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Supporting Material

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Supplementary Theoretical Framework (STF)

We provide below, for completeness, an addition to the Theoretical Framework outlined in the main text and Appendix. We have broken this addition into parts. In *Part I*, we provide a more explicit discussion of the reduced degrees of freedom used to treat the host in complex with an ion. *Part II* provides a statistical rationale for the decomposition of the canonical probability density of an ion complexed in a host, which further elaborates on the correlation function written in Eq. 4. The small system grand canonical ensemble is described for the limiting cases of a “fluid” and a gas in *Part III.* A more explicit discussion of the definition of the chemical potential in the small system grand canonical treatment of the complex is given in *Part IV*. Finally, *Part V* provides definitions for various physical properties discussed in the main text.

I. Degrees of Freedom in the Abstracted Ion-Host System

To explain further the reduced degrees of freedom we utilize in the main text $\{\boldsymbol{r}^N,\boldsymbol{R}\}$, let us write all degrees of freedom in terms of the position of the ion, effectively placing the ion at the origin, $E(\boldsymbol{x}_0,\boldsymbol{S}) = E(\boldsymbol{S}')$. In this work, we explicitly state the position, $\boldsymbol{x_0}$, (e.g. whether it is in the bulk or at a particular site) when it is of consequence.

If we consider the protein as a set of *N* “coordinators” or “ligands” (generally, polyatomic or monatomic moieties that can coordinate an ion) covalently bonded to their protein [as depicted in Fig. 1 (top)], we may write $E(\boldsymbol{S}') = E(\boldsymbol{r}^N,\boldsymbol{\Psi}^N,\boldsymbol{R}),$ where $\boldsymbol{r}^N = \{\boldsymbol{r}_1,\boldsymbol{r}_2,\ldots,\boldsymbol{r}_N\}$ are the positions of the coordinators (with respect to the position of the ion), $\boldsymbol{\Psi}^N = \{\boldsymbol{\Psi}_1,\boldsymbol{\Psi}_2,\ldots,\boldsymbol{\Psi}_N\}$ are the rotational degrees of freedom of the coordinators, and $\boldsymbol{R}$ represents the remaining degrees of freedom (all degrees of freedom that do not qualify as ion or coordinator), including the protein to which the coordinators are bonded and all solvent degrees of freedom, the membrane (if the protein is membrane bound, such as a channel or transporter), and all surrounding aqueous solution. Examples of coordinators might include carbonyl, amide, or hydroxyl groups. A coordinator does not necessarily consist of more than one atom. For example, it could simply be the oxygen atom of a carbonyl group, or the hydrogen atom of a hydroxyl group. In such cases, a carbonyl might be said to “coordinate” an ion if the carbonyl oxygen atom is in contact with the ion.

It facilitates discussion to treat the orientations of the coordinators implicitly. Thus, we may define a potential of mean force where the orientations are integrated

$$U(\boldsymbol{r}^N,\boldsymbol{R}) = -k_B T \ln \int d\boldsymbol{\Psi}^N e^{-\beta E(\boldsymbol{r}^N,\boldsymbol{\Psi}^N,\boldsymbol{R})} \qquad \text{[S1]}$$

Though we treat these orientations implicitly, it is worth noting that they are important. For example, a site in a protein might enforce the orientation of coordinators possessing a significant dipole moment in order to determine whether a positive or negative ion will bind favorably. In order to address selectivity among ions of like sign in valence, however, an implicit treatment suffices.

II. Breakdown of the Probability Density Function, ρ

For the purposes of this discussion, the notation $\{R,N\} = \{R,n,N-n\}$ is taken to mean, "the event that the configuration, $\{\boldsymbol{R},\boldsymbol{r}^N\} = \{\boldsymbol{R},\boldsymbol{r}^n,\boldsymbol{r}^{N-n}\}$, occurs." The notation $P(\{A\}|\{B\})$ means, "the conditional probability that event $\{A\}$ occurs given that event $\{B\}$ occurs."

In terms of conditional probability, one may always write (1)

$$P(\{R,N\}) = P(\{R\} \cap \{N\}) = P(\{R\})P(\{N\}|\{R\}) \qquad \text{[S2]}$$

Conditional probabilities in configuration space are often re-expressed for convenience in terms of correlation functions (2). Doing so for the right hand side of Eq. S2, we have

$$P(\{R\})P(\{N\}|\{R\}) = P(\{R\})P(\{N\})C_R(\{R,N\},\xi_R) \qquad \text{[S3]}$$

where C_R accounts for the mutual dependence of events $\{R\}$ and $\{N\}$, and ξ_R is the coupling parameter defined in Eq. 4. When $\xi_R = 1$, there is full interaction between $\{R\}$ and $\{N\}$ degrees of freedom (including the ion at the origin). As $\xi_R \to 0$, $C_R \to 1$, and these degrees of freedom are fully uncoupled.

