Case study of Rb\textsuperscript{+}(aq), quasi-chemical theory of ion hydration, and the no split occupancies rule

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Quasi-chemical theory applied to ion hydration combines statistical mechanical theory, electronic structure calculations, and molecular simulation, disciplines which are individually subjects for specialized professional attention. Because it combines activities which are themselves non-trivial, quasi-chemical theory is typically viewed with surprise. Nevertheless, it provides a fully-considered framework for analysis of ion hydration. Furthermore, the initial calculations are indeed simple, successful, and provide new information to long-standing experimental activities such as neutron diffraction by hydrated ions. Here we review quasi-chemical theory in the context of a challenging application, Rb\textsuperscript{+}(aq).

1 Introduction

Water is a chemically active liquid. Probably the most primitive aspect of that chemical activity is dissolution of electrolytes, and the chemical processes based on availability of dissolved ions. One example is salt as a trigger of autoimmune disease.\textsuperscript{1–4} Another example, presumably related to the first,\textsuperscript{5,6} is the selective transport of dissolved ions across membranes.\textsuperscript{7–9} Rubidium (Rb\textsuperscript{+}) is interesting in this respect because it serves as an analog of potassium (K\textsuperscript{+}) that conducts current through potassium ion channels, even though Rb\textsuperscript{+} is slightly larger (by 0.2 Å).\textsuperscript{10,11}

In addition to this chemical activity, water has long been a serious challenge for statistical mechanical theory of liquids, which itself is properly almost entirely classical mechanical theory.\textsuperscript{12} The challenge presented by liquid water is the variety of intermolecular interactions that must be considered with a wide range of interaction strengths (Fig. 1).\textsuperscript{13} Those interactions include excluded-volume repulsions, essential since liquids and liquid water are dense materials. Those interactions also include H-bonding interactions that are attractive on balance, much stronger than thermal energies, and essential for the characteristic behavior of liquid water.

Attractive interactions that involve many neighbors are good candidates for treatment by mean-field approximations.\textsuperscript{16,17} Of course, if those attractive interactions are individually weak on a thermal energy scale, that characteristic is favorable for simple theories also.

Here we consider rubidium dissolved in aqueous solution, Rb\textsuperscript{+}(aq), to provide a contrast with theories of liquids more broadly,\textsuperscript{16,17} and to pursue a specific discussion of what is yet required theoretically to treat solvated electrolytes. The hydration free energy of Rb\textsuperscript{+}(aq) is known to be roughly $-100 k_B T$ under standard conditions, favorable enough to dissolve sim-
ple Rb\(^+\) salts, and indeed large on the thermal energy scale. Additionally (Fig. 2), the number of near-neighbors is modest, between four and seven. As another contrast, the isoelectronic Kr(aq) has about eighteen (18) near-neighbors.\textsuperscript{15} From this comparison it is clear that the features of strong attractive interactions and a reduced number of near-neighbors are correlated: the reduced number is a consequence of the crowding of near-neighbors drawn close by the interesting attractive interactions.

This discussion suggests that we seek a way forward by focusing on the small number of near-neighbors, deploying direct quantum mechanical computation for Rb(H\(_2\)O)\(_n^+\) with a small number \(n\) of neighbors, then stitching those computational results into the broader theory of liquids. That was indeed the idea of quasi-chemical theory discussed here. At a formal level that theory is fully conclusive, but it is surprising that it was not worked-out until fairly recently.\textsuperscript{30,33,37,41} It was also surprising that the initial applications of the theory, to Li\(^+\)(aq)\textsuperscript{39} were highly effective — predictions of hydration free energy matched experiment\textsuperscript{27} and ab initio molecular simulation estimates.\textsuperscript{28} Further, the initial applications provided new information to long-standing neutron diffraction work on hydrated ions\textsuperscript{69} and indeed motivated renewed effort on those experiments.\textsuperscript{30}

The initial applications of quasi-chemical theory could be understood on a physical and intuitive basis. That encouraged the generation of simple mimics that were less fully thought through. A focused discussion of the statistical thermodynamic formalities was given by Asthagiri,\textit{et al.}\textsuperscript{31} with the intention of reducing the confusion that can result from a crowd of imitators. The presentation of Asthagiri,\textit{et al.}\textsuperscript{31} will be the basis of the discussion that follows.

