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Cages of Water Coordinating Kr in Aqueous Solution

Randall A. LaViolette* and Kristina L. Copeland

Idaho National Engineering and Environmental Laboratory, P.O. Box 1625, Idaho Falls, Idaho 83415-2208

Lawrence R. Pratt*

Theoretical Division, Los Alamos National Laboratory, P.O. Box 1663, Los Alamos, New Mexico 87545

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Using molecular simulation and inherent structure ideas, we study the coordination number statistics for a Kr atom dissolved in liquid water with a classical force field. We quench compact Kr$(H_2O)_n$ clusters extracted from the liquid. In order that stable cage structures enclosing the Kr atom be obtained with high probability upon quenching of the coordinating water, more water molecules than the mean liquid phase hydration number should be included. The stable enclosing cluster structures obtained here are not simply related to the cage structures of clathrate hydrates. These results confirm the central features of the coordination number distribution of the recent ab initio molecular dynamics work of Ashbaugh et al. [*Biophys. Chem.* **2003**, *105*, 321−336], and that distribution is further characterized in the wings of the previous results. In contradiction to a simple clathrate structure hypothesis, no magic number features are observed under the conditions of the present work.

1. Introduction

Hydrophobic effects are a fundamental issue in a physical chemical understanding of biomolecular structure, stability, and function.[1] Embedded in the enormous literature[2−5] is a surprising lack of consensus on molecular mechanisms of hydrophobic effects.[6−13]

In view of the wide-spread availability of simulation calculations, the necessity of a valid molecular mechanism in a classic sense of physical chemistry, i.e., understanding on a molecular level as well as predicting, might be questioned. But if most current theories are not mostly false, then different mechanisms should be anticipated for low temperatures in contrast to high temperatures,[14,15] for low pressures in contrast to high pressures,[16−18] and for inert gas molecule solutes in contrast to macromolecular and amphiphilic solutes solutes.[7−9] A valid molecular mechanism is nontrivial. Such a mechanism might be expected to develop from justifiable and tested molecular theories. In fact, the most completely worked out and tested theories[3,5,19] have suggested unexpected mechanistic connections. As an example, we note here that those recent theories suggest that the temperature of entropy convergence can be validly estimated as

$$T \approx \frac{1}{2\alpha_\sigma}$$

with α_σ denoting the coefficient of thermal expansion along the coexistence curve.[3,5,19] This parameter α_σ is distinctive of liquid water, being typically more than 5 times smaller for water than for common organic solvents.[20]

A “clathrate-like” mechanistic view, either an orthodox or reformed picture,[19] has widespread appeal but recently was reexamined critically.[19] The present paper gives the results of further study of critical issues raised there. Specifically, using simulation tools we search for *magic number* features in the coordination number distributions of a ideal hydrophobic solute (Kr) that might be suggestive of hydration structures of clathrate type. Additionally, we characterize more precisely the stability of the inner shell structures observed in conventional simulation studies of Kr in liquid water solution.

The wide-spread use of the euphemism “clathrate-like” does not imply that it has an accepted quantitative identification nor does it have accepted quantitative consequences for solution thermodynamics.[19] Often, “clathrate-like” directs attention to orientational preferences for water molecules proximal to hydrophobic groups.[19] The perspective of the present work is that average radial ordering of those proximal water molecules would be expected to be as important as the average orientational ordering, perhaps more so. But that radial ordering is typically not considered when “clathrate-like” is employed as a mechanistic descriptor; where that radial ordering has been examined with care, it is distinctively “clathrate-unlike”.[19]

An extension of that average radial structure information is provided by inner shell hydration number distributions, sometimes called “quasi-component distributions”.[19] Being a distribution, such a quantity presents more information than just the mean value. In this respect “clathrate-like” has been assumed[21] to imply specifically that mean inner shell occupancies should be quantized in jumps of four water molecules, as suggested by crystal structures of clathrate hydrates.[22] This idea has the important virtues of a simple, definite hypothesis. A related idea is that the corresponding quasi-component distribution should exhibit structuring, i.e., *magic numbers*, corresponding to these quanta. Previous ab initio molecular dynamics study of Kr(aq)[19] did not find any magic number structuring.