Applying the logic of Eq. S2 to $P(\{N\})$, we may further write

$$\begin{aligned} P(\{N\}) &= P(\{n,N-n\}) = P(\{n\})P(\{N-n\}|\{n\}) \\ &= P(\{n\})P(\{N-n\})C_C(\{n,N-n\},\xi_C) \end{aligned} \qquad \text{[S4]}$$

where ξ_c couples the interaction of the n coordinators and the ion inside v with the N-n coordinators inside V^C. Hence, substituting Eq. S4 into Eq. S3, we may write

$$P(\{R,N\}) = P(\{R\})P(\{n\})P(\{N-n\})C_R(\{R,N\},\xi_R)C_C(\{n,N-n\},\xi_C) \qquad \text{[S5]}$$

which implies

$$\rho(\boldsymbol{r}^N,\boldsymbol{R}) = \rho_n(\boldsymbol{r}^n)\rho_{N-n}(\boldsymbol{r}^{N-n})\rho_R(\boldsymbol{R})C_n(\boldsymbol{r}^n,\boldsymbol{r}^{N-n},\boldsymbol{R},\xi_C,\xi_R) \qquad \text{[S6]}$$

as we write in Eq. 4, where the correlation function, C_n, may be expressed as a product of correlation functions,

$$C_n(\boldsymbol{r}^n,\boldsymbol{r}^{N-n},\boldsymbol{R},\xi_C,\xi_R) = C_C(\boldsymbol{r}^n,\boldsymbol{r}^{N-n},\xi_C)C_R(\boldsymbol{R},\boldsymbol{r}^N,\xi_R) \qquad \text{[S7]}$$

III. Small System Grand Ensemble: Ion Complexation in Fluid or Gas

For the case of an ion in a fluid composed of coordinators (or model compounds such as water or, say, ethanol or formamide under prescribed macroscopic conditions) *without* any external influence (external field) of protein or other system components as shown in Fig. 1(middle), we may follow the procedure outlined in the Appendix, but with $\xi_R = 0$ for the entire derivation. Thus, $U_\sigma^{CR}(\xi_C,\xi_R \to 0) = U_\sigma^C(\boldsymbol{r}^n,\boldsymbol{r}^{N-n},\xi_C)$, and the free energy of opening a cavity of volume, *v*, around the central ion [analogous to term (a) of Eq. A19], $\phi_{cavity} \to \phi'_{cavity}$, refers to work done against only a fluid of *N* external coordinators (no other system components contribute). And, the "uncoupling" free energy [analogous to term (b) of Eq. A19], $\phi_{uncouple} \to \phi'_{uncouple}$, refers to uncoupling only ionic interactions with all coordinators in the complementary volume.

The surface free energy as defined in Eq. A13 becomes, for a fluid,

$$\varepsilon_n^C = \left\langle e^{-\beta U_\sigma^C} \right\rangle_0 = \int_v d\boldsymbol{r}^n \rho_n \int_{V^C} d\boldsymbol{r}^{N-n} \rho_{N-n} e^{-\beta U_\sigma^C} \qquad \text{[S8]}$$

The superscript "*C*" (as opposed to "*CR*") indicates the fact that we are dealing with an ion solvated in coordinators alone ($\xi_R = 0$). Finally, the partition function for the system within the ion-coordination sub-volume is

$$\Xi_C = \sum_{n=0}^{N} Q_n^C e^{\beta n\mu} = \sum_{n=0}^{N} \frac{z^n Z_n^C}{n!} \qquad \text{[S9]}$$

where $Z_n^C \equiv Z_n^0 e^{-\beta\varepsilon_n^C}$ and $Q_n^C \equiv Q_n^0 e^{-\beta\varepsilon_n^C}$. And the probability density that the system within the sub-volume, *v*, contains *n* coordinators with the configuration $\boldsymbol{r}^n$ is

$$P^C(n,\boldsymbol{r}^n) = \frac{z^n}{n!\Xi_C} e^{-\beta\left[U_n(\boldsymbol{r}^n)+W_n^C(\boldsymbol{r}^n)\right]} \qquad \text{[S10]}$$

where, $W_n^C = W_n^{CR}(\xi_C,\xi_R \to 0)$.

For completeness, we address the problem of ion complexation in a hypothetical gaseous environment of coordinators. In this situation, the interfacial energy, $U_\sigma^C(\boldsymbol{r}^n,\boldsymbol{r}^{N-n},\xi_C \to 0) = 0$ [see Fig. 1(bottom)], thus the open ionic *n*-complex interacts with *nothing* outside of the coordination sphere (i.e. the complex, itself, may be considered a gaseous molecule). It will require no work to form a cavity of volume, *v*, thus $\phi_{cavity} \to 0$, and since the ion is already uncoupled from all degrees of freedom outside the coordination sphere, $\phi_{uncouple} \to 0$. There is no *excess* free energy involved in removing a coordinator from a homogenous ideal gas of coordinators, so the chemical potential in Eq. S9 becomes $\mu \to \Delta\mu^{id} = k_B T \ln(v/V)$. Finally, the configuration integral for the complex will simply be Z_n^0, since the ion complex has no interaction with external species (i.e. the interfacial free energy $\varepsilon_n^C \to 0$), and the partition function for the ionic complex surrounded by a homogenous ideal gas of coordinators is

$$\Xi_{id} = \sum_{n=0}^{N} Q_n^0 e^{\beta n \Delta\mu^{id}} = \sum_{n=0}^{N} \frac{q_c^n Z_n^0}{V^n n!} \tag{S11}$$

