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A Density Functional Theory Evaluation of Hydrophobic Solvation: Ne, Ar and Kr in a 50-Water Cluster. Implications for the Hydrophobic Effect

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Abstract

The physical explanation for the hydrophobic effect has been the subject of disagreement. Physical organic chemists tend to use a explanation related to pressure, while many biochemists prefer an explanation that involves decreased entropy of the aqueous solvent. We present DFT calculations at the B3LYP/6-31G(d,p) and X3LYP/6-31G(d,p) levels on the solvation of three noble gases (Ne, Ar, and Kr) in clusters of 50 waters. Vibrational analyses show no substantial decreases in the vibrational entropies of the waters in any of the three clusters. The observed positive free energies of transfer from the gas phase or from nonpolar solvents to water appear to be due to the work needed to make a suitable hole in the aqueous solvent. We distinguish between hydrophobic solvations (explicitly studied here) and the hydrophobic effect that occurs when a solute (or transition state) can decrease its volume through conformational change (which is not possible for the noble gases).

The hydrophobic effect causes nonpolar molecules to aggregate or fold in aqueous solution. This effect has been invoked to explain the acceleration of certain organic reactions in water (compared to organic solvents), the formation of micelles in water, and (perhaps most importantly) protein folding. However, there appears no universal agreement on what the physical explanation for this effect might be. In 1945, Frank and Evans[1] published a paper widely cited by biochemists which suggested that the hydrophobic effect be due to a negative entropy associated with the *reorganization of the liquid water*, presumably near the solute. They based this conclusion upon the experimental observations that nonpolar molecules (including the noble gases) had a positive free energy of transfer into water, but heat was given off. Since they equated the heat given off with the enthalpy, they used the familiar $\Delta G = \Delta H - T\Delta S$ relationship to conclude that ΔS for this process must be negative. Famously, they invoked the argument that water must form small 'icebergs' in the proximity of the solute. For the transfer of Ne from the gas phase to aqueous solution, they calculated

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ΔS to be -28.8 cal/degree-mole at 298 K. Since the heat of fusion of water/ice is only about 1.4 kcal/mol, and at the melting point $\Delta G=0$, so $\Delta H=T\Delta S$, ΔS for the freezing of water is $-1400/273$ or -5.2 cal/degree-mol, so the rough equivalent of six waters per Ne would form an 'ice-berg'. Kauzmann,[2] in his much cited chapter, recognized the problems with the iceberg explanation (as have many others since), but he endorsed the entropy of solvent reorganization explanation, which persists.

Physical organic chemists appear not to recognize the entropy argument. They rarely (if ever) cite the Frank and Evans paper or the Kauzmann chapter. Instead of Frank and Evans, they often cite a paper by Abraham[3] which reports the ΔG 's of transfer from the gas to water, but not the ΔH 's or ΔS 's. Significantly, Abraham found that while hydrocarbons and noble gases behaved similarly when dissolved in organic solvents, their behavior differed significantly when dissolved in water. He concluded that a hydrophobic effect exists for hydrocarbons, but not for noble gases. If the entropy change of the water be the leading cause of the hydrophobic effect, why would it be different for solution of a noble gas than for a hydrocarbon? One should note that neither study took into account the corrections later suggested by Ben-Naim.[4,5]

Organic chemists also noted the hydrophobic effect on reaction rates. Breslow[6–12] has extensively studied the hydrophobic effect upon the rate of Diels-Alder reactions, which are markedly accelerated in water compared to organic solvents. He also noted that these reactions are further accelerated by the addition of electroconstricting salts, such as LiCl, which could not be due to entropy. Le Noble, et al.,[13–15] have published several reviews of the effect of applied pressure upon organic reactions. Many examples of the effect of pressure on Diels-Alder reactions are included in these reviews. Applied pressure accelerates these reaction as they have a negative volume of activation. One example, the addition of N-Ethylmaleimide to Anthracene-9-carbinol, has been studied in various solvents and under applied pressure. Both applied pressure[16] and aqueous solvent increase the rate of the reaction.[8] Electroconstricting salts (i. e., LiCl) in aqueous solution further increase the rate. Such salts decrease the volume of the solution when added to water, indicating an increase in the pressure within the solution.

