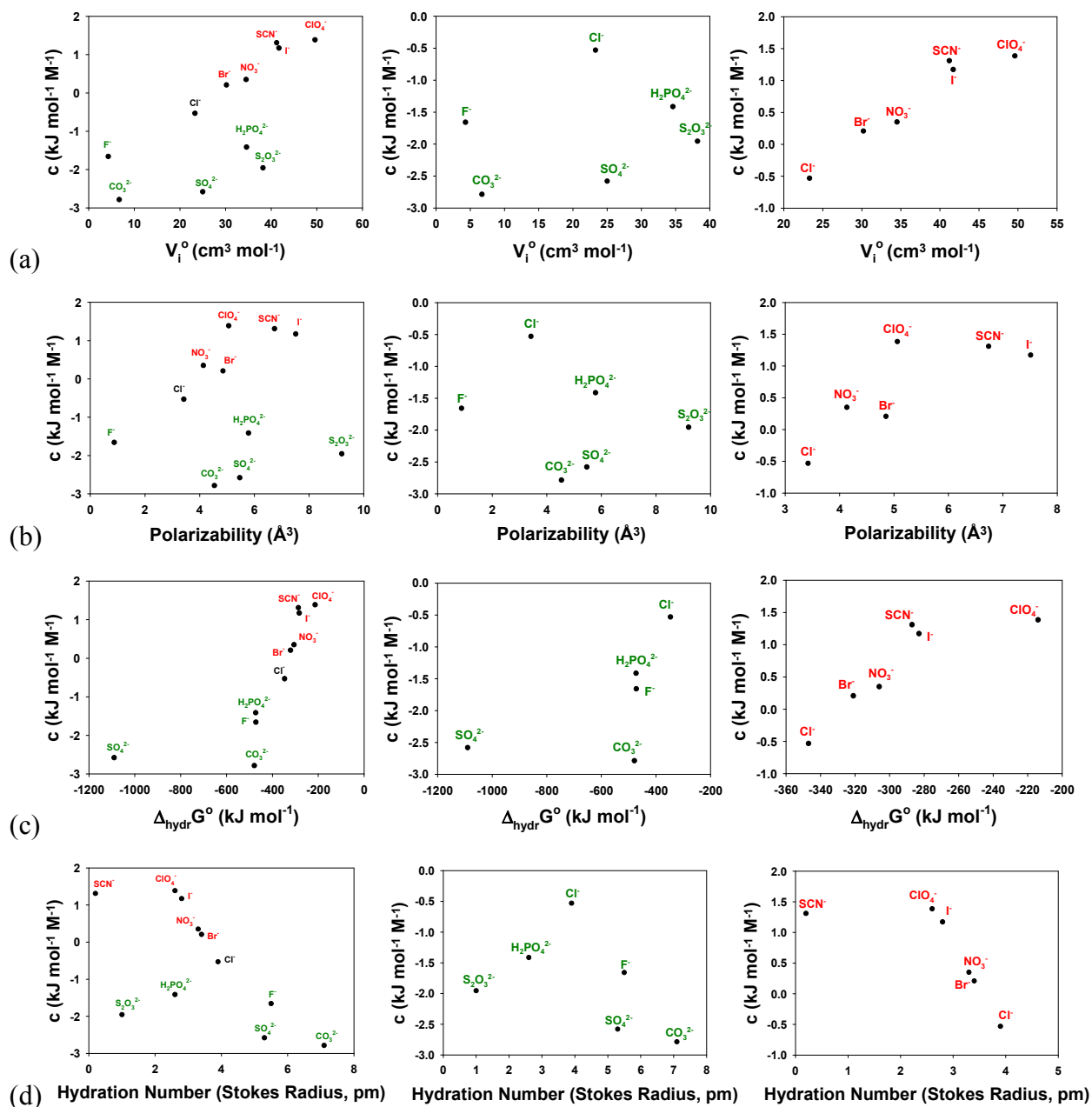
Figure 9. Concentration coefficient correlations to specific anion physical properties. (a) partial molar volume (b) polarizability, (c) free energy of ion hydration, and (d) hydration number. Correlations are shown for the entire Hofmeister series, kosmotropes, and chaotropes from left to right for each property.

increase. Herein, it is proposed that chaotropic ions may partition from bulk water to the water-caffeine interface, particularly at hydrophobic methyl groups, partially positive nitrogen atoms, and the electron poor aromatic pi system above and below the fused xanthine rings.

Kosmotropic anions, exhibiting high charge density, produce a different set of hydration

properties in aqueous solution that strongly correlate to observable Hofmeister effects. Namely,

strong ion-solvent interaction and a highly ordered hydration shell characterize kosmotrope

solvation. The B-coefficient is a physical parameter related to ion-solvent interaction in viscosity

studies for specific ion solutions. The kosmotrope hydration sphere is a highly ordered structure

of solvated water molecules. Order is quantified through the entropy of hydration, $\Delta_{hydr}S^o$, where

increasing values correlate to more ordered hydration shell. Both the B-coefficient and entropy

of hydration quantitatively describe the strong, ordered ion-solvent interaction present in

kosmotropic anion hydration. Specific kosmotropic anion effects on caffeine partition exhibited

excellent correlation with entropy of hydration and viscosity B-coefficients as summarized in

Figure 10. Trends of ion hydration entropy and B coefficients exhibited strong correlations to

kosmotropic anions and poor correlation to chaotropes. It is suggested that increased order of ion

hydration shells and strong ion-solvent interaction ultimately reduce caffeine solubility in the

aqueous phase. The proposed mechanism incorporates an entropy driven process in which tightly

bound hydration shells of kosmotropes proportionally reduce the number of water molecules

participating in solvation at the caffeine molecule surface. In short, kosmotropic anions reduce

caffeine solubility by strong ion-solvent interactions, which serve to disrupt favorable hydration

forces necessary for caffeine solvation. Affected surface sites of caffeine include caging

networks at hydrophobic methyl substituents as well as hydrogen bonding at carbonyl oxygens

and N9 nitrogen.

In addition to the correlations suggesting separate mechanisms, several physical

properties displayed uniform trends across the Homeister series implying contribution to both

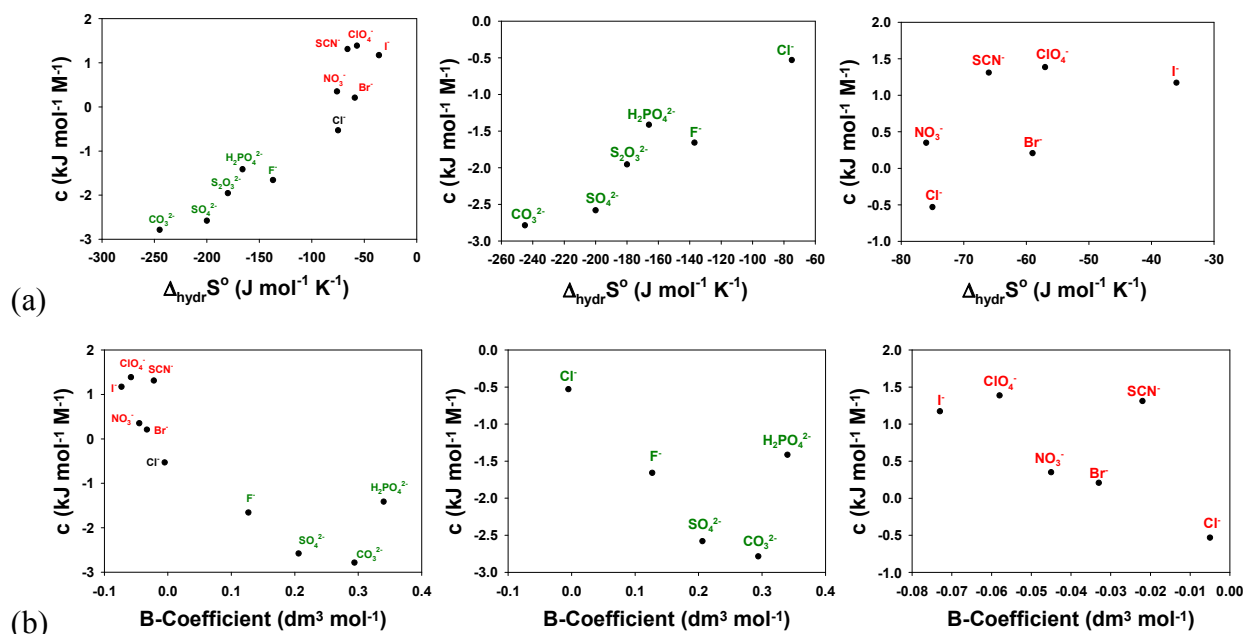chaotropic direct-interaction and kosmotropic entropic effects. These parameters include surface