Thus, the probability density that the system within the sub-volume, *v*, contains *n* coordinators with the configuration $\boldsymbol{r}^n$ is

$$P^{id}(n,\boldsymbol{r}^n) = \frac{q_C^n e^{-\beta U_n(\boldsymbol{r}^n)}}{V^n n! \Xi_{id}} \tag{S12}$$

IV. Chemical Potential in the Small System Grand Ensemble

In the Appendix and Part *III*, above, the chemical potential, μ, is defined in terms of the macroscopic system in the volume, *V*. As we explain in the Appendix, $\mu = \mu^0 + \Delta\mu^{id}$, where $\Delta\mu^{id} = k_B T \ln(v/V)$ is the free energy to move an uncoupled gaseous coordinator from *v* to *V*, and μ^0 is the free energy to insert the coordinator into a fluid of *N* free coordinators in *V*. However, we may also express μ in terms of the small system alone. In order to facilitate this expression, we make use of a common procedure [see for example refs (3-7)] to define μ in a grand canonical ensemble.

We begin by writing the average number of coordinators in *v* as follows:

$$\langle n \rangle = \sum_{n \geq 0} n P(n) = \frac{z}{\Xi} \sum_{n \geq 1} \frac{z^{n-1} Z_n}{(n-1)!} \tag{S13}$$

where $P(n)$ is the probability to find *n* coordinators in the open sub-volume within an arbitrary medium. Let us define the potential function, $\phi_n(\boldsymbol{r}^n) = U_n(\boldsymbol{r}^n) + W_n(\boldsymbol{r}^n)$, where U is the internal potential defined in Eq. A3, and W is an external field (such as that of Eqs. A24 or S10) representing the arbitrary surrounding environment. Furthermore, let us define the so-called "binding energy" (3,4), $\psi(\boldsymbol{r}^n) = \phi_n(\boldsymbol{r}^n) - \phi_{n-1}(\boldsymbol{r}^{n-1})$ describing the interaction between a single coordinator in *v* and an *n*-1 complex. Note that ψ includes the influence of the system remainder (i.e. from the external field, *W*). The following well-known relation (4,8,9):

$$Z_n = \int_v d\boldsymbol{r}^n \exp(-\beta\phi_{n-1}) \exp(-\beta\psi) = Z_{n-1} v \langle \exp(-\beta\psi) \rangle_{n-1} \tag{S14}$$

Allows us to rewrite Eq. S13,

$$\langle n\rangle = \frac{zv}{\Xi}\sum_{n\geq 1}\frac{z^{n-1}Z_{n-1}}{(n-1)!}\left\langle \exp(-\beta\psi)\right\rangle_{n-1} \qquad \text{[S15]}$$

Shifting the dummy variable in the above summation, $n \rightarrow n+1$, we obtain (8,9)

$$\langle n\rangle = \frac{zv}{\Xi}\sum_{n\geq 0}\frac{z^{n}Z_{n}}{n!}\left\langle \exp(-\beta\psi)\right\rangle_{n} = zv\left\langle \exp(-\beta\psi)\right\rangle \qquad \text{[S16]}$$

Inserting the definition of the activity, *z*, we invert the above equation to obtain an expression for μ in the context of the small system,

$$\mu = \overbrace{-k_BT\ln\left(q_C/\langle n\rangle\right)}^{\mu^{id}}\overbrace{-k_BT\ln\left\langle \exp(-\beta\psi)\right\rangle}^{\mu^{ex}} \qquad \text{[S17]}$$

where the first and second terms on the right hand side of Eq. S17 represent ideal and excess portions of the chemical potential, respectively.

V. A Few Physical Properties of the Ionic Complex

The development we give in this work, allows us to connect the structural parameters that are normally associated with ion binding via coordination (for example, coordination number and radius) with their probabilistic (and free energetic) implications for the binding event. Here, we define a few physical properties of an ion-bound complex using the concepts developed. Given the probability density that an ion-coordinated complex is composed of *n* coordinators at configuration, $\boldsymbol{r}^n$, in an arbitrary medium, $P(n,\boldsymbol{r}^n) = P(n)\rho_{(n|n)}(\boldsymbol{r}^n)$, among the most obvious properties are the average coordination number of the complex,

$$\langle n\rangle = \sum_{n} nP(n) \qquad \text{[S18]}$$

and the fluctuation in coordination number of the complex,

$$\sigma_n^2 = \left\langle n^2\right\rangle - \langle n\rangle^2 = \sum_{n}\left(n-\langle n\rangle\right)^2 P(n) \qquad \text{[S19]}$$