Diels-Alder reactions often can give rise to both endo and exo products (which have different ΔV_{act} 's). Since these products are similar and form from exactly the same reagents at the same time under the same reaction conditions, the relative effects of most solvent properties (i.e., polarity) other than internal pressure should be small. The endo/exo product ratios follow the expected dependence on applied pressure[13–15] and display the same qualitative behavior in water as under applied pressure. Berson studied the effect of 12 different nonaqueous solvents upon the endo/exo ratios of three Diels-Alder reactions.[17] We use his data to plot the log (endo/exo) versus the cohesive energy densities (CED's) of the solvents he used as figure 1. The CED, often taken as a 'pressure' inside the solvent (although internal pressure has a different definition, $\delta U/dV$ at constant T), is the $(\Delta H_{\text{vaporization}} - RT)$ divided by the molar volume for the solvent. For water, the CED is 0.55 kcal/cm³, or 2.297 GPa, or about 22,700 atm. The CED's for nonpolar organic solvents are roughly 1/10 of this value. For example, the CED for hexane is 0.058 kcal/cm³. Thus, the effects of aqueous solvation is similar to applied pressure for the Diels-Alder reaction. In a comprehensive study of solvent effects upon organic reactions, Gajewski[18] noted that the reaction rate of the Diels-Alder reaction correlate best with the CED of the solvent, in agreement with the above.

Returning to $\Delta G = \Delta H - T\Delta S$, the heat reported by Frank and Evans[1] is equivalent to the enthalpy if the only work done is against constant (atmospheric) pressure. But work must be done to make a hole for the (basically non-interacting) solute in the liquid water. This work can be thought of as $P\Delta V$, where P is the pressure within the water, and ΔV is the volume of the hole made by the solvent. What is the magnitude of this work? Should this have been taken into account in the interpretation of the solute transfers described by Frank and Evans?

Thermodynamics tells us that $G = H - TS = U + PV - TS$, $dH = TdS + VdP$, and $dG = -SdT + VdP$. Thus, $(dG/dP)_T = V$, and, $(dH/dP)_S = V$. So we must consider the VdP term. One can imagine the VdP term to be the negative work done by removing the solute of fixed volume, V , from a nonpolar solvent (or from the gas phase at 1 atm) plus the positive work done by inserting it in water. The difference in the work would be $V\Delta P$ (at constant V), where ΔP is the difference in the pressure in the two environments. In this case $\Delta G = V\Delta P$ (at constant T and V) and $\Delta H = V\Delta P$ (at constant S and V), which is exactly what we get from integrating $dH = VdP$ (at constant S). We shall see from the results discussed below that we calculate ΔS to be ~ 0 for transfer of Ne, Ar and Kr from the gas phase to a 50 water cluster, which validates the condition of constant S for $dH = VdP$. To estimate $V\Delta P$, we need to know both P (the pressure against which the work is done, i.e., the internal pressure in the liquid water) and V (the volume of the hole the solute makes). It is not completely clear that we know either of these. Makhatadze and Privalov measured the heats of hydration of several nonpolar solutes. [19] However, like Frank and Evans,[1] they did not consider the work term when converting the heats to enthalpies.

In this paper, we shall attempt to determine the magnitude of the work done by making solute sized holes in clusters containing 50 waters using density functional theory (DFT) calculations. We shall use other data, such as Van der Waals (vdw) radii to estimate the size of the hole and the cohesive energy density (CED) to estimate the pressure within the water. We shall also evaluate the vibrational entropy of the water cluster with and without the solute as an independent test of the entropy rationalization of hydrophobic solvation. We shall consider neon, argon and krypton as the noble gases. The noble gases provide excellent candidates for these computer experiments as they should have little interaction with water. Whatever interactions that persist will be underestimated by the B3LYP and X3LYP functionals which do not account for Van der Waals interactions very well and by optimizations on counterpoise (CP) corrected potential surfaces,[20] which will remove the non-physical attractions between the gases and the waters due to basis set superposition error (BSSE). Thus, we can approximate the work done against the pressure within the water droplet as that of inserting a non-polar solute. The ΔG_{solv} 's of Ne, Ar and Kr in water are known experimentally. These gases are among the solutes whose aqueous solvation was studied both by Abraham[3] and by Frank and Evans.[1] Thus, they provide apt candidates for this study. What we treat here can be referred to as hydrophobic 'solvation', rather than the hydrophobic 'effect'. However, the hydrophobic solvation would give rise to the entropic effect due to rearrangement of the solvent structure suggested by Frank and Evans, who reported the entropies of solvation of the noble gases along with other molecules. Other entropic effects observed in protein folding could arise from other sources (see discussion).