2 Theory

The primary theoretical target for quasi-chemical theory has been the excess (or interaction part) of the partial molar Gibbs free energy (or chemical potential) of the species of interest, here the Rb\(^+\)(aq). This \(\mu_{\text{Rb}^+}^{(\text{ex})}\) is indeed a basic characteristic of the solution and the Rb\(^+\) ion in it, but it is also comparatively simple. The potential distribution theorem\textsuperscript{12} offers a partition function for evaluation utilizing information obtained on the local environment of the ion. It is found that the desired free energy can be cast as

\[ \mu_{\text{Rb}^+}^{(\text{ex})} = -kT \ln K_n^{(0)} \rho_{\text{H}_2\text{O}}^n + kT \ln \rho_{\text{Rb}^+} (n) + \mu_{\text{Rb}^+}^{(\text{ex})} + \mu_{\text{Rb}(\text{H}_2\text{O})_n^+}^{(\text{ex})} - n \mu_{\text{H}_2\text{O}}^{(\text{ex})} \]  

On the right side, notice the reference to the molecular complex Rb(H\(_2\)O)\(_n^+\) and its excess free energy \(\mu_{\text{Rb}(\text{H}_2\text{O})_n^+}^{(\text{ex})}\); the treatment of the complex itself as a chemical constituent is a characteristic feature of this quasi-chemical theory.\textsuperscript{12,22,24,31}

Other features of Eq. (1) properly fill-in a picture of the chemical equilibrium of this complex. The combination \(\mu_{\text{Rb}(\text{H}_2\text{O})_n^+}^{(\text{ex})} - n \mu_{\text{H}_2\text{O}}^{(\text{ex})}\) begins a free energy balance for the association reaction

\[ \text{Rb}^+ + n\text{H}_2\text{O} \rightleftharpoons \text{Rb}(\text{H}_2\text{O})_n^+ . \]  

Similarly,

\[ K_n^{(0)} = \frac{\rho_{\text{Rb}(\text{H}_2\text{O})_n^+}}{\rho_{\text{Rb}^+} \rho_{\text{H}_2\text{O}}^n} , \]  

with \(\rho_X\) the number density of species X, is the equilibrium ratio for that association reaction (Eq. (2)) treated as in an ideal
Fig. 3 The coordination number distribution, for the inner-shell radius of $\lambda = 3.76$ Å, from the AIMD simulations and an “LJ model.” For the LJ model, we used Åqvist Lennard-Jones parameters for the Rb$^+$ ion, ($\sigma = 1.71 \times 10^{-9}$ kcal/mol, $\sigma = 5.62177$ Å), and the SPC/E potential for water intermolecular interactions. We carried out standard NVT molecular dynamics calculations using the GROMACS package (version 3.1.4). The system consisted of one Rb$^+$ and 2177 water molecules in a (40 Å)$^3$ cell. A single Cl$^-$ was included for charge balance. For electrostatic interactions, the particle mesh Ewald technique was implemented with Fourier spacing of 1.5 Å, a sixth-order interpolation, a 10 Å cutoff in a direct space, and a tolerance of $10^{-5}$. A cutoff distance of 16 Å was adopted for the Lennard-Jones interactions. Intramolecular geometric constraints on water molecules were enforced by the SETTLE algorithm. Data was collected during a 1.0 ns production phase, following a 1.0 ns equilibration phase. The Nose-Hoover thermostat with a coupling constant of 0.2 ps maintained $T = 298.15$ K. The variation in coordination number $n$ is substantially smaller for the LJ model data than for the AIMD results; but remember that the AIMD results correspond to the slightly higher $T \approx 350$ K.