Figure 10. Concentration coefficient correlations to specific anion physical properties. (a) entropy of ion hydration and (b) viscosity B coefficients. Correlations are shown for the entire Hofmeister series, kosmotropes, and chaotropes from left to right for each property.

tension increments, enthalpy of hydration, and water structure through hydrogen bonding participation. The correlations are summarized in Figure 11. Surface tension correlations infer that ion effects on surface tension are proportional to observed caffeine solubility. Specifically, increased surface tension representing an increased energetic cost associated with cavity formation of solute solvation produces adverse solubility effects for caffeine molecules in the aqueous phase.

Enthalpy of ion hydration may be interpreted to represent the release of energy associated with water molecule participation in ion solvation. Accordingly, this should coincide with the relative amount of energy require for partial desolvation and contribution to increased ion-solvent interaction for chaotropic and kosmotropic mechanisms, respectively. The presence of two separately correlating trends may offer support for enthalpy contribution both mechanisms.
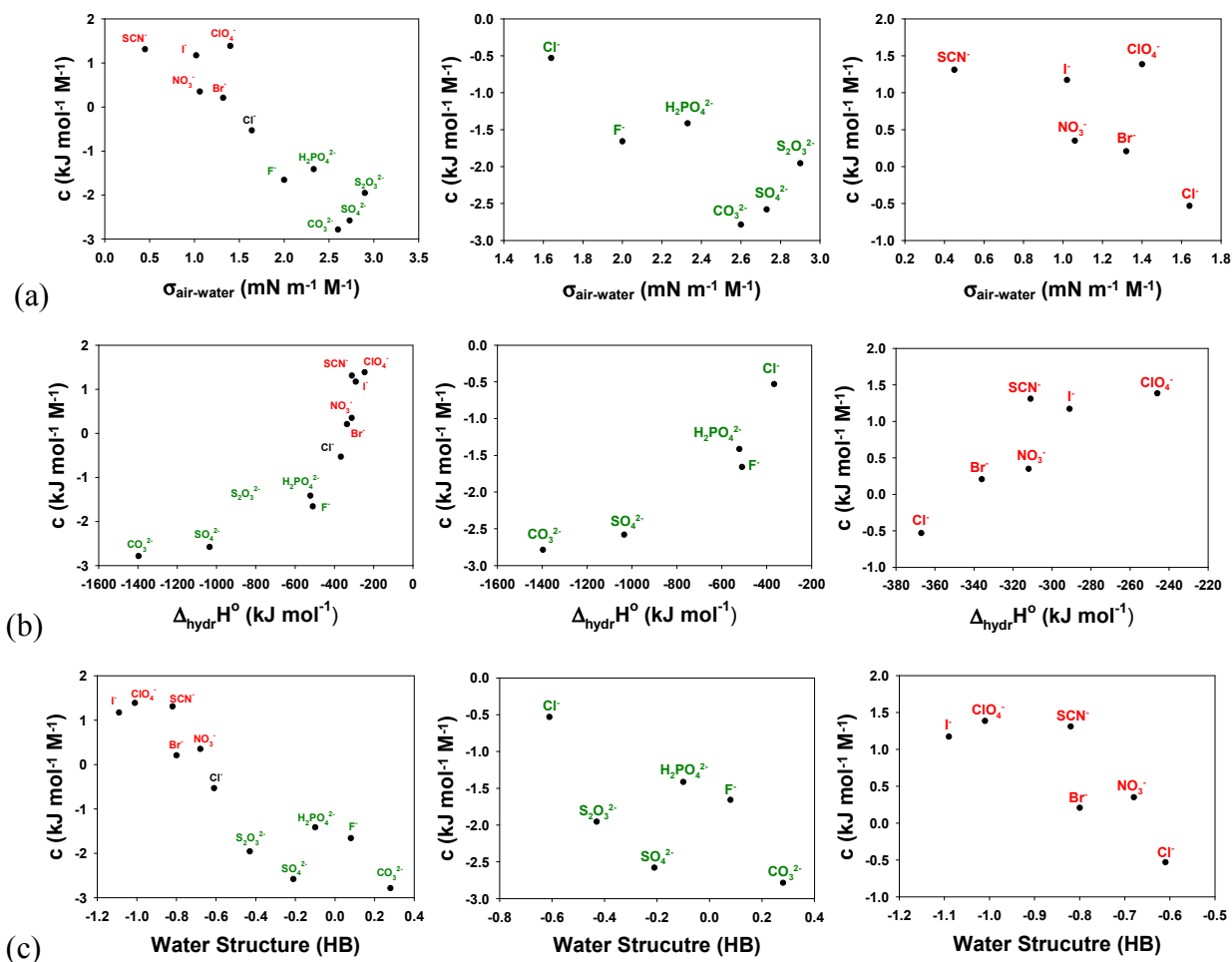
Figure 11. Concentration coefficient correlations to specific anion physical properties. (a) surface tension increments, (b) enthalpy of ion hydration and (c) HB water structure values. Correlations are shown for the entire Hofmeister series, kosmotropes, and chaotropes from left to right for each property.

A final trend observed throughout the Hofmeister series was present in the water structure by hydrogen bonding parameter. This property describes the structural characteristics of water through the average number of hydrogen bonds in which a water molecule participates. The scale is given by a value of 4 for ice and 0 for water vapor. Liquid water at room temperature is given by 1.55 and may be determined through condensation thermodynamics. The specific ion term used in correlation is the change in the average number of hydrogen bonds that a water molecule may participate in, ΔG_{HB}, determined by a proportionality factor associated

with ion transfer from heavy, D_2O, to light water, H_2O. Increased and decreased values of ΔG_{HB} correspond to a proportional increase or decrease number of hydrogen bonds that a water molecule close to ions may participates in. The observed trend is decreased caffeine solubility with increased water structure.

Temperature Dependence of Gibbs Free Energy for Caffeine Transfer

Gibbs free energy for caffeine partition as function of temperature was investigated for the 11 sodium salts at 0.5 M concentration for temperatures ranging from 295 to 320 K. Each data point is an average of three trials of measurements. The summary of Gibbs free energy vs. temperature plots for each anion of the Hofmeister series are shown in Figure 12. The free energy-temperature plots for each salt were fit with a linear regression curve. The negative slopes and y-intercept values correspond to entropy, $\Delta_{0.5}S^o$, and enthalpy, $\Delta_{0.5}H^o$, respectively. The extrapolated values for entropy and enthalpy are summarized in Table 2.

