Anion Complexation Hot Paper

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Anion Complexation and The Hofmeister Effect**

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Abstract: *The ^{1}H NMR spectroscopic analysis of the binding of the ClO_4^- anion to the hydrophobic, concave binding site of a deep-cavity cavitand is presented. The strength of association between the host and the ClO_4^- anion is controlled by both the nature and concentration of co-salts in a manner that follows the Hofmeister series. A model that partitions this trend into the competitive binding of the co-salt anion to the hydrophobic pocket of the host and counterion binding to its external carboxylate groups successfully accounts for the observed changes in ClO_4^- affinity.*

The growth in anion recognition during the last two decades has relied on many distinct functional groups,[1] but across all the examples of receptors it is arguably those that utilize strong charge–charge attractions and hydrogen-bond donation that have served the field best. Nevertheless, as the attenuation of ion–ion interactions is significant in water, and as the high enthalpy of hydration of anions competes with ion recognition through hydrogen bonding,[2] the majority of anion complexations have been studied in organic solvent. This is unfortunate, as the chemistry of aqueous salt solutions is central to all aspects of life.[3] Furthermore, the chemistry of aqueous salt solutions is rich with ambiguities, the most general example of which is the Hofmeister effect. Thus, for over 125 years it has been known that salts influence the solubility of molecules.[4] Salting-out salts such as NaF decrease solubility (apparently increasing the hydrophobic effect), whereas salting-in salts such as NaSCN increase solubility (apparently weakening it). Irrespective of the solute examined, studies repeatedly reveal the "Hofmeister series" of anions: F^-, SO_4^{2-}, AcO^-, Cl^-, Br^-, NO_3^-, ClO_3^-, I^-, ClO_4^-, and SCN^-. Furthermore, investigations examining salt effects on more than 38 macroscopic phenomena[5] such as lower critical solution temperatures of polyamides,[6] surface tension changes,[7] and changes in water surface potentials,[8] all reveal this Hofmeister series.

Historically, the Hofmeister effect has been attributed to salts modulating water structure. Hence salting-out salts are often referred to as water-structure makers or "kosmotropes",[5a] whilst salting-in salts have been termed water-structure breakers or "chaotropes".[9] However, direct ion–solute interactions are also likely to make major contributions to the Hofmeister effect. Thus, there is increasing evidence of polarizable anions accumulating at the air–water interface[5b,10] (without violating the thermodynamic theories arising from the observed negative Gibbs surface excess[11]), and powerful examples of surface–bulk ion partition models[7,12] that suggest ion–solute interactions are important. Moreover, specific ion–solute interactions have recently been quantified, namely the interactions between anions and hydrogen-bonding groups[6,13] and anions with a hydrophobic concavity.[14] Additionally, very recent studies of how salts interact with peptides have revealed a nuanced and complex interplay between ions and functional groups.[15] It is, therefore, evident that there is much to learn at the molecular level about the interactions between ions and solutes, and how this "folds" into the Hofmeister effect.

Recently, we demonstrated that salting-out salts enhanced the binding of a hydrophobic guest to the hydrophobic pocket of a host (octa acid, OA, Figure 1),[16] whilst salting-in salts decreased this association.[14] Furthermore, it was ascertained that this latter effect was induced by a strong (up to 2.7 kcal mol^{-1}) affinity of the anion for the hydrophobic pocket of OA, which led to direct competitive binding between the anion and hydrophobe. These results were intriguing because the host is ostensibly an octa anion under the basic conditions used; Coulombic interactions did not play a role in the affinity between it and the salting-in anions.

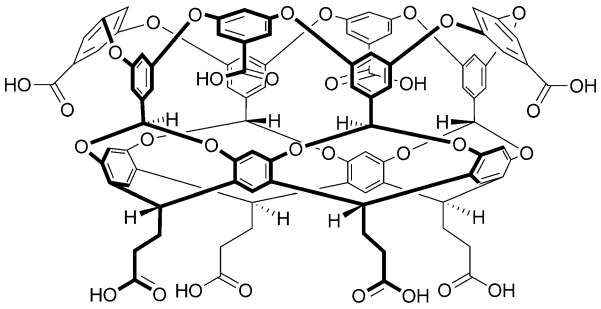

Figure 1. Structure of the octa acid host (OA).

Here we report an NMR study that reveals that the binding of ClO_4^- to OA is modulated by the presence of other salts, and that this strength of association is controlled by the nature and concentration of the co-salts in a manner that follows the Hofmeister series. A model that partitions this trend into the competitive binding of the co-salt anion to the pocket of the host and counterion binding to its external carboxylate groups successfully accounts for the observed changes in ClO_4^- affinity. To our knowledge, the results represent the first link between anion binding to hydrophobicity and the Hofmeister series, and illustrate the

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complex relationship between the components of a salt and how they interact with a solute.