Many other research groups have discussed and treated the hydrophobic effect using different computational techniques. As there are too many for us to cite all, we mention several that we find significant and we concentrate on the more recent literature. The studies include ab initio MO theory,[21–23] empirical[24,25] and first principles[26,27] molecular dynamics[28–30] and other approaches.[31–37] A review of the hydrophobic effect on large systems has been recently published.[38]

Computational Details

The molecular orbital calculations were performed at the, density functional theory (DFT) level using the Gaussian 03[39] and Gaussian 09[40] programs using B3LYP and X3LYP hybrid functional and the 6-31G(d,p) basis set. We used this basis set rather than D95(d,p) which we have used for many of our past studies involving water[41–43] as D95(d,p) does not have defined basis sets for the noble gases. The B3LYP functional combines Becke's 3-parameter functional,[44] with the non-local correlation provided by the correlation functional of Lee, Yang and Parr.[45] The clusters were completely optimized without any geometric restraints. Several different optimizations were performed for each cluster. We replaced the solutes in the optimized structures with the other solutes in turn to increase our confidence that we had found the lowest energy local minima to a reasonable error tolerance. The calculations (including the vibrational analyses) on the clusters containing the solutes were optimized on a counterpoise corrected surface.[20] We considered only two fragments for these calculations: the solute and the aggregate of all the waters. Vibrational frequencies were calculated using the harmonic approximation as programmed in GAUSSIAN 03 and 09. We have shown that the B3LYP functional can be extremely accurate for the energy of water dimer[41] and small clusters[43] when the optimization is performed on a CP-corrected energy surface. Nevertheless, due to some recent criticisms of the B3LYP functional,[46] we repeated the calculations on the best optimized structures using the X3LYP functional [47], which has been shown to accurately treat water dimer[48], using the GAUSSIAN 09 program[40]. Both B3LYP and X3LYP are among the better functionals tested with moderate basis sets for the CP-corrected calculation of water dimer. [49] We calculated the vibrational frequencies from which the enthalpies and entropies at 298 K were obtained from by standard statistical mechanical analyses[50] as described in a 'white paper' available from Gaussian[51] and include the zero-point vibrational energy in addition to the electronic, vibrational, rotational and translational energies and RT. We used the normal harmonic approximations encoded in GAUSSIAN 03 and 09 for the vibrational calculations. All calculated frequencies are real indicating true minima. The enthalpies and vibrational entropies were also calculated from the CP-corrected calculations.[20]

The energies for forming the hole made by each gas in the 50 water cluster were calculated by subtracting the energy of the relaxed 50 water cluster from the energy obtained from a single point calculation of the optimized noble gas + 50 water cluster with the noble gas removed (leaving a hole). We could not do a proper vibrational analysis on the latter structure as it does not correspond to a local minimum on the potential energy surface. Hence, we can only report energies (no enthalpies or entropies) for making the hole.

We note that several different estimates of the Van der Waals radii can be found in the literature. The values used here are those of Bondi,[52] which have been included in Truhlar's latest evaluation.[53] The calculated volumes will depend on the radii used.

Results

The energetic results for all three solutes in 50 waters are collected in table 1 (X3LYP values in parentheses). These results use the best (i.e. lowest energy) local minima that we have obtained from multiple optimization attempts for the 50 water cluster. If the energy of a local minimum found be within an acceptable error of the global minimum, the enthalpies and the vibrational (but not the total) entropies should also be within an acceptable error. The optimized structures for the cluster containing the solutes are necessarily local minima since the global minimum would correspond to the noble gas atom escaping from or attaching to the outer surface of the cluster. As the differences for the values calculated by B3LYP and X3LYP are quite small (probably within the errors anticipated for a study such

as this), we shall use the values calculated by B3LYP in our discussion. The full geometries of all optimized structures are provided in the supplementary information (SI).

Neon

Neon provides one of the best examples to test the effect of a small non-interacting solute in water. Larger noble gases may have significant interactions with the aqueous solvent. For example the free energies of solvation of He, Ne, Ar, Kr, in aqueous solution decrease in that order (i.e., the gases become more soluble). The Henry's law constants,[54] which correspond to the partial pressure in equilibrium with a dilute solution of the gases decrease in the same order. Thus, the larger gases must have more favorable interactions with water than do neon or helium. Helium, poses a different computational problem due to its small size. It can fit into some of the vacant space in liquid water (see discussion of volume below). Neon appears to have a reasonable balance between size (similar to that of water) and limited interaction with water.

Using the Van der Waals radius of neon as 1.54 Angstroms [52] one obtains 9.2 cm³/mol as the volume of spherical neon. However, packing spheres into a confined space leaves vacant space between them. Another approach would be to use cubes that are tangent to the spheres. Such cubes have volumes that are 1.91 (6/π) that of the corresponding spheres, or 17.6 cm³/mol for neon. These could pack into a cubic container without leaving vacant space. However, this would be an idealized situation, especially in a liquid. We suggest that the real molar volume should fall somewhere between these extremes, which they do[55] (see table 1).

We have calculated the energy of making a neon-sized hole in the 50-water cluster as 7.0 kcal/mol and the energy of inserting a neon in the water cluster as 7.5 kcal/mol using B3LYP. The difference between the energy of placing the neon in the cluster and that of the hole (0.5 kcal/mol or -0.2 using X3LYP) reflects a slightly repulsive or attractive interaction between the Ne and the 50 waters around it which depends upon the functional used. Thus, maximizing the strongly attractive water-water interactions might result in a slightly repulsive interaction between the water cluster and the neon according to B3LYP.