To analyze the relationship between specific ion effects and the thermodynamic quantities obtained from temperature dependence studies it is necessary to provide interpretations of entropy, $\Delta_{0.5}S^o$, and enthalpy, $\Delta_{0.5}H^o$. Entropy concerns the degree of disorder associated with caffeine distribution in the presence of a given anion where an increase infers a more disordered distribution at equilibrium. Each anion of the Hofmeister series yielded positive values of entropy. Chaotropic anions were found to exhibit larger values of $\Delta_{0.5}S^o$ indicating a highly disordered system compared to Kosmotropic anions. The enthalpy of caffeine transfer at 0.5 M salt concentrations, $\Delta_{0.5}H^o$, represents the thermal energy investment for caffeine transfer into the cyclohexane phase. The positive enthalpy values imply that the transfer of caffeine from the aqueous to organic phase is enthalpically unfavorable, energetically costly. A general trend in which chaotropic anions exhibited increasingly positive values of enthalpy was discovered. Thus
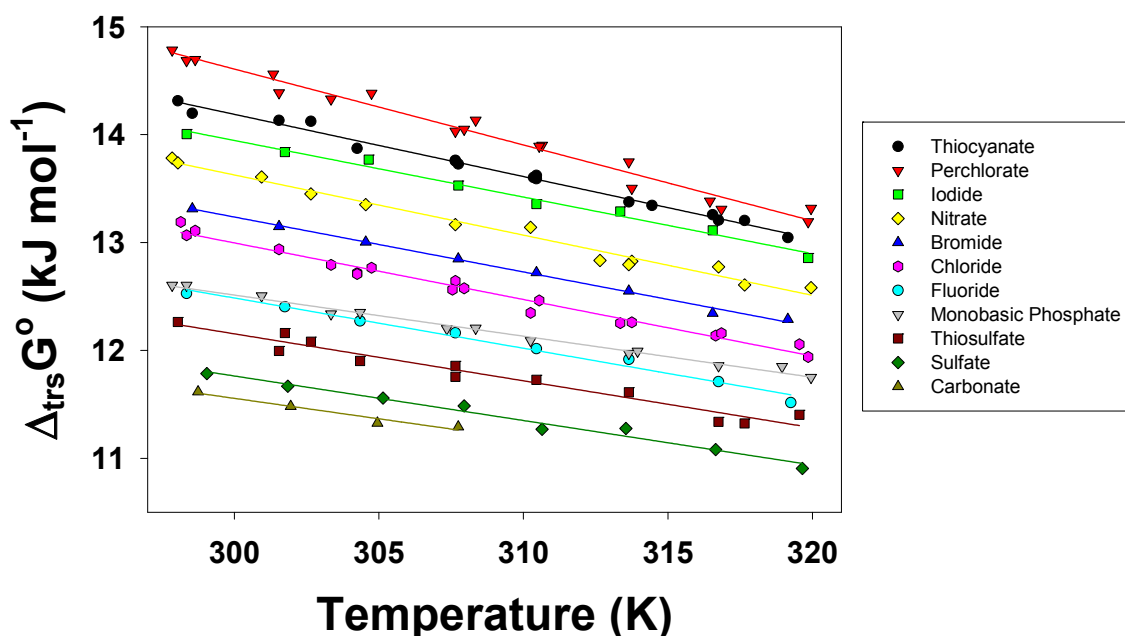
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Figure 12. Gibbs free energy of caffeine partition versus temperature for 0.5 M of each salt. Slope and y-intercept of each plot correspond to negative entropy and enthalpy of caffeine transfer.

Table 2. Summary of entropy and enthalpy data extracted from linear fits of the Gibbs free energy-temperature plots at 0.5 M salt concentration.

Anion	Entropy $\Delta_{0.5}S^o$ (J mol^{-1} K^{-1})	Enthalpy $\Delta_{0.5}H^o$ (kJ mol^{-1})
SCN$^-$	57.7	31.49
ClO$_4^-$	70.4	35.72
I$^-$	52.5	29.69
NO$_3^-$	55.8	30.38
Br$^-$	50.9	28.51
Cl$^-$	52.5	28.73
F$^-$	46.6	26.46
H$_2$PO$_4^-$	38.1	23.95
S$_2$O$_3^{2-}$	43.5	25.22
SO$_4^{2-}$	41.3	24.15
CO$_3^{2-}$	37.9	22.92

chaotropic anion presence serves to raise the thermal energetic cost of caffeine transfer into the cyclohexane phase more so than kosmotropic anions. The trends of entropy and enthalpy against equally spaced kosmotropic/chaotropic character of anions in the Hofmeister series are displayed in Figure 13. It should be noted that the perchlorate ion exhibits outlying entropy and enthalpy values due to a steep temperature dependence plot while the monobasic phosphate exhibits similar outlying character due to a flatter slope. Repeated experimentation for these 0.5 M salts should be performed to ensure this discrepancy is not from experimental error.
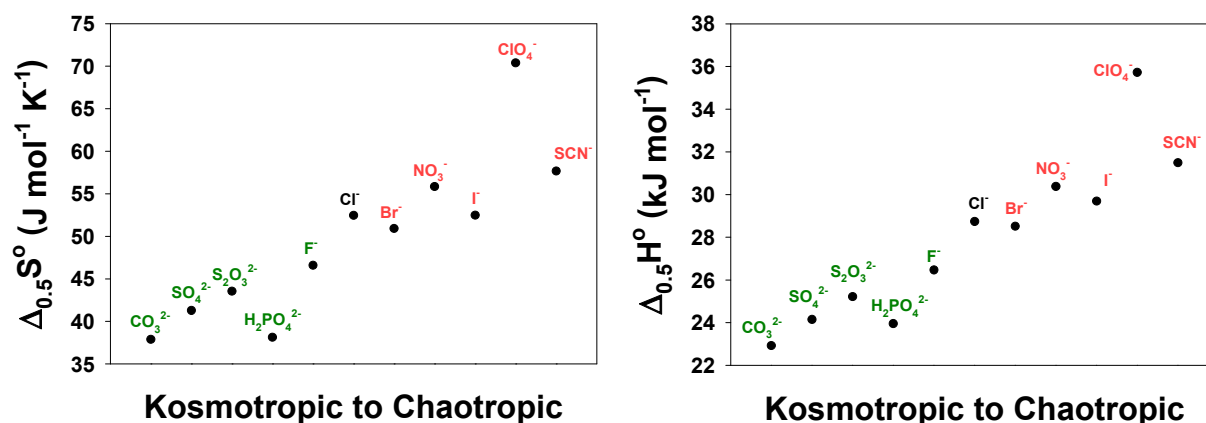
Figure 13. Relative entropy, $\Delta_{0.5}S^o$, and enthalpy, $\Delta_{0.5}H^o$ trends across the kosmotropic to chaotropic spectrum of the Hofmeister series.

Specific Ion Entropy Contributions

Chaotropic entropy values obtained from temperature dependent investigations were found to correlate well with physical properties of size and poor hydration. Properties of polarizability and hydration number, which showed correlation to c values, were also assessed but did not show correlation to entropy. The summary of entropy, $\Delta S_{0.5}$, correlations to physical properties of partial molar volume, free energy of hydration, polarizability, and hydration number are summarized in Figure 14.

As previously mentioned chaotropic ions can partition to the hydrophobic methyl groups of caffeine in accordance to their ability to shed their hydration sphere. This principle of partitioning could also explain the increased disorder in caffeine distribution in the presence of chaotropes. The correlation of poor hydration and increased disorder, displayed in Figure 14a, suggests that the extent of partial hydration of ions, which have undergone partition to the caffeine surface, affect the observed order of caffeine distribution within the system. Specifically, ions with particularly poor hydration, which produce increased caffeine solubility, may do so through favorable entropy that creates a more disordered system. Secondly, entropy correlation to ion size can be rationalized through system order changes during an ions partition to the aqueous-caffeine interface. Water molecules involved in cage-like interactions shielding methyl groups by the hydrophobic effect should be released as a function of ion proximity. The solvent molecule's transition from highly ordered hydrophobic cage structures to the disordered bulk should produce increased entropy values. It follows that this effect will be more pronounced for larger ions and is supported by the correlations in Figure 14b. Additionally, the discussed mechanism of chaotropic affinity for the caffeine surface could serve to polarize the water-cyclohexane interface exhibiting similar effects on disorder by the release of water molecules into the dense, disordered bulk solution.