It is useful to know the probability that a particular coordinator (say, the first coordinator out of *n*) is in *dr* at a distance *r* from the ion in an ion-bound *n*-complex, irrespective of the positions of the other *n*-1 coordinators:

$$\begin{aligned}\rho_n(r) &= \int_v\cdots\int_v d\boldsymbol{r}_2\ldots d\boldsymbol{r}_n\int_\Omega d\Omega_1 r^2 P(n,\boldsymbol{r}^n) \\ &= P(n)\int_\Omega d\Omega_1 r^2 \rho_{(1|n)}(\boldsymbol{r}_1)\end{aligned} \qquad \text{[S20]}$$

where $\int_{\Omega} d\Omega$ represents an integral over solid angle. The probability that a particular coordinator is in *dr* at distance *r* from the ion irrespective of the number of other coordinators in the sub-volume *or* their positions may be written as

$$\rho(r) = \sum_{n\geq 1} \rho_n(r) \qquad [S21]$$

With this in hand, we may define the optimal coordination radius as

$$R_c = \max_r \left[\rho(r)\right] \qquad [S22]$$

Note that this quantity is generally not equal to the average coordination radius

$$\langle r \rangle = \int_0^{r_c} dr\left[r\rho(r)\right] \qquad [S23]$$

unless the binding site is in a solid phase (i.e. a crystal), in which case we can expect a nearly Gaussian distribution for $\rho(r)$. Finally, we may define the isothermal compressibility of the coordinated ion complex

$$\chi_T = -\frac{1}{v}\left(\frac{\partial v}{\partial p}\right)_T = \frac{\beta v \sigma_n^2}{\langle n \rangle^2} \qquad [S24]$$

which is easily derived in the context of a grand canonical ensemble(4,10) and is equal to the inverse of the bulk modulus, $\kappa = 1/\chi_T$.

Supplementary Text

A Note on the Difference between the Order Parameters: R_{avg} (average coordination radius) and r (the coordination radius, itself – i.e. the radial position of any given oxygen in an ionic complex)

In viewing the $[\Delta\Delta J_{CR}^{A\rightarrow B}(R_{avg})]$ profiles of Fig. 6, from the main text, one might note that, in most cases, the "zero-point" of neutral selectivity, judging from Table I, sometimes lies somewhere between the optimal hydration radii, R_{opt}, for ions *A* and *B*. The exception to this trend is the curve, $\Delta\Delta J_{CR}^{Br\rightarrow Cl}(R_{avg})$, which gauges selectivity for Br^- over Cl^-. This exception is explained by considering the linear probability density for finding a water oxygen atom at a given distance from the central ion [not to be confused with the distributions, $P^C(R_{avg})$, in Fig. 6 – see Fig. S3]. These density functions generally reveal maxima that occur at smaller radial distances with respect to the distributions of Fig. 6, because the distance of closest approach for a single oxygen atom in a complex may be smaller than that presented by the *average* of Eq. 17 presented in the main text. On one hand, the difference in maxima can be small enough for the resulting neutral selectivity "zero-point" to occur at nearly coincidental radial positions (e.g. see Figs. S3C and S3D, which yield neutral selectivity for K^+ over Na^+ at a radial position of 2.62 Å. This is comparable with the radial position of 2.66 Å – the value of R_{avg} derived from the red curve in Fig. 6B). On the other hand, the difference in maxima can be large enough such that the R_{avg} position of zero selectivity exceeds R_{opt} of the larger ion. For example, see Figs. S3A and S3B, which yield neutral selectivity for Br^- over Cl^- at 3.38 Å [a radial position that falls between the R_{opt} values for these respective ions – 3.23 Å for Cl^- and 3.41 Å for Br^- (see Table I)]. This value is much smaller than that derived from the red curve in Fig. 6D, 3.53 Å, which, in fact, exceeds the optimum coordination radius, R_{opt}, of Br^- (3.41 Å). The similarities and/or differences between the points of neutral selectivity derived from the different constructs of Fig. 6 compared with Fig. S3 should not be assigned specific meaning, because their varying results are merely due to a particular choice in order parameter (i.e. the parameter R_{avg} is not equivalent to the coordination radius, itself – see STF *Part V*, above).

A Note on the Molecular Models (Force Fields) Used in this Work

Our analyses make use of tested polarizable molecular models for smaller Family IA (Li^+, Na^+, K^+) ions, VIIA (F^-, Cl^-, Br^-) ions, and water (11-15). In the case of cations, we further explore the implications of choice in force field by performing analogous analyses of trajectories derived from pairwise additive models (16,17). As with similar previous analyses (18), we found qualitative agreement between the structural and corresponding free energetic (potential of mean force) results derived from simulations employing the polarizable and pairwise additive force fields (see the comparisons outlined in Table I, Figs. 3-4, and Fig. 5B. Also, compare the distributions of Fig. 5A with the analogous distributions in Fig. S1A, and the distributions of Fig. 6A with those of Fig. S2A). Among these comparisons, the largest differences were seen in the case of Li^+. Such differences can be expected, because the smaller; more kosmotropic Li^+ ion should induce larger polarization of nearby water molecules. Nonetheless, the observed differences for Li^+ do not qualitatively change the results or conclusions of this work. We extend our analysis to a tested model of Rb^+ in the case of pairwise additive models (16,17). Given the observed agreement in (polarizable and pairwise additive) population analyses for larger cations, we do not expect the analyses of Rb^+ coordination to qualitatively change upon introduction of electronic degrees of freedom. However, we do not pursue validation of such expectations for Rb^+ here.