2. Methods

The analysis that we bring newly to the problem of understanding cage structures that might be involved in hydra-

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* Corresponding authors. E-mail: R.A.L., yaq@inel.gov; L.R.P., lrp@lanl.gov.

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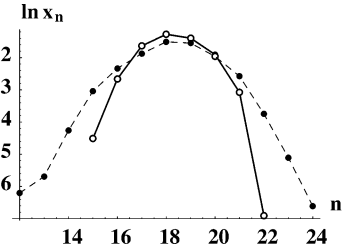

Figure 1. Distribution of the number of oxygen atoms within 5.1 Å of the Kr atom. The solid line indicates the AIMD result of ref 19, and the dashed line is the present result. These distributions agree near the mode; the middle three points track each other. Differences away from that center are likely due to the system size and sampling time limitations of the AIMD calculation. The last points in the wings in each case are likely to be only qualitatively reliable. No magic number features are observed. The coordination numbers $n = 20$ or $n = 24$ are unexceptional here.

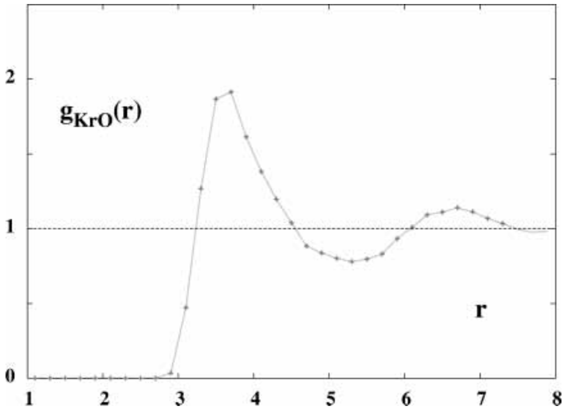

Figure 2. Radial distribution of water oxygen atoms surrounding the Kr atom obtained from the molecular dynamics simulation described in the text.

tion of simple hydrophobic solutes is the inherent structure method.[23] The application of inherent structure methods to clathrate hydrates was suggested at the first introduction of those ideas.[24] Although inherent structures have been studied on the basis of simulation results on an aqueous solution of Ne/Xe,[25] the present work studies the correspondence to stable cage structures for the first time. [In fact, that previous study[25] did employ the customary "clathrate-like" language, but only in the customary way, i.e., without a specific proof of the correspondence assumed.]

The clusters studied here were generated from a model water−Kr atom solution as follows. The solution consisted of 198 waters and one Kr atom in a fixed periodic cell with orthogonal sides of length 17.9663, 18.0765, and 18.2954 Å, respectively. The density (1.020 03 g/cm^3) was chosen so that the density of water would be 1 g/cm^3 with the Kr atom removed. To generate the molecular dynamics trajectories, we employed the COMPASS proprietary force field library[26,27] [a successor to CFF95 and now distributed by Accelrys Inc.; see also their website for an overview: http://www.accelrys.com/cerius2/compass/overview.html]. COMPASS employs Coulomb forces with partial charges, van der Waals forces (with a smoothly truncated 9-6 Lennard-Jones), and harmonic angular forces for the water molecule itself. The Kr atom was modeled only with van der Waals forces. The harmonic bond force normally employed in the COMPASS model was overridden here with the RATTLE[28] algorithm, i.e., dynamically imposed bond constraints between the oxygen and the hydrogen. We employed the Ewald method for the Coulomb forces in periodic boundary conditions. The model solution was equilibrated during