Increased polarization is associated with ion affinities for hydrophobic surfaces that showed correlation to increased caffeine solubility. However, the poor correlation between entropy and polariability, displayed in Figure 14c, suggests that ion softness does not significantly affect the system order. Poor correlation was also observed with specific ion hydration number, Figure 14d. The lack of entropic correlation to properties of polarizability and hydration number can be interpreted to suggest that the "salting-in" effects of chaotropic ions
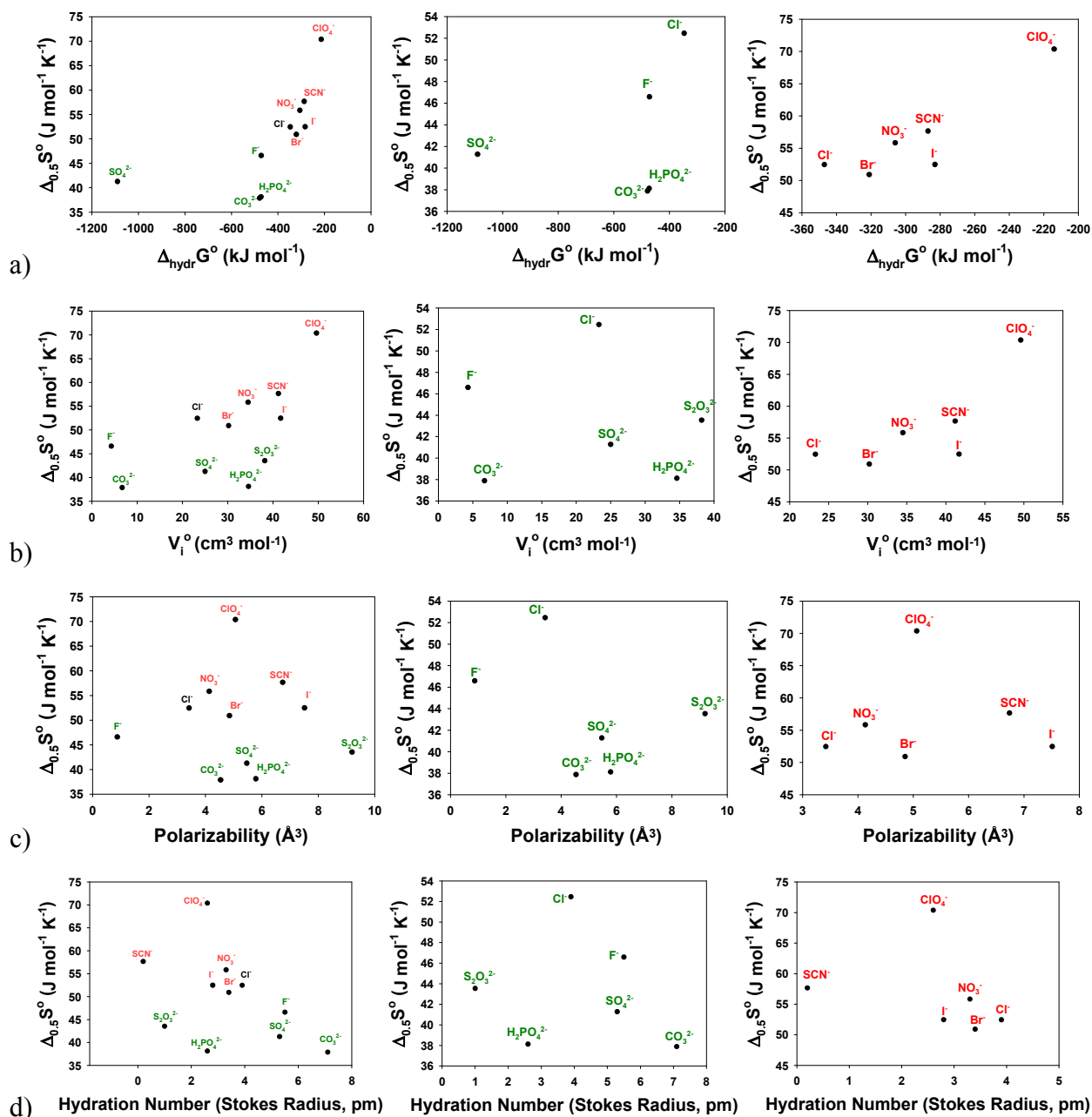
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Figure 14. Entropy correlations to specific anion physical properties. (a) free energy of ion hydration, (b) partial molar volume, (c) polarizability, and (d) hydration number. Correlations are shown for the entire Hofmeister series, kosmotropes, and chaotropes from left to right for each property.

may be strongly affected by direct interactions with caffeine molecules, as opposed to a mechanism driven by increased system disorder. The determined caffeine partition entropy

values for 0.5 M kosmotropic ion presence were found to correlate well the entropy of ion

hydration and the ion-solvent interaction strengths. The correlations plots for $\Delta S_{0.5}$ to the

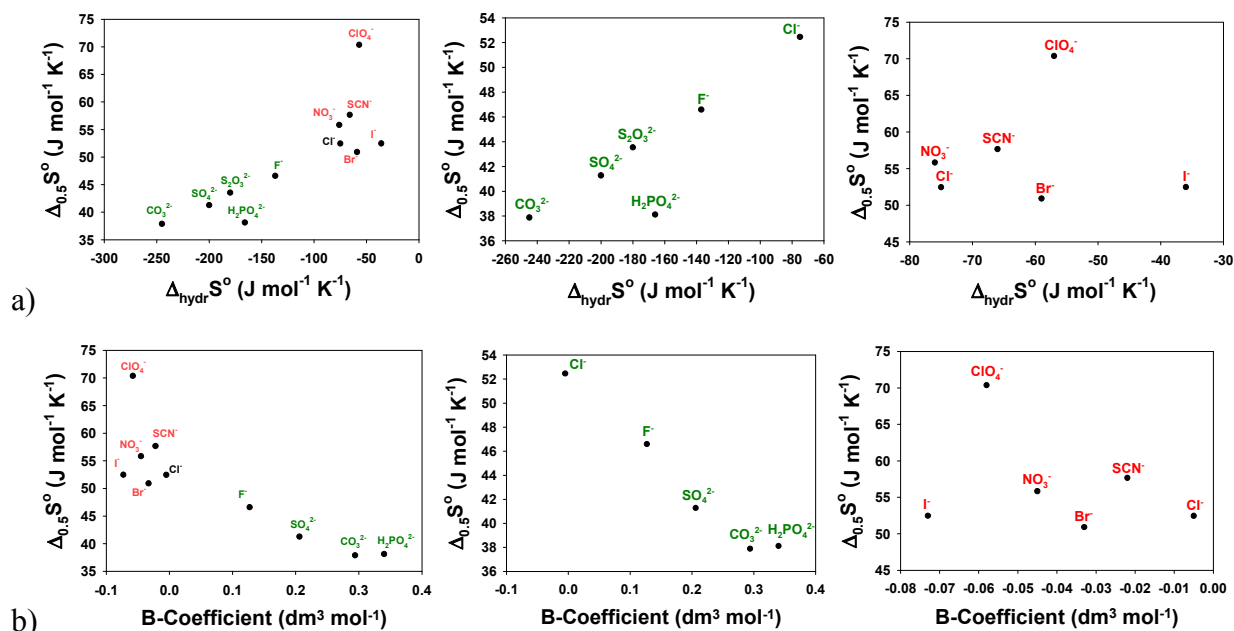hydration entropy and B-coefficients of the anions are summarized in Figure 15.

Figure 15. Entropy correlations to specific anion physical properties. (a) entropy of ion hydration and (b) B-coefficient. Correlations are shown for the entire Hofmeister series, kosmotropes, and chaotropes from left to right for each property.

The correlation of physical properties to determined entropy values held striking

consistency to the correlations of the concentration dependence of Gibbs free energy.

Concentration dependence discussion implies that increasingly ordered hydration of kosmotropic

ions can effectively reduce the water molecule interaction participating in caffeine solvation. The

proposed kosmotropic mechanism is further supported by direct proportionality between ion

hydration and the observed caffeine distribution orders displayed graphically in Figure 15a. This

observation is consistent with the proposed mechanism in which increasingly ordered ion

hydration may induce order of the hydrating water molecules, which ultimately inhibits

solubility favoring solvent-caffeine interaction.

The correlation in Figure 15b implies that strong ion-solvent forces are involved with the highly ordered caffeine distribution at equilibrium through low entropy observables. Increased ion-solvent interaction affords the ability of kosmotropic anions to alter hydrogen-bonding networks within the first shell, and even second hydration shell with extremely kosmotropic anions. For the scope of caffeine partition, the ability to reorder immediate hydrogen bonding networks, like those involved in caffeine-solvent H-bonds or hydrophobic cages, is enhanced through strong ion-solvent interactions. In short, the correlations suggest that kosmotrope interaction with water molecules affords a proportionally stable and ordered system that offers support for the entropically driven "salting-out" mechanism for kosmotropic ion presence.