To further inform previous results pertaining to cation complexation by "bare" fictitious carbonyl moieties (18-23), we extended our (HCF) fluid analyses of Na^+, K^+, and Rb^+ in the context of such coordinators (see Methods, and Figs. 3-5, Figs. 7-9, and Figs. S1-S2). We did not extend this analysis to Li^+, because we expect Li^+ to induce a large polarization in carbonyl moieties (as compared to water molecules), and because we do not pursue comparison of these results with polarizable models of carbonyl-containing compounds. Moreover, given that a fictitious carbonyl group does not represent a "real" chemical species, but a construct where a C=O moiety is "stripped" of two of its bonds, it can only be reasonably defined in the context of available pairwise additive force fields. This makes direct comparison with polarizable models more difficult. Nonetheless, the trends in our analyses with such models is in qualitative agreement with results from prior studies of carbonyl-containing compounds that include electronic degrees of freedom (23-26). We must note, however, that the uncoupled contribution to the K^+/Na^+ selectivity for the carbonyl HCF, $\Delta\Delta J_C^{K\rightarrow Na} \approx 1.8$ kcal/mol, is similar to that obtained from pairwise additive models of liquids comprised of carbonyl-containing compounds, such as N-methylacetamide [~1.6 kcal/mol (20)] or formamide [~0.9-1.3 kcal/mol (11)]. However, both experimental measurements and molecular models employing electronic degrees of freedom suggest that the selective free energy for K^+ over Na^+ in organic liquids such as these will be lower (less than ~1 kcal/mol) or slightly negative (11,23,24,27). Given this, we might expect the positive shift in K^+/Na^+ selective free energy mappings (due to the uncoupled $\Delta\Delta J_C^{K\rightarrow Na}$) in Figs. 5B, 7A(right), 8A(right), and 9A(right) to be slightly lessened upon incorporation of electronic degrees of freedom.

Supplementary Figures

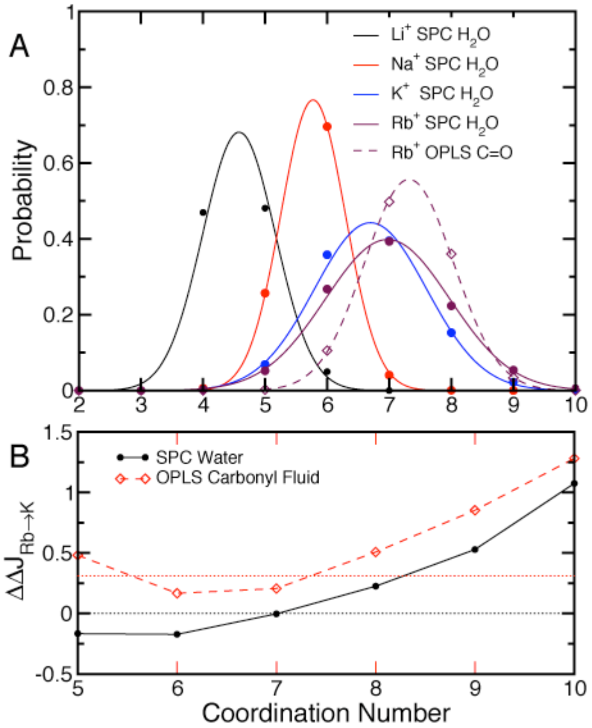

Fig S1: Population analysis of coordination numbers for cations in SPC water or OPLS carbonyl HCF for models not included in the main text. (A) Quasicomponent distributions. Note that the SPC water distribution functions are qualitatively similar to those derived from the AMOEBA forcefield (Fig. 5A), although the distribution for Li$^+$ is more broad in SPC water than observed with AMOEBA. We also note that the distributions gleaned from the carbonyl fluid give qualitatively similar distributions to those derived from either of the water models, although the carbonyl HCF distributions are slightly less broad (indicating a stiffer coordination shell). (B) Selective free energy (kcal/mol) for Rb$^+$ over K$^+$ in water and carbonyl HCF as a function of coordination number. The horizontal dotted lines indicate the uncoupled selectivity, $\Delta\Delta J_C$ (see Eqs. 10 or 16) in each uncoupled fluid medium [zero, by definition, for water, and calculated to be 0.31 ± 0.04 kcal/mol in the carbonyl HCF using a thermodynamic integration protocol described in previous work (18)]. It is interesting to note that, at 8-fold coordination, both water and carbonyl HCF slightly select Rb$^+$ over K$^+$, indicating that, in a canonical 8-fold K$^+$ channel binding site, the K$^+$ channel protein must exert additional force on the complex to maintain a mild [$S_{\mathrm{Rb}\rightarrow\mathrm{K}} \approx 1.25$ corresponding to a selectivity of -0.13 kcal/mol (28)] K$^+$ selectivity.