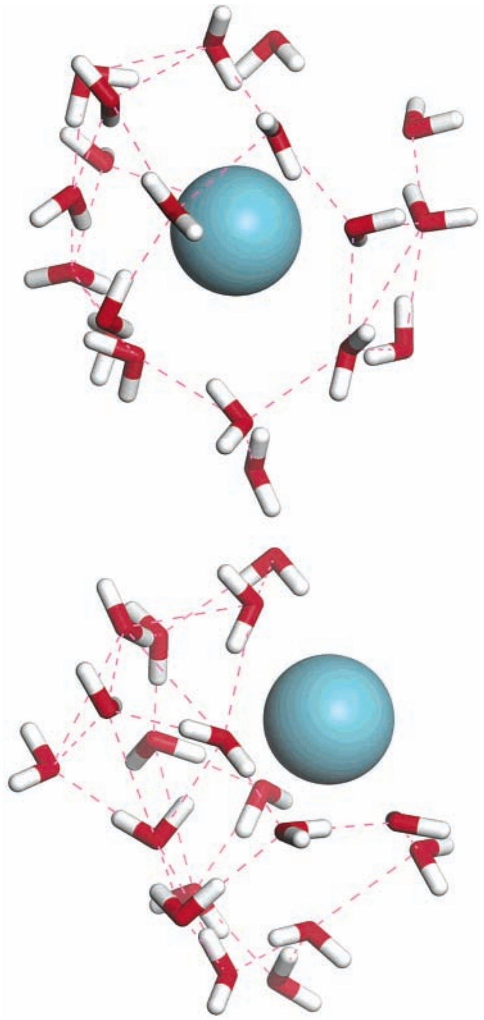

Figure 3. (Top) smallest cluster (with 20 water molecules), in one particular series, for which the Kr atom is contained in the convex hull of the water's oxygen atoms. The exclusion radius (between the Kr and the oxygen atoms) is 4.9 Å. The lower panel (with 18 waters) shows the expulsion of the Kr atom from the next smallest cluster, obtained by shrinking the exclusion radius to 4.6 Å, the distance at which at least one water was excluded (in this case, two waters were excluded simultaneously.) The large blue sphere is the Kr atom, the bent cylinders are the water molecules (red for oxygen, white for hydrogen). The dashed magenta lines connect pairs of oxygen atoms that are within 3.5 Å of each other. The perspective is the same for both panels.

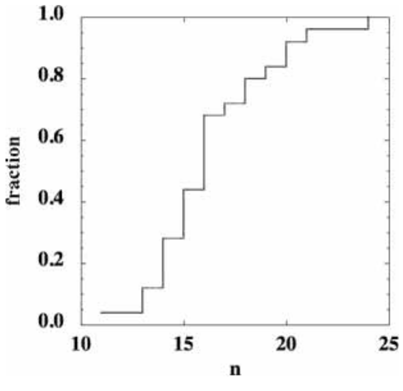

Figure 4. Fraction of central Kr(H$_2$O)$_n$ clusters extracted from the simulation that produce stable minimum energy structures enveloping the Kr atom, as a function of n, the number of water molecules in the cluster. Below $n \approx 16$ stable Kr(H$_2$O)$_n$ clusters are not probable, and $n \approx 24$ practically guarantees a stable Kr(H$_2$O)$_n$ cluster.