As in the correlations to the c coefficient, some physical properties appear to correlate across the entire Hofmeister series. Surface tension at the air-water interface, enthalpy of hydration, and water structure (HB) showed trends spanning both kosmotropes and chaotropes. The summary of cross series entropy trends are summarized in Figure 16. The plot of air-water surface tension increments displayed correlation across the Hofmeister series. This correlation, displayed in Figure 16a, suggest that surface tension effects for each ion are involved with the observed order or disorder of caffeine distribution. Specifically, entropy is increasingly small, more ordered for high surface tensions. High surface tension represents an increased energy requirement to create an indention of aqueous solution at the caffeine-water interface necessary for solubility as well as the cyclohexane-aqueous interface. It follows that salts contributing to high surface tension should yield a caffeine distribution, which requires significant energy to alter the established equilibrium.

Increasingly positive values of entropy correlate with increased system disorder. The interpretation of ion hydration enthalpy to represent the energy release during ion solvation can

be also be interpreted as the energy required for dehydration. Using the latter interpretation, ions

that require significant energetic investment for dehydration, i.e. kosmotropes, were observed to

bring about more ordered caffeine partitioning. It should be noted that enthalpy of ion hydration

displayed separate correlations for kosmotropic and chaotropic anions. This correlation suggests

that the stability of caffeine distribution is proportional to the energy required for dehydration.

The final entropy correlation in Figure 16c displays the relationship between water structure

effects of specific ions and ultimately the order, stability of caffeine distribution throughout the
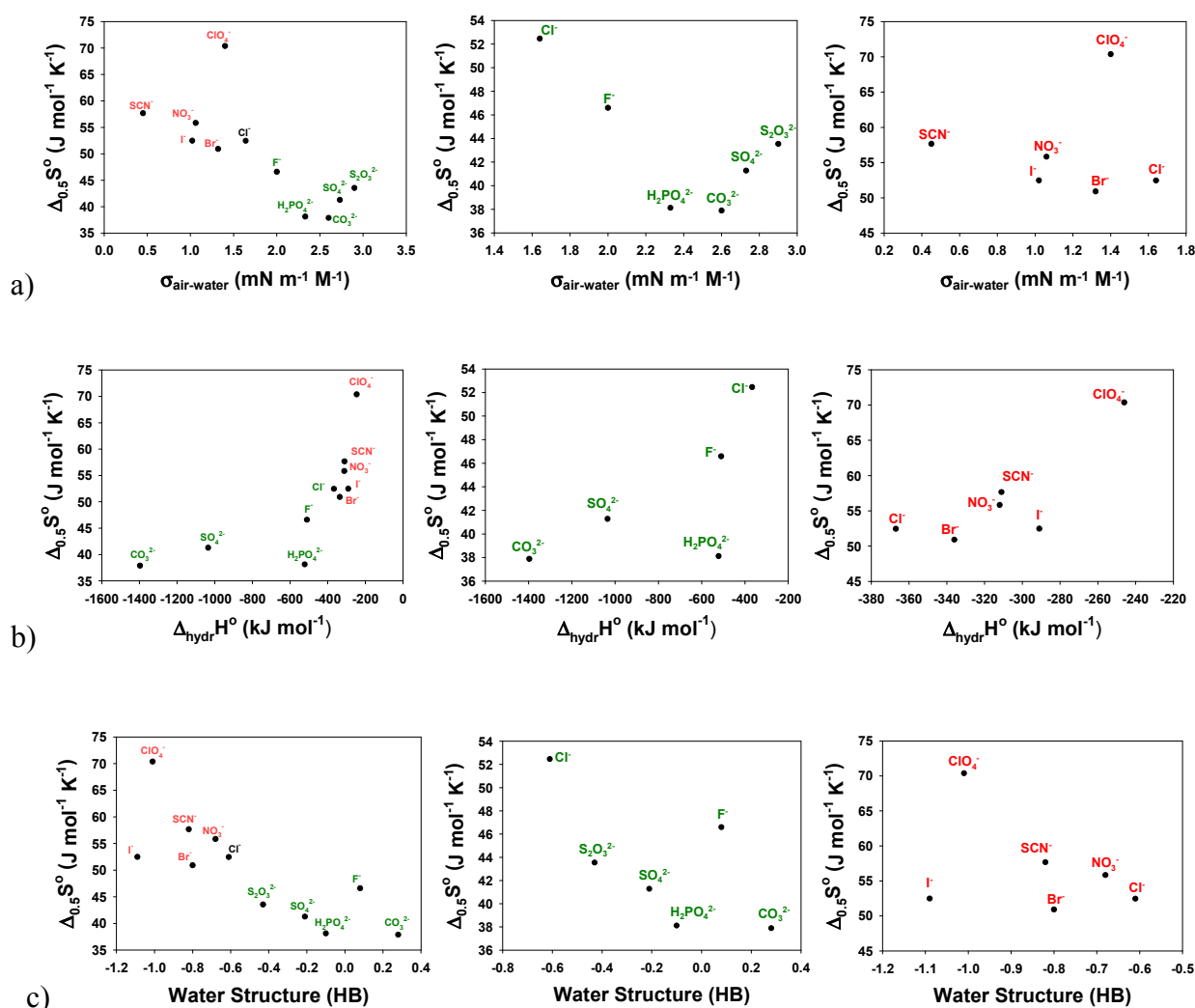

Figure 16. Entropy correlations to specific anion physical properties. (a) surface tension, (b) enthalpy of ion hydration, and (c) water structure (HB). Correlations are shown for the entire Hofmeister series, kosmotropes, and chaotropes from left to right for each property.

partition. The trend shows that the ions that contribute to higher degree of water structure produce stable caffeine distributions.