The remaining feature of Eq. (1) is the probability $p_{Rb^+}(n)$ of observing $n$ ligands within a defined inner shell (Fig. 3). That inner shell is a fundamental concept for this approach, and we return below to discuss it further. For now, note that if only one coordination number $n$ were ever observed, then $p_{Rb^+}(n) = 1$ and that contribution in Eq. (1) would vanish. Ultimately, that contribution in Eq. (1) carries the full thermodynamic effect of whatever actual variability of inner-shell occupancy does occur.

Leaving the occupancy probability for general consideration, the left side of Eq. (1) is independent of $n$, and Eq. (1) therefore describes the $n$-dependence of the probability $p_{Rb^+}(n)$. If our goal is to evaluate the free energy, however, we can choose $n$ for our convenience. An interesting choice is $n = \bar{n}$, the most probable value (Fig. 4). This choice makes the negative contribution $kT \ln p_{Rb^+}(\bar{n})$ as small as possible, and suggests neglecting that contribution to obtain the convenient approximation

$$\mu_{Rb^+}^{(ex)} \approx -kT \ln k_{\bar{n}}^{(0)} \rho_{H_2O} \bar{n} + \mu_{Rb(H_2O)_{\bar{n}}}^{(ex)} - \bar{n} \mu_{H_2O}^{(ex)} \tag{4}$$

The neglected contribution is negative, and the approximate result Eq. (4) will be higher than the true free energy. Nevertheless, a specific evaluation of $p_{Rb^+}(\bar{n})$ can be straightforwardly extracted from standard molecular simulations and thus the significance of fluctuations of composition of the inner shell is obtained merely by noting the size of the neglected $kT \ln p_{Rb^+}(\bar{n})$. Those results are obtained and discussed below.

3 Application to Rb$^+$ (aq)

The primitive quasi-chemical theory, Eq. (4), has indeed been applied to several hydrated metal ions as well as other solvation problems. For transition metals, as examples, the near-neighbor water molecules are clearly located on the basis of chemical considerations, and this theory is straightforwardly successful. Generic procedures for those standard cases were given by Pratt and Asthagiri. For other cases, some physical judgement is required, and evaluation of the various contributions to Eq. (1) requires analysis. We consider application to Rb$^+$ (aq) to show how that goes.

3.1 No split occupancies

It is important that theories teach how to understand physical problems in addition to reproducing numerical values of central properties. For our present problems, that learning is focused on how to categorize near-neighbor water molecules to make simple theories effective.

For cases like Rb$^+$, in contrast to transition metals, the important observations arise from the AIMD simulation results
of Fig. 4. The first minimum of the radial distribution is remarkably mild and does not provide a convincing identification of an inner shell. Instead, we consider the neighborhood decomposition of that radial distribution. We see that the 7th-most nearest neighbor \((n=7)\) contributes to the first maximum (with negligible contribution to the peak), the second maximum, and the first minimum. In other words, the contribution of the 7th-most distant water neighbor to \(g(r)\) is multi-modal.

To make our problem simple, we try to set an inner-shell volume so that the 7th neighbor does not contribute. We see from Fig. 5 that \(p_{Rb^+}(n=7)\) is particularly small for an inner-shell radius of \(\lambda = 3.2 \text{ Å}\). With the indicated choice of inner hydration shell, we notice further that neighbors 1-4 fill-out the principal maximum of that radial distribution function.