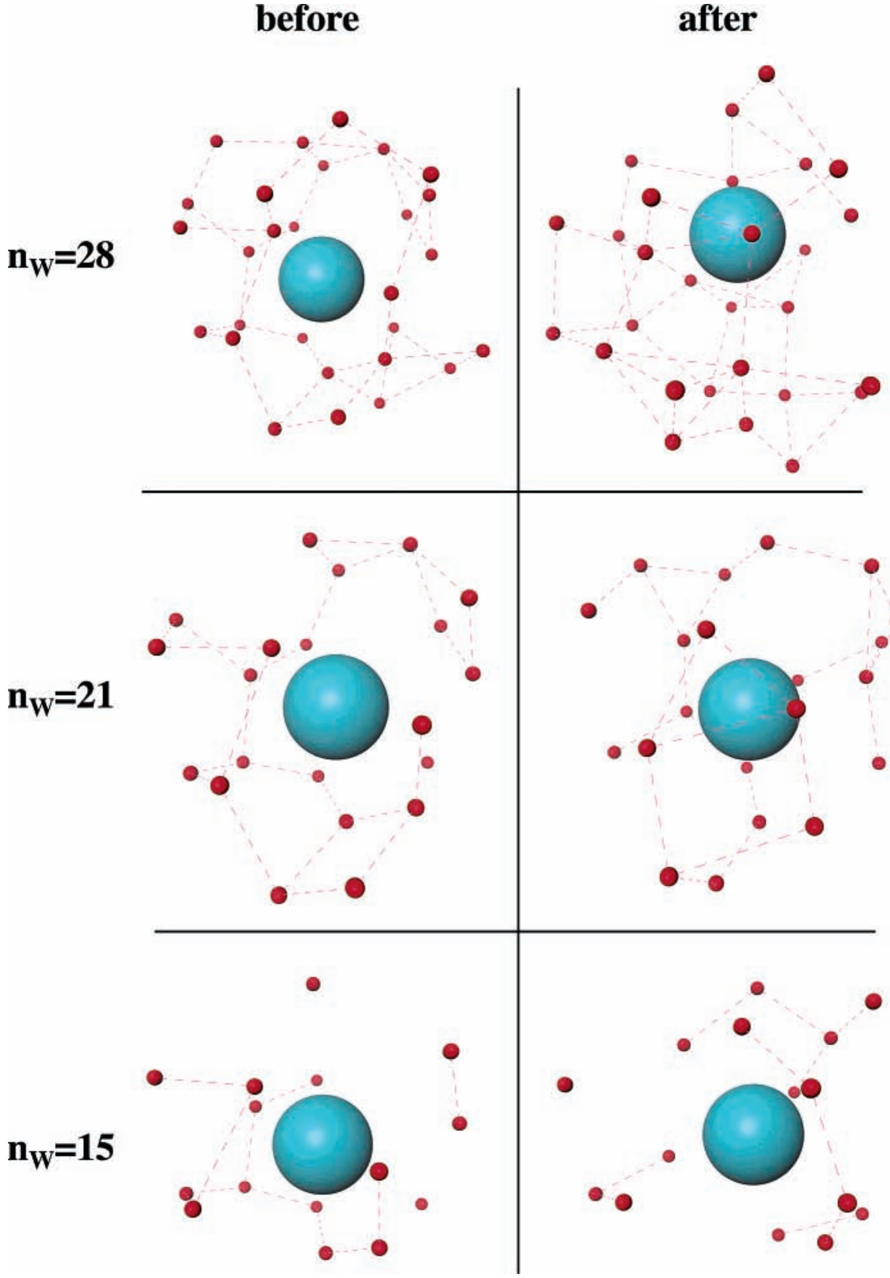

Figure 5. Examples of quenched Kr$(H_2O)_n$ clusters that entrap the Kr atom. The cluster on the left side is the Kr and n H_2O molecules, as extracted from the molecular dynamics simulation (upper panel); subsequent panels on the left side correspond to the unquenched cluster after eliminating the furthest neighbors, achieved by reducing the cluster's cutoff radius, as described in the text. The cluster directly to the right in each case is the structure produced by quenching, i.e., finding the nearest local minimum on the potential energy hypersurface. The large blue sphere is the Kr atom. The oxygen atoms are represented by the smaller red spheres, whose varying size and shade indicate relative distance to the viewer; the hydrogen atoms are omitted for clarity. The dashed magenta lines connect pairs of oxygen atoms that are within 3.5 Å of each other.

several preliminary NVE molecular dynamics calculations at temperatures between 350 and 400 K for a total of 300 ps. The 25 configurations were extracted from two subsequent NVE trajectories of 250 ps each (at mean temperature $\bar{T} = 393$ K), by including only those water molecules for which the oxygen atom was within 6.0 Å of the Kr atom, at intervals of 20 ps. Figure 2 shows the Kr−O radial distribution function extracted from molecular dynamics calculations. This result is in reasonable agreement with that of previous calculations[29] in view of the differences in thermodynamic state.