Specific Ion Enthalpy Contributions

Enthalpy for caffeine transfer at 0.5 M of salts, $\Delta_{0.5}H^o$, represents the energetic cost necessary to dehydrate and transport caffeine into the cyclohexane phase. Caffeine transfer enthalpy at 0.5 M for sodium salts showed a general trend of small to large positive values for kosmotropic to chaotropic anions. Enthalpy of caffeine transfer for chaotropic anions showed significant correlation with size and poor hydration. As in the entropy discussion, polarizability and hydration number did not exhibit significant correlation to experimental enthalpy values. Correlations of size, hydration, polarizability, and hydration number are compiled in Figure 17. Increased caffeine solubility corresponds with more positive enthalpy terms results through heftier energetic investment to dehydrate caffeine for transfer into the organic phase. The sum of increasingly favorable interactions between caffeine and aqueous solvent molecules yields a higher enthalpic investment associated with transfer into the cyclohexane. The enthalpy correlation to ion size, Figure 17a, suggests that larger ion size bring about more solubility favoring interactions between caffeine and solvent molecules. In accordance with the proposed chaotropic affinity for methyl substituents, large ions should further shield the unfavorable interactions between hydrophobic moieties and water by polarization of the caffeine surface. A similar trend is observed in the correlation of caffeine transfer enthalpy to Gibbs free energy of anion hydration. The trend may be interpreted to suggest poorly hydrated ions may interact in closer proximity to the hydrophobic interface thus contributing to increased solubility through shielding effects. Both partial molar volume and Gibbs free energy of hydration showed poor correlation when plotted against kosmotropic enthalpy values, providing further support for the
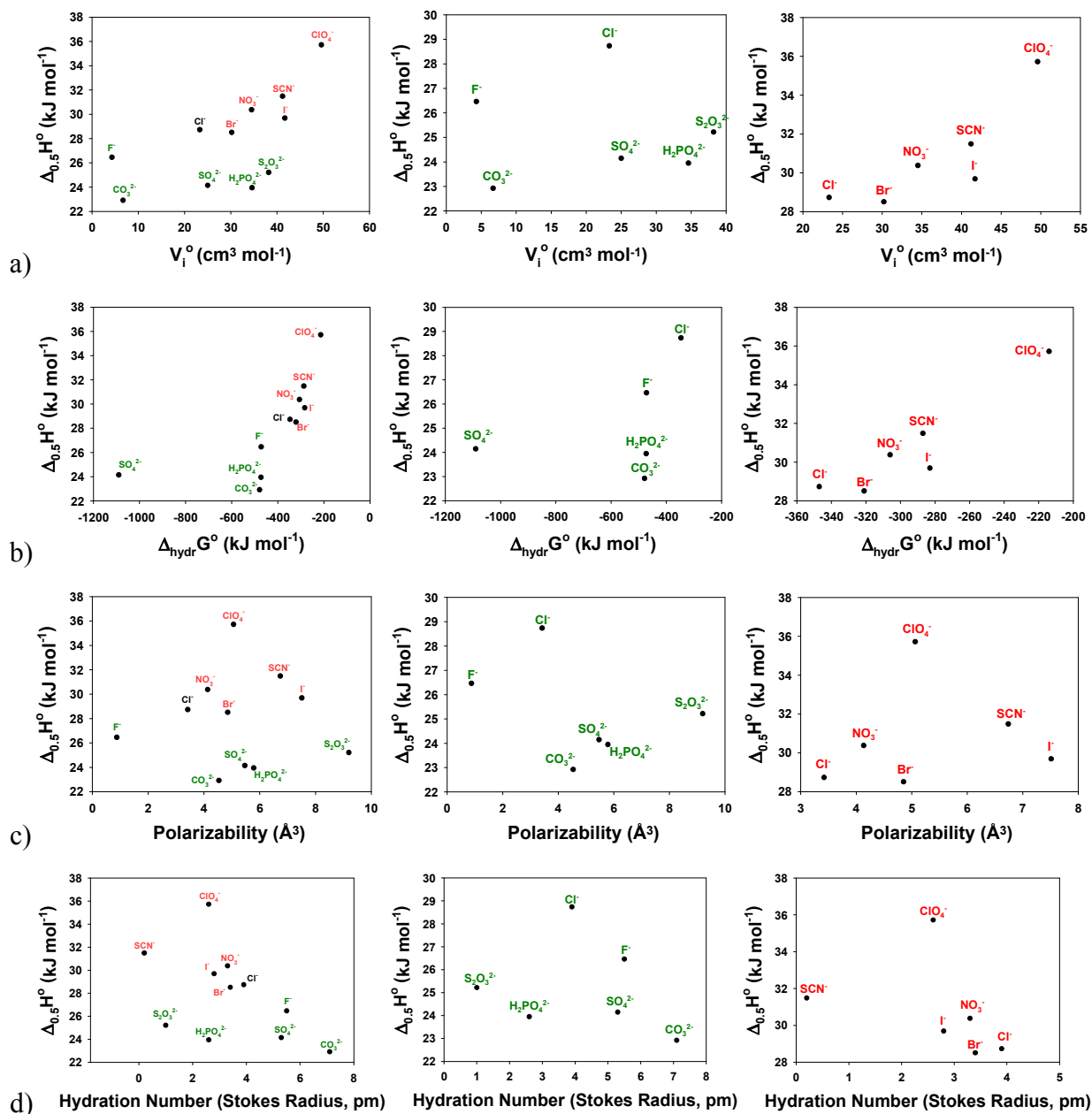
Figure 17. Enthalpy correlations to specific anion physical properties. (a) free energy of ion hydration, (b) partial molar volume, (c) polarizability, and (d) hydration number. Correlations are shown for the entire Hofmeister series, kosmotropes, and chaotropes from left to right for each property.

notion of separate chaotropic and kosmotropic mechanisms. Polarizability did not correlate to the caffeine transfer enthalpy. The lack of correlation may be rationalized when considering the accessibility of hydrophobic surfaces that chaotropes interact with. Methyl substituents reside

outside and in the plane of the xanthine ring and accordingly are very exposed to the aqueous environment. Due to the methyl groups' substantial accessibility chaotropic association, yielding favorable water-caffeine interaction is not proportional to anion polarizability.

Hydration number also did not correlate to 0.5 M enthalpy potentials. The absence of this trend indicates that the number of water molecules surrounding an ion does not significantly affect caffeine-solvent interactions that determine solubility and the partition. Entropy of ion hydration and viscosity B-coefficient describing the order and strength of the ion hydration shell showed excellent correlation to the caffeine transfer enthalpy for kosmotropic anions. The correlations are display in Figure 18. Correlations between caffeine transfer enthalpy and physical properties which describe overall entropic characteristics for ion hydration shell offer further support for the proposed kosmotropic mechanism. In addition to ion hydration entropy, the strength of ion-solvent interactions are proportional to the energy required for caffeine transport. The decrease of enthalpic cost associated with increasing kosmotropic character correlations are consistent with the hypothesized solubility decrease that results from entropic distruption of favorable caffine-sovent interactions. In short, caffeine transfer is enhanced for kosmotrope anions through an entropic mechanism in which caffeine-solvent interactions are reduced by highly ordered ion hydration shells "stealing" caffeine hydrating water molecules. Surface tension, enthalpy of hydration, and water structure (HB) parameters showed trends throughout the Hofmeister as observed in entropy and c value correlations. The specific ion enthalpy potentials at 0.5 M are summarized in Figure 19.

The increase of surface tension brings about an increased energetic cost associated with cavity formation necessary for solvating caffeine molecules in the aqueous phase. It follows that
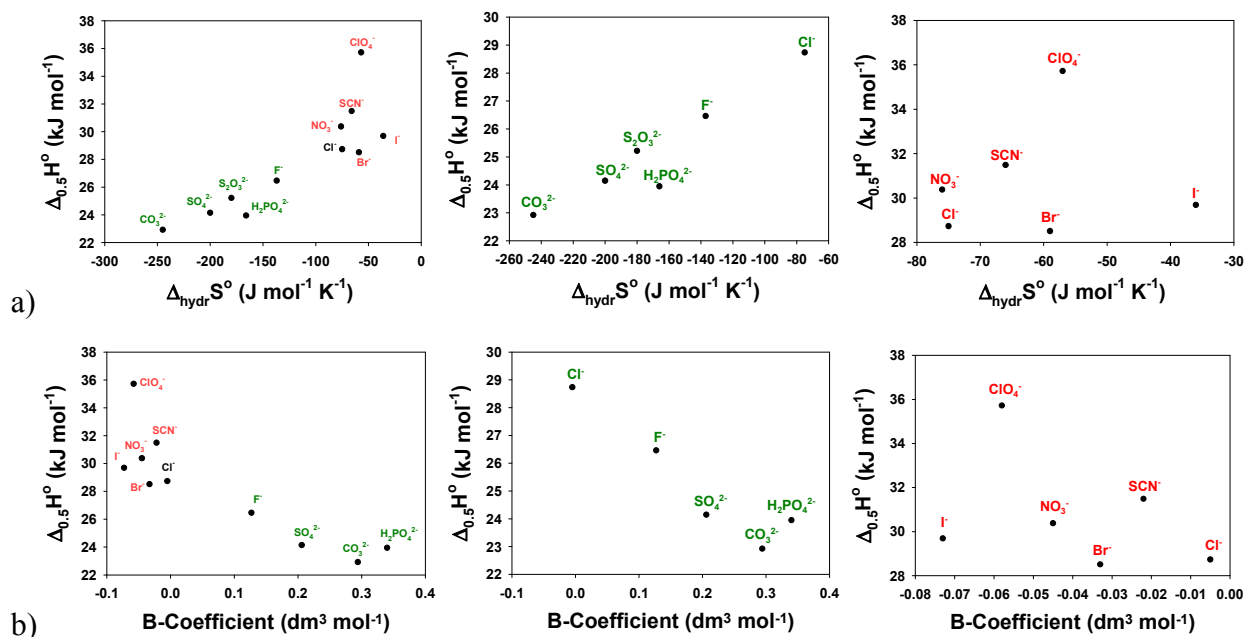
Figure 18. Enthalpy correlations to specific anion physical properties. (a) entropy of ion hydration and (b) viscosity B-coefficient. Correlations are shown for the entire Hofmeister series, kosmotropes, and chaotropes from left to right for each property.

increased surface tension, resulting in poor caffeine solubility, should reduce the energetic investment required to dehydrate and phase transport caffeine molecules. This postulation is supported by the negative correlation between caffeine transfer enthalpy and surface tension increments for specific ions displayed in Figure 19a. Surface tension increments producing energetically costly aqueous environments serve to increase caffeine transfer into the cyclohexane, quantified through decreased enthalpy of caffeine transfer.