This lesson we will call the no split occupancies rule. These neighborhood analyses have become characteristic of quasi-chemical theories and were used previously for \(\text{Li}^+(aq), \text{Na}^+(aq)\) and \(\text{K}^+(aq)\).\(^{53,56,79}\)

### 3.2 Methods

To evaluate the quasi-chemical free energy contributions to \(\mu_{Rb^+}^{ex}(aq)\), we start with the first term of Eq. 4. This term gives the free energies for association of \(Rb^+\) with \(n\) water ligands to form clusters within our choice of inner-shell radius \((\lambda = 3.2 \text{ Å}.)\). These clustering equilibria take place in an ideal gas with a water density corresponding to a pressure of 1 atm.

Gas-phase thermochemical data required for the association reactions (Eq. 2) were obtained by electronic structure calculations using the Gaussian09 program\(^{64}\) and density functional theory with Becke’s three-parameter exchange functional\(^ {65}\) and the LYP\(^ {66}\) electron correlation function (B3LYP). All structures were fully optimized with a basis including polarization and diffuse functions (6-311++G(2d,p)) on oxygen and hydrogen centers, and the L3NL2dz effective core potential and basis set on \(Rb^+\). At the lowest-energy geometry, confirmed by zero-valued slopes of the electronic energy with respect to atomic displacements, a standard Hessian analysis was performed to compute normal mode vibrational frequencies\(^ {67,68}\) using the same basis set. Quantum mechanical partition functions were then calculated,\(^ {69}\) thus providing a determination of the free energy changes of the association reactions due to atomic motions internal to water and the clusters at temperature \(T = 298\) K and 1 atm pressure.

In a subsequent step, the cluster results were adjusted with a ligand replacement contribution, \(n \ln \rho_{H_2O}\), to account for the actual concentration of water ligands in liquid water at the density \(\rho_{H_2O} = 1 \text{ g/cm}^3\). If this density is tracked as an adjustment of the ideal gas pressure, then it corresponds to a pressure factor of 1334 atm.

To compute the last two terms of Eq. 4, \(\mu_{Rb(H_2O)}^{ex(aq)} - \mu_{Rb(H_2O)}^{ex(g)}\)
Fig. 5 Coordination number distributions within inner hydration shells defined by various \( \lambda \): upper AIMD, lower LJ model. The AIMD results display a modest but distinct tendency toward lower coordination numbers. This is possibly connected to the generally incorrect description of overlap repulsions by LJ interactions.

\( n \mu_{(ex)}^{Rb+} \), we treated the solvent external to individual water ligands and the inner-shell clusters as a reaction field using a polarizable continuum model (PCM). We subtracted the gas-phase electronic structure energy for the \( n \)-coordinate cluster geometry to obtain the desired excess free energies. These two terms combined make up the outer-shell electrostatics contribution. Finally, we evaluated \( \text{Rb}^+ \) hydration free energy, \( \mu_{(ex)}^{Rb+} \), by summing the quasi-chemical components for formation of the most probable complex (Eq. 4), \( \text{Rb}^+(\text{H}_2\text{O})_n \).

The integral equation formalism (IEF-PCM) was implemented for the outer-shell electrostatics calculations. A radius of 3.2 Å around \( \text{Rb}^+ \) defined the inner-shell boundary. In addition, default parameters were used to define hydrogen and oxygen radii used to create the solute cavity as a set of overlapping spheres. The dielectric constant of the outer-shell medium was set to 78.35 to represent liquid water.

### 4 Results

The principal maximum of the Rb-O radial distribution function (Fig. 2) is near \( r \approx 3.0 \) Å. Experimental studies report similar results for the location of this maximum: 2.93 ± 0.3 Å, 2.90 Å, and 3.05 Å.

The free energy results (Fig. 6) show that the coordination number \( n = 4 \) is indeed the most probable within the inner hydration shell defined by \( \bar{\lambda} = 3.2 \) Å. This then implies \( \mu_{(ex)}^{Rb+}(\text{aq}) = \mu_{(ex)}^{(\text{H}_2\text{O})_n} = -65.4 \text{ kcal/mol} \), which agrees reasonably with the experimental value of \( -69.51 \text{ kcal/mol} \).