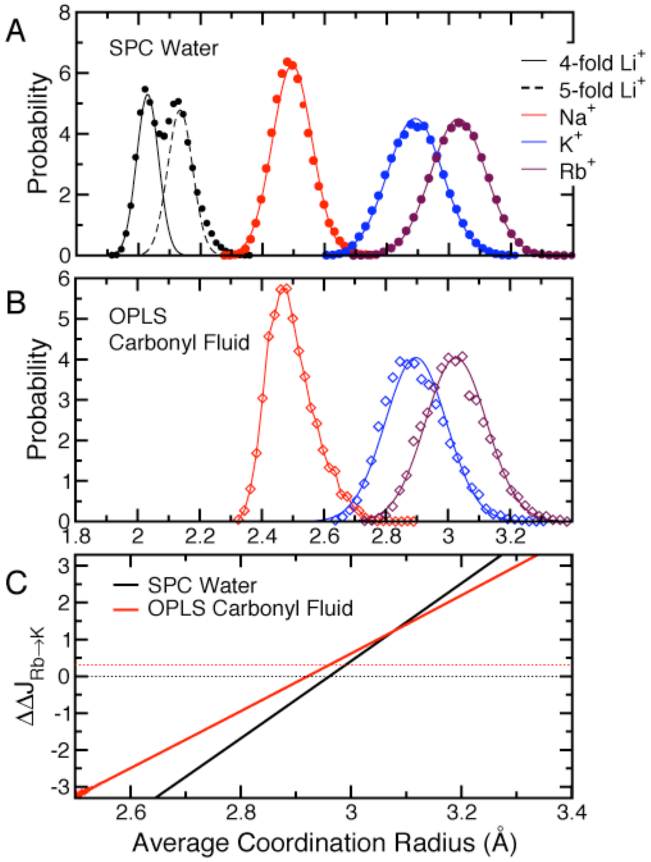

Fig S2: Population analysis of average ion-oxygen coordination radius (irrespective of the complex coordination number) for cations in SPC water or OPLS carbonyl HCF. (A) Probability of attaining a particular average coordination radius for small monovalent Family IA cations in SPC water. As in Fig. 5 of the main text, the distributions are reasonably approximated with Gaussian probability models except for that of Li$^+$, which displays multimodality due to the tight correlation between the average coordination radius and the coordination number. Thus, for Li$^+$, we show how the net distribution (closed circles) is largely accounted for by the 4-fold and 5-fold coordinated states taken together. The distributions are in qualitative agreement with those from the AMOEBA force field (see Fig. 6A). (B) Probability of attaining a particular average coordination radius for small monovalent Family IA cations in an OPLS carbonyl HCF. Only the distributions for K$^+$ and Rb$^+$ were modeled with Gaussians due to the skewness of the Na$^+$ distribution. The Na$^+$ raw probabilities are shown interpolated with straight lines. Note that the distributions are similar to those provided by both water models (see Figs. 6A and S2A). (C) Free energy of selectivity for Rb$^+$ over K$^+$ as a function of the average coordination radius. Horizontal dotted lines are drawn to indicate $\Delta\Delta J_C$ for either fluid as in Fig. S1B. We note that since constraints on the coordination number irrespective of the configuration (Fig. S1B) produces only mild to no selectivity for K$^+$ over Rb$^+$, the steeper dependence of the selectivity on the average coordination radius shown here indicates that constraints on this parameter will be a more effective way to elicit selectivity for either species.