During NMR titration studies to quantify the affinity that anions such as ClO_4^- have for OA, we noted a strong dependence upon the overall ionic strength of the solution. Thus, when NaCl was utilized to hold the ionic strength constant, and using the benzal protons in the binding pocket of the host as reporter atoms, the K_a value of ClO_4^- increased from $166 \pm 3\,M^{-1}$ in a solution of constant $I = 120$ mM, to $191 \pm 3\,M^{-1}$ at $I = 150$ mM.

If the binding of anions to OA is dependent on the I value, does the nature of a co-salt also influence the K_a value? To address this question we opted for a more atom-economical and operationally straightforward titration procedure, whereby the I value was varied by adding $NaClO_4$ to the host solution. We chose the sodium salts of six monovalent anions that cover the Hofmeister continuum and examined how the K_a value of ClO_4^- to OA was affected by the concentration of these co-salts (phosphate buffer, pH 10.8). The results are presented in Figure 2.[17]

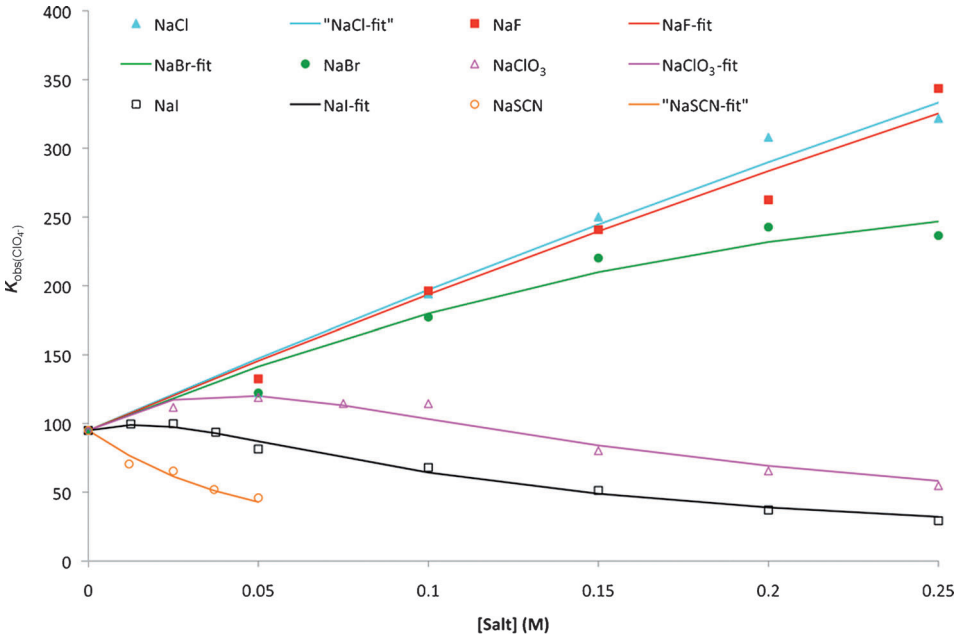

Figure 2. The effect of [salt] on the K_a value of ClO_4^- binding to the OA host. Each point represents the average of two or three determinations. The lines represent fitting of the data using Equation (2) (see text).

The addition of salting-out salts such as NaF enhance ClO_4^- binding, whilst those salts that reduce the apparent strength of the hydrophobic effect (e.g. NaSCN) weaken it. In between these extremes, $NaClO_3$ (and to a lesser extent NaI) is observed to slightly enhance ClO_4^- binding at low concentrations but weaken it at higher concentrations. This suggests there are at least two factors leading to the observed data, which overall follows the Hofmeister series.

The major factor behind the reduction in the observed ClO_4^- binding constant $\left(K_{obs(ClO_4^-)}\right)$ in the presence of salting-in anions is the simple direct competition for the hydrophobic pocket of OA [Eq. (1)],

$$K_{obs(ClO_4^-)} = \frac{K_{(ClO_4^-)}}{1 + K_{(salt)} S_t} \quad (1)$$

where $K_{(ClO_4^-)}$ is the association constant of the ClO_4^- guest in the absence of any competing co-salt ($95\,M^{-1}$), $K_{(salt)}$ is the corresponding binding constant of the competing anion from the co-salt, and S_t is the total concentration of the co-salt. A plot of the difference between the data in Figure 2 and a model using Equation (1) reveals that the equation slightly over-estimates the drop in the K_a value from competing ions (see the Supporting Information).