Addressing Eq. (4), several approximations have accumulated. The first of those is the neglect of population fluctuation. From Fig. 5 we see that this error amounts to \( kT \ln p_{Rb^+}(\bar{n}) \approx -0.6 \text{ kcal/mol} \), roughly a 1% error on the predicted hydration free energy. This could be easily appended to the final result, but it is not significant here.

Further approximations entered to evaluate the free energies on the right side of Eq. (4). A normal mode analysis yields harmonic frequencies that are expected to represent the vibrational motions for small ion-water clusters. A perturbative analysis of anharmonicity in the electronic energy surface confirmed that vibrations in the \( \bar{n} = 4 \) cluster are well-described by normal mode analysis. If anharmonicity were important, the corrections could easily be included in the final result.

A serious approximation is the treatment of the external environment as a dielectric continuum when considering \( \mu_{(ex)}^{Rb(\text{H}_2\text{O})_n} - n \mu_{(ex)}^{\text{H}_2\text{O}} \). This approximation is clearly not realistic on a molecular scale, i.e., the solvent is not actually a dielectric continuum. But in this application, the dielectric continuum model is used for outer-shell electrostatic effects, and thus molecular-scale inaccuracies should be less serious.
Contributions from the primitive quasi-chemical evaluation of $\mu_{\text{Rb}^+(\text{aq})}$. The predicted hydration free energy is $-65.4$ kcal/mol when the outer-shell electrostatics contribution is based on a single $n = \bar{n} = 4$ solvent-adapted cluster configuration. Using instead many configurations sampled from the AIMD simulation record, the outer-shell electrostatics contributions are similar, but slightly lower, and predict $\mu_{\text{Rb}^+(\text{aq})} = -70.5$ kcal/mol. The modeled inner-shell occupancy distributions $p_{\text{Rb}^+(n)}$ resemble the observations from the AIMD simulation (Fig. 3, $\lambda = 3.2$ Å), plotted with open boxes where the constant $c$ is adjusted to match the single-point QCT model at $n = \bar{n} = 4$. This qualitatively satisfactory comparison achieved with both single and multiple solvent-adapted structures (highlighted by shading) stands in contrast with a previous primitive assessment\(^{20}\) for K$^+$ (aq) that is expected to be physically similar. That previous work did not attempt a detailed examination of the theory, nor did it consider specifically a neighborship analysis (Fig. 5), as has been long customary.\(^{25,29,56,57,59}\)

Moreover, because of the balance of free energies in this contribution, there is an opportunity for molecular-scale inaccuracies to cancel to some extent.

It is also remarkable and approximate that we calculated $\mu_{\text{Rb}^+(\text{H}_2\text{O})_4}^{(ex)}$ on the basis of a single cluster configuration and electronic charge distribution. Moreover, we based the estimate of $\mu_{\text{Rb}^+(\text{H}_2\text{O})_4}^{(ex)}$ on the geometry and electronic charge distribution of the cluster that has been subtly altered by the environment. This inclusion of a solvent reaction field is expected\(^{25}\) to be an improvement for simple dielectric and Gaussian distribution theories of solvation free energies. Further, this approach represents a distinct change from typical procedures used previously.\(^{25}\) Although the cluster structures ($n=1$-8) are only subtly different on the basis of casual inspection, the results of Fig. 6 for $n \geq 5$ are decisively improved. With previous procedures, the present results become qualitatively like the published, and puzzling, results for K$^+$ with $n \geq 5$\(^{25}\). Of course, the similarity of Rb$^+$ and K$^+$ is the natural physical expectation. The implied computed hydration free energy based on $\bar{n} = 4$ is not much changed in quality compared to estimates based on the earlier procedures as also noted previously.\(^{52}\) For example, $\mu_{\text{Rb}^+}$ is only 2 kcal/mol more positive using Eq. 4 based on a single cluster geometry and electronic charge distribution independent of the environment. The difference here is that now the overall occupancy distribution (Fig. 5) is also qualitatively reasonable.