Correlation between caffeine transfer enthalpy and ion hydration enthalpy was observed for both chaotropic and kosmotropic anions. Slopes differ in the two trends suggesting mechanistic differences in the produced correlations. Kosmotropes display a trend where enthalpy of ion hydration induces small changes in caffeine transfer enthalpy. Kosmotropic thermodynamic hydration is extremely favorable, i.e. very negative. This property assists in the strong interaction between ion and solvent molecules characterizing kosmotropic hydration

shells. Favorable ion hydration provides support for the hypothesized disruption of caffeine-solvent interactions that are necessary for aqueous solvation. Small influence, correlation slope, may provide support for the transfer by entropic effects. Chaotropes display a trend characterized by heavy influence of ion hydration enthalpy on caffeine transport enthalpy. Chaotropes' low energy requirement for partial dehydration affords increased surface polarization through direct ion partition to the caffeine surface. Chaotropic polarization by direct interaction ultimately increases caffeine solubility and correspondingly hefty energetic requirement for dehydration
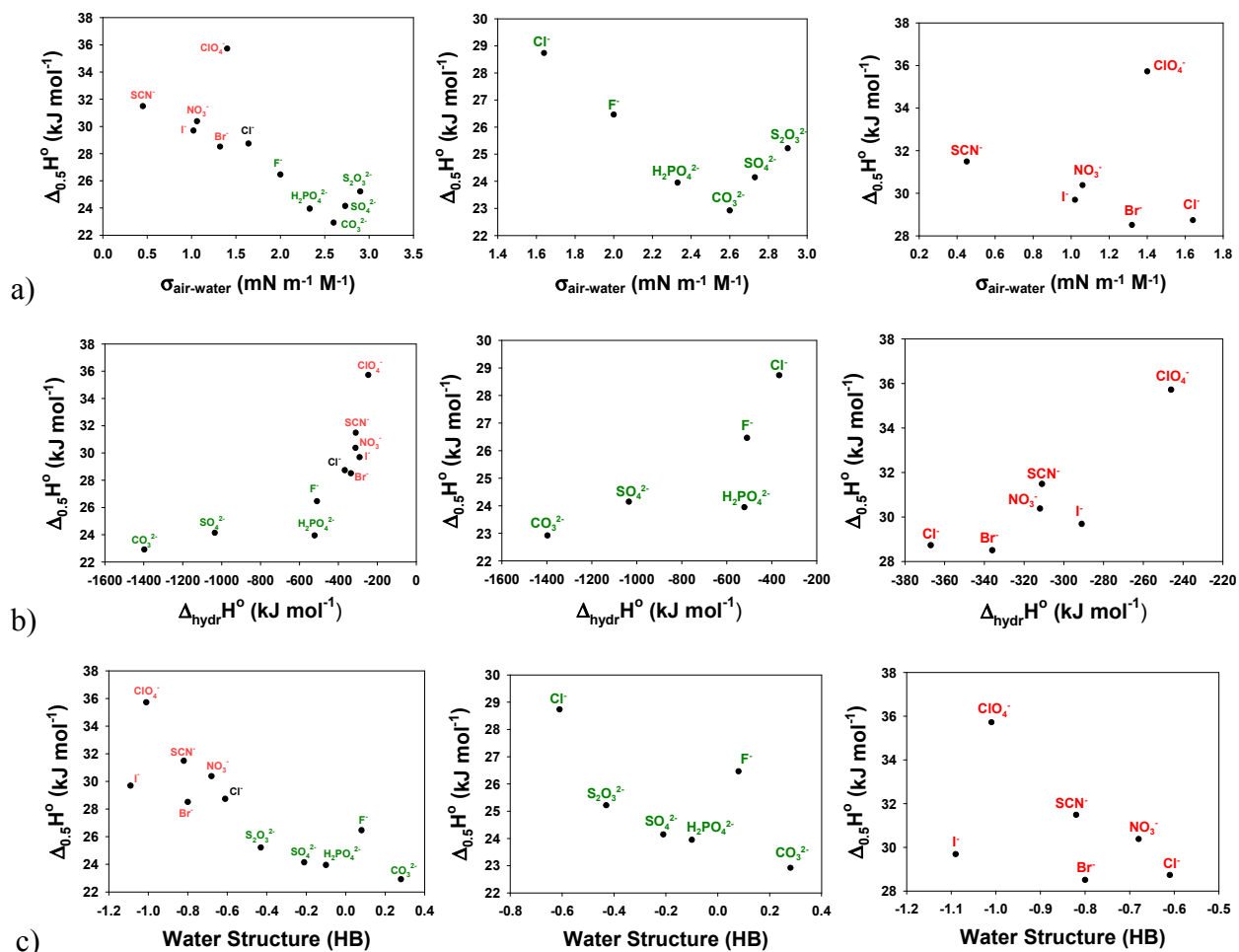

Figure 19. Enthalpy correlations to specific anion physical properties. (a) surface tension, (b) enthalpy of ion hydration, and (c) water structure (HB). Correlations are shown for the entire Hofmeister series, kosmotropes, and chaotropes from left to right for each property.

and phase transfer. The large correlation slope implies stronger influence of partial transfer

caffeine out of the energetically costly environment by transfer into the cyclohexane

dehydration, thus direct interaction, as opposed to entropic contribution. The physical parameter

describing specific ion effects on immediate solvent hydrogen bonding environment, water

structure (HB), showed correlation to caffeine transfer enthalpy across the Hofmeister series.

Mechanism Overview

The discussion concerning the relationship between partition coefficient thermodynamics, which

quantitatively describe aspects of caffeine distribution, and physical properties of anions

encompasses an expanse of correlations. Correlation analysis serves a method to elucidate ion

properties of thermodynamic significance and by virtue infer mechanistic importance. The

culmination of the discussion has produced two mechanistic propositions describing chaotropic

and kosmotropic anion influence on caffeine partition. Thermodynamic descriptions for

chaotropic and kosmotropic influence on partition coefficient are summarized in Table 3.

Table 3. Thermodynamic summary for chaotropic and kosmotropic Hofmeister anion influence
on caffeine partition coefficient. Thermodynamic potentials include *c* coefficient, entropy, and
enthalpy.

	Chaotrope	Kosmotrope
Concentration Coefficient c ($\partial\Delta G_{transfer}/\partial\Delta M$)	Positive (equilibrium shift to aqueous)	Negative (equilibrium shift to cyclohexane)
Entropy (0.5 M) $\Delta_{0.5}S^o$ (J mol^{-1} K^{-1})	Increase (unstable distribution)	Decrease (stable distribution)
Enthalpy (0.5 M) $\Delta_{0.5}H^o$ (kJ mol^{-1})	Decrease (costly energetic transfer)	Increase (cheap energetic transfer)

Physical properties which exhibit correlation to the thermodynamics of the entire Hofmeister

series, chaotropes, or kosmotropes are summarized in Table 4. The combined influence of these

properties provide support for the proposed kosmotropic and chaotropic mechanisms.

Table 4. Summary of the physical properties exhibiting correlation to thermodynamic potentials. Correlations are summarized by respective sets including the Hofmeister series, chaotropic, or kosmotropic anions.