What is the cause of the increase in $\left(K_{obs(ClO_4^-)}\right)$ as a function of I? At the most basic level, this increase could be because the solution becomes less favorable to ClO_4^-, or because OA becomes a better host. This latter idea is primarily based on the notion that, similar to polyelectrolyes such as DNA,[18] the −8 charge of the host means that cations condense strongly with it, and as the value of I is increased the host becomes less negatively charged and is a stronger binder of anions.[19] Confirmation that this is the case came from ζ-potential measurements of OA as a function of added NaCl (see the Supporting Information). Thus, at concentrations of added NaCl of 0–280 mM, the ζ-potential of OA reduced in an approximately linear fashion from −39 to −21 mV. Two other lines of evidence support Na^+ condensation. First, the increase in the $\left(K_{obs(ClO_4^-)}\right)$ value in the presence of the more weakly condensing cesium ion[19] of CsCl (see the Supporting Information) was attenuated relative to NaCl. Second, half the concentration of Na_2SO_4 was required to bring about the same effect upon the K_a value as NaCl (see the Supporting Information).

Looking at cation condensation from the perspective of binding constants, to our knowledge the K_a value for Na^+ complexation to carboxylate groups ($-CO_2^-$) in water has not been accurately determined. However, it has been estimated by the Cremer research group to be $4.5\,M^{-1}$ from changes in the lower critical solution temperature of elastin-like polypeptides.[20] To account for the observed enhanced binding by Na^+ complexation, Equation (1) was modified (see the Supporting Information) by defining $K_{(salt)} = (1 + \alpha\theta)K_{0,salt}$ and $K_{(ClO_4^-)} = (1 + \alpha\theta)K_0(ClO_4^-)$, where θ is the fraction of host–Na^+ complex ($\theta = [HNa^+]/H_t$), $K_{0(salt)}$ and $K_0(ClO_4^-)$ are the reference association constants for the co-salt and perchlorate, respectively, at "zero" added salt, and α is a unitless factor that relates the extent of cation condensation

to the carboxylate groups and how this affects anion binding to the pocket. Substituting these definitions into Equation (1) gives Equation (2).

$$K_{\mathrm{obs}(\mathrm{ClO_4^-})} = \frac{(1+\alpha\theta)K_{0(\mathrm{ClO_4^-})}}{1+(1+\alpha\theta)K_{0(\mathrm{salt})}S_t} \quad (2)$$

Examining different K_{Na^+} values for θ, we fitted Equation (2) to the obtained data by letting α float. All the other factors in this equation are known, although in the case of Br^- and ClO_3^- we also opted to let $K_{0(salt)}$ float because their low affinities to the pocket of OA likely possess large errors. The results of the closest fit ($K_{Na^+} = 0.5\,\mathrm{M}^{-1}$) are given in Figure 2. These fits gave $K_{(salt)}$ values for Br^- and ClO_3^- very close to those anticipated (0.4 and $5.8\,\mathrm{M}^{-1}$, respectively), and α values from 21.8 to 40.8 (see the Supporting Information). The residuals from these fits are $<21\,\%$ of the empirical data, with the overwhelming majority within $<10\,\%$ of the observed values (see the Supporting Information). With larger K_{Na^+} values, for example, $4.5\,\mathrm{M}^{-1}$,[20] the fits are poorer with slight curvatures to the lines for F^- and Cl^-, and greater curvature for the Br^- data, a reflection of greater saturation of the host with Na^+ ions.

Overall these results reveal several key points: 1) anion binding to OA is dependent on both the ionic strength of the solution and the nature of the co-salt used to alter the ionic strength; 2) the observed variation as a function of the nature of the co-salt follows the Hofmeister series; 3) relatively poorly hydrated and polarizable anions demonstrate strong salting-in properties through competitive binding; 4) in the absence of strong salting-in properties, the salts demonstrate typical salting-out binding enhancement that can be mostly accounted for by cation binding to the outside of the OA, thereby reducing the net charge on the host; 5) salts such as $NaClO_3$ demonstrate both (anion-induced) salting-in effects and (cation-induced) salting-out properties depending on its concentration.

The two binding sites of OA are, to a first approximation, operationally independent of each other. One, a hydrophobic pocket, has strong affinity for salting-in anions but no affinity for either salting-out anions or metal cations. The other binding site of eight carboxylate groups has affinity for cations. For these reasons, OA differs considerably from other molecular probes[15] used to illustrate the complex supramolecular relationships between anions, cations, and solutes. We therefore anticipate that these cavitands will offer a unique, molecular-level insight into the Hofmeister effect.

It is also worth noting that the binding of large anions such as perchlorate to the hydrophobic concavity suggests a new strategy for anion recognition: rather than counteract their relatively high enthalpy of hydration by attempting to remove all waters of solvation, an alternative approach is to take advantage of their thermodynamic preference to reside on the surface of water clusters.[21] In other words, partial dehydration may be sufficient to bring about their recognition in water. We will report progress on these notions at a future date.

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