This single-point estimate of the cluster free energy was tested by sampling inner-shell structures from the AIMD simulation record and evaluating electrostatic contributions to the free energies using a simple dielectric continuum solvation model. In that case, the excess free energies of the sampled clusters and individual water ligands were estimated using the APBS-version 1.3 software\(^{27}\) with the same parameters described earlier.\(^{53}\) Results for the sampled clusters were then combined in the thermodynamically consistent fashion, i.e., by adding the inverses of the Boltzmann factors. That test produced slightly lower outer-shell electrostatic contributions and $\mu_{\text{Rb}^+(\text{aq})} = -70.5$ kcal/mol, thus confirming the results above. The conclusion appears to be that isolated $n \geq 5$ clusters are sufficiently unusual in structure to cause trouble for single-point estimates of $\mu_{\text{Rb}^+(\text{H}_2\text{O})_4}^{(ex)}$ based on gas-phase structures. Single solvent-adapted structures, or structures sampled from liquid-phase simulations, result in a satisfactory improvement.

5 Concluding Discussion

Using AIMD simulation and primitive quasi-chemical theory, we find that $n = 4$ waters preferentially solvate Rb$^+$ within a spherical inner shell defined by radius $\lambda = 3.2$ Å. This boundary extends slightly beyond the first peak of the Rb-O radial
distribution function observed in AIMD simulations and reported in experiments \( (r = 3.0 \text{ Å}) \), but lies well within the putative minimum at \( r = 3.8 \text{ Å} \) occupied by \( n = 7 \) waters. As customary, we intentionally chose a smaller inner hydration shell for free energy analysis to avoid split occupancy between first and second hydration shells observed for the 7th-most distant water from Rb\(^+\) in AIMD simulations.

The hydration free energy for Rb\(^+\) predicted by primitive quasi-chemical evaluation agrees reasonably well with experiment. Good agreement is achieved when treating the most probable aqueous coordination complex within the defined inner hydration shell as a single energy-optimized gas-phase species using quantum mechanical methods and coupling that cluster to an implicit model of the solution. For example, coupling Rb\(^+\)(H\(_2\)O)\(_4\) to a dielectric continuum model, whether or not the cluster adapts to that environment, results in a hydration free energy of \( \approx -65 \text{ kcal/mol} \). In comparison, coupling many \( n = 4 \) configurations sampled from AIMD simulation to an implicit solvation model results in a similar hydration free energy prediction of \(-70.5 \text{ kcal/mol} \), a result within 1 kcal/mol of experiment.

Although the overall hydration free energy remains similar, a significant improvement does occur in the distribution of inner-shell coordinations predicted when treating solvent-adapted clusters (one or many) compared to prior procedures that treated only gas-phase clusters. Comparison of the occupancy distribution from AIMD with those from a LJ model indicates that AIMD results exhibit slightly lower coordination numbers with greater variability.

Based on similarity in size (within 0.2 Å) and identical charge, Rb\(^+\) and K\(^+\) ions are expected to share similar solvation characteristics in water and other environments. Foremost, hydration free energies are nearly identical according to experiments, a result also predicted by quasi-chemical analyses. Further similarities can be highlighted by comparing AIMD simulation and quasi-chemical free energy analysis of Rb\(^+\) with earlier studies of K\(^+\)\(\text{aq}\). For example, the first peaks in ion-O radial distribution functions fall in similar locations, but slightly closer for the smaller K\(^+\) ion \( (r = 2.8 \text{ Å}) \), as anticipated. In both cases, a weak minimum obscures identification of a coordination shell. For K\(^+\), this minimum ostensibly occurs closer \( (r = 3.5 \text{ Å}) \) with occupation by \( n = 6 \) waters, one less than Rb\(^+\). Similar to Rb\(^+\), split occupancy observed in the AIMD record of K\(^+\)(aq) simulations, specifically relating to the 6th-most distant water, motivated definition of a more restricted inner hydration shell for free energy analysis.