	Hofmeister Series	Chaotrope	Kosmotrope
Concentration Coefficient c ($\partial \Delta_{trs} G^o / \partial \Delta M$)	-Surface Tension - $\Delta_{hydr} H^o$ -Water Structure (HB)	$-\Delta_{hydr} S^o$ -B Coefficient	- Volume $-\Delta_{hydr} G^o$ -Polarizability -Hydration Number
Entropy (0.5 M) $\Delta_{0.5} S^o$ (J mol^{-1} K^{-1})	-Surface Tension - $\Delta_{hydr} H^o$ -Water Structure (HB)	$-\Delta_{hydr} S^o$ -B Coefficient	-Volume $-\Delta_{hydr} G^o$
Enthalpy (0.5 M) $\Delta_{0.5} H^o$ (kJ mol^{-1})	-Surface Tension - $\Delta_{hydr} H^o$ -Water Structure (HB)	$-\Delta_{hydr} S^o$ -B Coefficient	-Volume $-\Delta_{hydr} G^o$

Chaotropes (Direct Interaction)

Analysis of the physical properties showing correlation to chaotropic thermodynamics provided foundation for a mechanism of chaotropic influence on the caffeine partition coefficient. The proposed chaotropic mechanism involves direct ion-caffeine interaction that ultimately results in solute-solvent interactions favoring solubility. Specifically, the hypothesized direct interaction serves to polarize the surface of caffeine yielding increased solvation. This mechanistic inference is supported by thermodynamic correlations to ion size, through partial molar volume, as well as poor hydration, Gibbs free energy of hydration. Proposed binding sites for ion-caffeine interaction include the hydrophobic methyl group moieties as well as ion interactions with the electron poor aromatic π system ultimately stabilizing caffeine's polarized resonance form producing increased solubility in the aqueous phase. An illustration of the proposed chaotropic mechanism exhibiting direct binding is shown in Figure 20a.

Kosmotropes (Entropic Effects)

Correlation analysis, involving thermodynamic descriptions of kosmotropic anion effects on caffeine partition and anion physical properties, provides a method for mechanistic inference. Namely, physical property correlations suggesting an entropy-driven mechanism include order of

ion hydration shell, by entropy of ion hydration, and ion-solvent interaction strength, through the

viscosity B-coefficient. The proposed mechanism is a process in which the ordered nature and

strong ion-solvent interactions of kosmotrope hydration shells effectively reduce caffeine

hydration by entropic effects. Furthermore, the hypothesis states that these ion hydration

characteristics disrupt and reduce solvent molecule participation in hydrogen bonds or

hydrophobic cages with the caffeine solute. The schematic illustration of the proposed

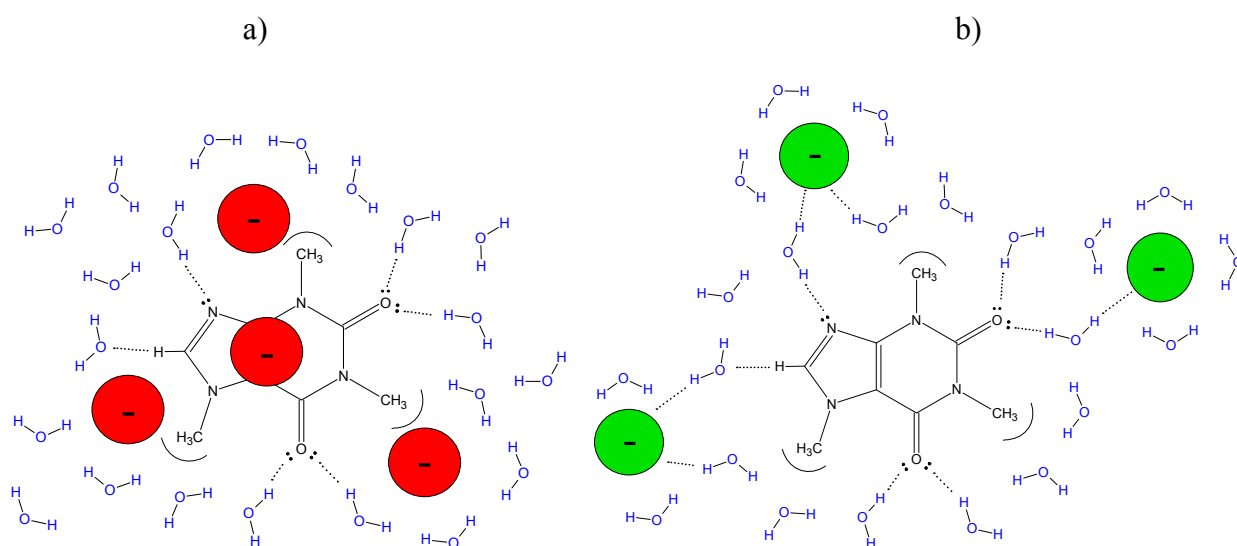kosmotropic mechanism is provided in Figure 20b.

Figure 20. Proposed machnisms for anion-caffeine interactions: (a) Chaotropic mechanism; (b) Kosmotropic mechanism.

The proposed chaotropic and kosmotropic anion-caffeine interactions rationalize the observed

partition coefficients. These mechanisms provide a potential explanation for Hofmeister effects

observed in a variety of aqueous processes.

Conclusion

Caffeine partition between aqueous and cyclohexane phases was implemented as model system to probe the mechanisms by which Hofmeister anions produce well documented "salting-in" and "salting-out" effects in aqueous solution. Anion influence of eleven sodium salts were assessed by concentration variation and temperature dependence at 0.5 M concentration. Chaotropic ions shift equilibrated caffeine distribution to the aqueous phase, while Kosmotropic ions produce shifts to the cyclohexane. Experimental thermodynamic values exhibit significant correlation to ion size and poor hydration for chaotropic anions in contrast to the correlations of hydration entropy and ion-solvent interaction strength for kosmotropic anions. Correlation proportionalities suggest a chaotropic mechanism involving direct ion-caffeine interactions and a kosmotropic mechanism governed by entopic effect of ion hydration shells. The proposed mechanisms offer potential explanations for a variety of observable Hofmeister effects in aqueous solution.

Future Work

Future work for mechanistic elucidation of the Hofmeister series will include several alterations of the partition coefficient experimental model. The partition coefficient of caffeine experiments will include temperature dependent studies at a 1.0 M salt concentration to assess enthalpy and entropy terms as a function of concentration. Computational simulations will be employed providing complementary data to analyze the proposed binding sites for chaotropic anions. Additional work involving the caffeine partitioning model will include concentration and temperature dependence for the cationic Hofmeister series using various chloride salts. Cation studies may elucidate interesting properties of cation interaction with caffeine's 10 π-electron aromatic xanthine core as well as partially negative charged carbonyl oxygen atoms. The method development on the aqueous-cyclohexane partition coefficient system affords a technique that may be applied to various macromolecules exhibiting mutual solubility and spectral detection. Exploration of specific ion effects on biologically relevant molecules, i.e. peptide sequences mimicking protein structures, provides a model for peptide hydration. Ultimately, these explorations should yield a more developed theory for ion mechanisms that produce Hofmeister effects at specific interfaces. In summary, future experimental designs will provide information concerning elucidation of mechanisms for Hofmeister series to explain observed specific ion effects in aqueous solution.

Publications and Presentations

1. "Effects of Hofmeister anions on the partition of caffeine between organic-aqueous phases"
   Rogers, B. A.; Zhang, Y. J.*
   The 246th ACS National Meeting, Indianapolis, Indiana, September 8-12, 2013 (poster, was selected to participate in the 2013 Physical Chemistry Symposium Workshop for Undergraduate Chemistry Majors)

2. "Specific ion effects on caffeine partition coefficient between aqueous-cyclohexane phases"
   Rogers, B. A.; Zhang, Y. J.*
   UMBC Undergraduate Research Symposium, Baltimore, MD, October 26, 2016 (Poster)

3. "Specific Ion Effects on Caffeine Partition between Aqueous and Cyclohexane Phases"
   Rogers, B. A.; Zhang, Y. J.*
   2013 James Madison University Summer Undergraduate Research Symposium, August 1-2, 2013 (Oral presentation)

4. "Specific Anion Effects on Caffeine Partition Thermodynamics between Aqueous and Cyclohexane Phases"
   Rogers, B. A.; Zhang, Y. J.*
   39th Annual Spring Undergraduate Research Symposium, Department of Chemistry and Biochemistry, James Madison University, April 3-4, 2014 (Oral presentation)

5. "Specific Anion Effects on Caffeine Partition Thermodynamics between Aqueous and Cyclohexane Phases"
   Rogers, B. A.; Zhang, Y. J.*
   Honors Program Symposium, James Madison University, April 25, 2014

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