The inherent structure for the clusters extracted from the liquid was obtained by quenching. We recall that in Stillinger's prescription[30,31] for the inherent structure, one follows the steepest descent path connecting the initial configuration (the cluster) to the nearest minimum on the potential-energy hypersurface (which almost always turns out to be a local minimum). This prescription instantaneously removes temperature from the configuration (hence the term "quench"), and most importantly, it removes the vibrational distortions due to thermal fluctuations. Therefore, the inherent structure approach is used here (as also by Stillinger) as an image enhancement technique. This procedure stands in strong contrast to the global minimization that has been pursued for clusters in the gas phase, which employs as much annealing (i.e., cycles of "melting" and "refreezing") as is needed, to find the lowest potential-energy structures, independent of the initial configuration.[32] Our purpose in studying the inherent structure of the extracted clusters is to obtain information about the structure of the liquid, which is often strongly distinguished from the structure of clusters in the gas phase. We expect, and observe, that the inherent structure of the extracted clusters is different in almost every respect from the structure that would result if the extracted cluster were annealed and driven to its global potential energy minimum.

Neither periodic boundary conditions nor the Ewald method was employed in the quench calculations, although the smooth truncation of the van der Waals forces was maintained. After such a pair of configurations (quenched and unquenched) had been produced, the unquenched configuration was reduced by shortening the maximum distance between the Kr atom and the oxygen atoms in the cluster, in increments of 0.1 Å, until at least one water molecule was removed. This reduced configuration was quenched, and the whole procedure was repeated until a quenched structure was found in which the Kr atom was no longer surrounded by the waters but expelled to the surface of the cluster. The quenched structure from the previous cluster was taken to be the smallest stable cluster. Figure 3 illustrates this last step by showing, for one of the clusters, the smallest quenched cluster containing the Kr, and the next quenched cluster in which the Kr atom has been expelled to the surface [the cluster with 19 water molecules is never encountered in this procedure because in this instance, shrinking the nearest-neighbor distance from the Kr atom to the oxygen atoms from 4.9 Å (top panel) to 4.6 Å, the next distance at which at least one water was excluded, resulted in the exclusion of two water molecules].

3. Magic Numbers?

The distribution x_n of the number n of water oxygen atoms within 5.1 Å of the Kr atom is shown in Figure 1. In the middle of this distribution there is good correspondence between the present calculation and the previous ab initio molecular dynamics (AIMD) results. The present calculation being more expansive, it gives more information about the wings of this distribution. No magic numbers are observed. The $n = 20$ case that could, but never did, form a dodecahedral cage [the small cage in the common known clathrates], is not exceptional in this distribution.

4. Stability of Inner Shell Structures

Figure 4 shows the fraction of quenched clusters obtained which stably enclose the Kr atom. Below $n \approx 16$, stable $Kr(H_2O)_n$ clusters are not probable, whereas $n \approx 24$ practically guarantees a stable $Kr(H_2O)_n$ cluster. We associate this value of 16 with the maximum (or the mean) of the distribution Figure 1, 17 and 18. Thus, when the number of water molecules in the cluster does not come up to the mean coordination number, a stable cage is unlikely.

$n = 24$ coincides with the size of the large cages (tetrakaidecahedra) in known clathrate structures, so that correspondence is suggestive. But none of the quenched clusters actually observed possessed the regular-geometric arrangements of the clathrate phases.

Figure 5 shows that even the stable smaller clusters can leave some portions of the solute bare, consistent with the hydrophobicity of Kr.

5. Conclusions

The central features of the coordination number distribution x_n of the AIMD work of ref 19 are confirmed, and that distribution is further characterized in the wings of the previous results. In contradiction to a simple clathrate structure hypothesis, no magic number features are observed under the conditions of the present work. In order that stable cage structures enclosing the Kr atom be obtained with high probability upon quenching of the coordinating water, more water molecules than the mean liquid phase hydration number should be included. The stable enclosing cluster structures obtained here are typically not simply related to the cage structures of clathrate hydrates.

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