Perhaps unexpectedly, these inner shells are defined at nearly identical distances for Rb\(^+\) and K\(^+\) ions \( (\lambda_{K^+} = 3.1 \text{ Å}) \) and have similar properties: the first \( n=1-4 \) waters fill-in the first peaks in the ion-oxygen radial distribution functions, and \( n=4 \) waters preferentially solvate both K\(^+\) and Rb\(^+\) according to AIMD simulation and quasi-chemical analysis. In contrast, \( n=4 \) waters fill-in the first peak and preferentially solvate Na\(^+\) within a closer inner-shell distance of \( \lambda = 2.6 \text{ Å} \). Finally, stable inner-shell hydration structures for both K\(^+\) and Rb\(^+\) exist in gas phase that are absent in AIMD simulations of the liquid phase. For example, the \( n = 8 \) non-split occupancy is a rare composition in AIMD simulation, but forms a stable skewed cubic structure with 4 waters in a plane above and 4 below K\(^+\)\(\text{aq}\) and Rb\(^+\)\(\text{aq}\) in the absence of stabilizing interactions with the more distant solvation environment. This high coordination contrasts with smaller inner-shell coordinations \( (n \leq 6) \) reported for Na\(^+\). Further, these 8-coordinate clusters resemble the crystallographic ligands resolved around K\(^+\) and Rb\(^+\) ions in the binding sites of potassium ion channels that conduct K\(^+\) and Rb\(^+\), but reject smaller Na\(^+\) ions.

Following previous studies of selective K\(^+\) and Na\(^+\) binding, quasi-chemical theory may be useful in future work to analyze the subtleties of Rb\(^+\) binding and conduction in potassium channels.

Quasi-chemical theory applied to ion hydration combines statistical mechanical theory, electronic structure calculations, and molecular simulation, disciplines which are individually subjects for specialized professional attention. Because it combines activities which are themselves non-trivial, quasi-chemical theory is typically viewed with surprise. Nevertheless, it provides a fully-considered framework for analysis of ion hydration.

It is striking that the three sub-disciplines noted (statistical mechanical theory, electronic structure calculations, and molecular simulation) are so distinct. Typical practice in each subdiscipline is to parameterize the ingredients from the other two in order to eliminate those complexities. Thus, for example, sophisticated electronic structure calculations are done with solution models (dielectric continuum models) that are not justified on the basis of more basic observation. Similarly, sophisticated statistical mechanical theory is typically pursued where molecular-scale realism of the model can be empirically eliminated, for example by treating parameterized pair-decomposable models of intermolecular interactions. Simulation calculations also, of course, adopt extensively parameterized models. But they also have the limitation of being non-theoretical, i.e., not requiring physical insight they most often do not result in any. Indeed, simulations can be high-resolution experiments of undetermined accuracy for any physical system.

Quasi-chemical theory is not a take-it-or-leave-it model, and not a series expansion, but a well-defined structure for combining computational results from distinct sources that treat separately near and more distant neighbors. As more advanced applications are encountered — here with the Rb\(^+\)(aq), which localizes near-neighbor water molecules slightly less definitely than some less advanced cases — some physical
learning and judgement is required. A big step in that learning has been to categorize near-neighbors on the basis of the neighborhood decomposition of the radial distribution as in Fig. 2. This is in contrast to identification of neighbors on the basis of the location of the first minimum of that radial distribution, which is often less than compelling. Another step in that learning has been to consider more sophisticated procedures for estimation of cluster hydration free energies. Our discussion here has emphasized further the clear learning point that fluctuations of the composition of the inner-shell are numerically non-significant for strongly bound cases such as $\text{Rb}^+$ and where a well-informed identification of inner-shell ligands has been achieved.

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