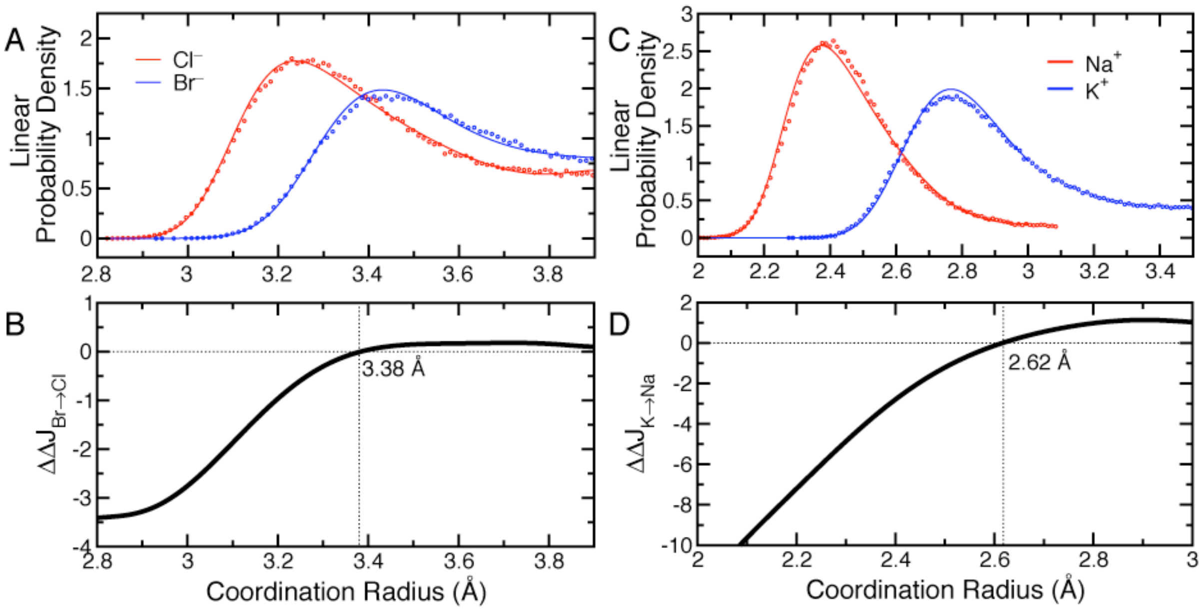

Fig S3: Exemplary analysis of monovalent anion and cation selectivity as a function coordination radius (not to be confused with *average* coordination radius) derived from solvated ion-water systems using the AMOEBA force field. (A) Linear probability density, $\rho(r)$, for finding a given coordinating water oxygen atom at a given distance, r, from a Cl^{-} (red data) or Br^{-} (blue data) ion. Raw data are shown as points, and solid lines are the results of polynomial fits to the raw potential of mean force, $w(r) = -\ln \rho(r)$. (B) Free energy of selectivity for Br^{-} over Cl^{-} as a function of the coordination radius. The point of zero selectivity is at $r = 3.38$ Å. Below this value, the hypothetical host will be Cl^{-} selective, and above this value, the host will be mildly Br^{-} selective, indicating that constraining the coordination radius, alone, is more effective in providing selectivity for smaller anions over larger ones (rather than vice versa). (C) Linear probability density, $\rho(r)$, for finding a given coordinating water oxygen atom at a given distance, r, from a Na^{+} (red data) or K^{+} (blue data) ion. Raw data are shown as points, and solid lines are the results of polynomial fits to the raw potential of mean force, $w(r) = -\ln \rho(r)$. (B) Free energy of selectivity for K^{+} over Na^{+} as a function of the coordination radius. The point of zero selectivity is at $r = 2.62$ Å. Below this value, the hypothetical host will be Na^{+} selective, and above this value, the host will be mildly K^{+} selective, indicating that constraining the coordination radius, alone, is more effective in providing selectivity for smaller cations over larger ones (rather than vice versa).

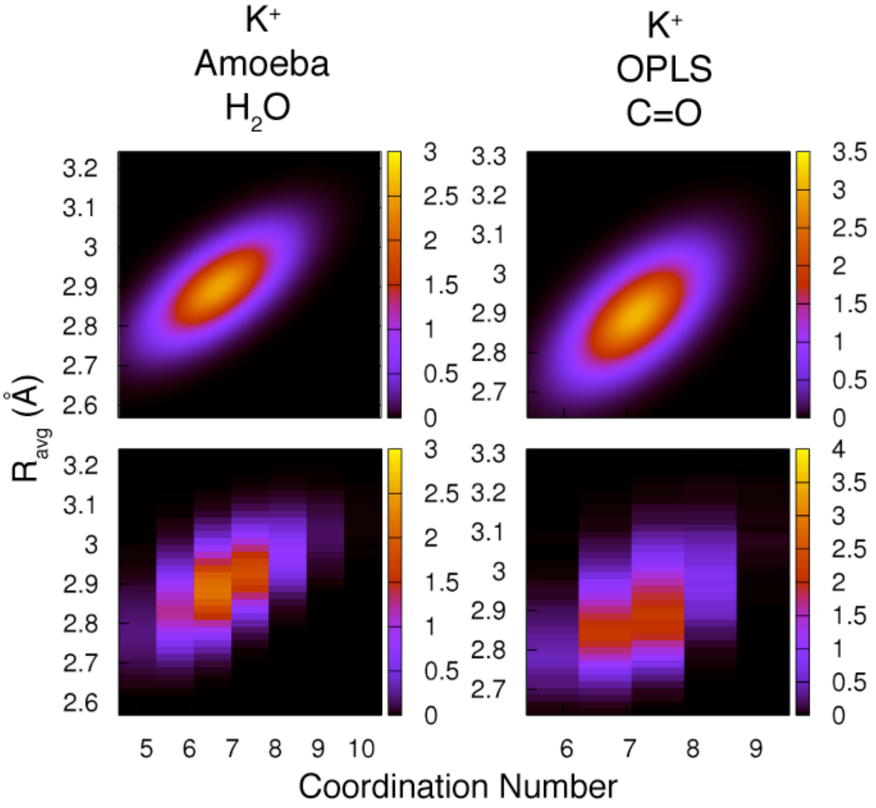

Fig S4: Probability distribution, $P(R_{avg},n)$, of observing a given ion-oxygen average coordination radius, R_{avg}, given attainment of coordination number, n, around K^+ derived from simulations of K^+ in either AMOEBA water (left panels) or an OPLS carbonyl HCF (right panels). These distributions were used to derive the selective domain mappings of Fig. 7A. Two-dimensional Gaussian probability models (top panels) were seen to be representative of the raw distributions (bottom panels).

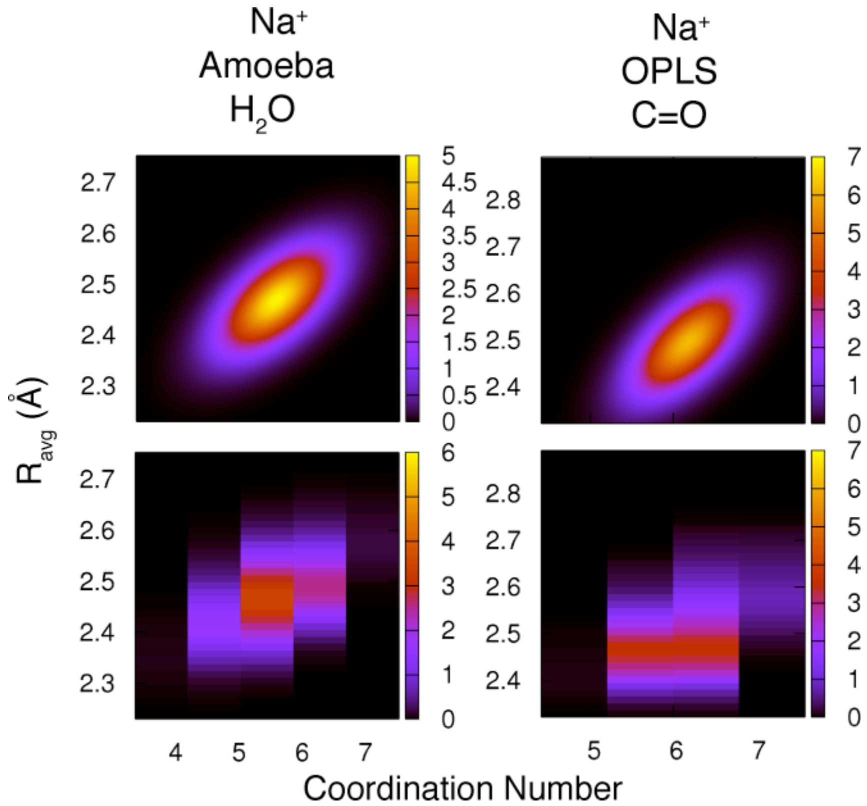

Fig S5: Probability distribution, $P(R_{avg},n)$, of observing a given ion-oxygen average coordination radius, R_{avg}, given attainment of coordination number, n, around Na^+ derived from simulations of Na^+ in either AMOEBA water (left panels) or an OPLS carbonyl HCF (right panels). These distributions were used to derive the selective domain mappings of Figs. 7A and 7B. Two-dimensional Gaussian probability models (top panels) were seen to be representative of the raw distributions (bottom panels).

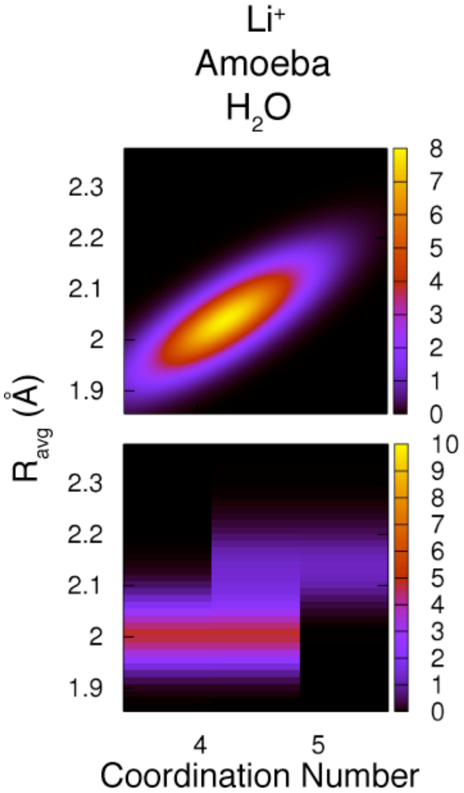

Fig S6: Probability distribution, $P(R_{avg},n)$, of observing a given ion-oxygen average coordination radius, R_{avg}, given attainment of coordination number, n, around Li^+ derived from simulations of Li^+ in AMOEBA water. This distribution was used to derive the selective domain mapping of Fig. 7B. A two-dimensional Gaussian probability model (top panel) was seen to be representative of the raw distribution (bottom panel).

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