We can estimate what pressure within the water corresponds to the work to make the hole using the volumes calculated above. These should bracket the effective pressure which we shall express as energies/volume (as are CED's). Using the ΔE of 7.5 kcal/mol, these values are 0.82 and 0.43 kcal/cm³, respectively, for spheres and cubes, which do bracket the experimental CED of 0.55 kcal/cm³ for water. Thus, making a neon sized-hole in the 50-water cluster is in reasonable agreement with the estimated work done against the pressure in liquid water taken as the CED.

Inspection of the water clusters containing Ne show essentially no change in the number of H-bonds in the waters around the solute(see figure 2). Each of the waters around the solutes maintains all its H-bonds. However, the H-bonding geometries differ somewhat from water in the bulk indicating that they are strained or weakened.

As mentioned above, the ΔH for the transfer of Ne from the gas to water at constant S and V is VΔP+q (where q=heat). If we take the internal pressure of water as its CED (~23,000 atm), we can neglect the 1 atm pressure of the gaseous state, so ΔH for the transfer would be 7.03 (work) – 1.88 (heat) = 5.15 kcal/mol. which is reasonably close (considering the uncertainty in the Van der Waals radii used to calculate the molar volume) to the experimental ΔG of solution (6.94 kcal/mol). This suggests that the TΔS term should be small. We shall analyze the entropic contribution in detail below.

Argon and Krypton

Ar and Kr being larger than Ne (and of a molecule of water) require larger holes in the aqueous solvent. The energies required to make the holes increase with the size of the noble gas, but not nearly so much as the ΔE or ΔH of transfer to the water. The differences between the energies of the hole and that of transfer of the solute (a measure of the interaction between the solute and the relaxed waters around it), close to zero for Ne, increases to 4.6 (3.2) for Ar and to 6.7 (5.1) kcal/mol for Kr. These results imply that the water structure around the large gases is more strained. Of course some of this strain will be relieved by the more stabilizing VdW interactions between the large gases and the waters which are largely neglected by these DFT methods. However, the strain that is accepted by the waters in the cluster indicate that considerable force between the solute gas and the solvating water cluster can be tolerated before the water cluster will reduce the number of H-bonds around the solute.

As in the case of Ne, the water clusters containing either Ar and Kr show essentially no change in the number of H-bonds around the solute. Each of the waters around the solute still maintains all its normal complement of H-bonds, indicating weakened H-bonds.

The greater energies required to make holes for Ar and Kr in the 50 water cluster reflect the larger sizes of Ar and Kr as compared to Ne. We have calculated the ΔH 's using $\Delta H = \Delta E_{\text{hole}} + q$ using the experimental heat from Frank and Evans.[1] Comparing these data and the value calculated for Ne follows the trend of the experimental $\Delta G_{\text{solution}}$'s.

Calculation of the work using the volume of the hole derived from the Van der Waals radii, as done above for Ne, result in slightly lower effective pressures which still bracket the 0.55 kcal/cm³ CED of water. The calculated effective CED's for Ar are 0.73 and 0.38 and for Kr 0.70 and 0.37 kcal/cm³ using the spherical and cubic volumes, respectively.

Thermodynamics and quantum mechanics

As thermodynamics predated quantum mechanics by many years, the laws of thermodynamics and the relations based upon them do not reflect the wave properties of matter nor much of matter's granular properties. Since we are using quantum mechanics to arrive at thermodynamic conclusions, these discrepancies affect our analysis in several ways.

The work considered in thermodynamics is classical work, such as $P\Delta V$, which will lead to a change in the potential energy of the system. The related expression, $\Delta H = V\Delta P + q$ (in which $V\Delta P$ can be thought of as a sum of two $P\Delta V$ terms at constant molar V_{solute} as shown above) affects the enthalpy. The enthalpy for a molecule differs from the classical potential energy by the zero-point energy plus a Boltzmann distribution over the vibrational levels of the system. There is no classical equivalent of the zero-point energy or of the correct distribution over the quantized vibrational (and other) levels. Should one consider the change in the calculated potential energy, ΔE , to be equivalent to the work done, or should the work be considered equivalent to the adiabatic change in ΔH ? The former does not take the vibrational wavefunctions into account, but the latter does.

Secondly, matter (in this case the water in the cluster) is granular, not homogenous as assumed by thermodynamics. Thus, the resistance to making a hole in it will depend upon the differential size and shape of the hole. For example, making a hole in water will lead to individually strained and/or broken H-bonds. The energy required to increase the size of a hole will depend upon the change in the microscopic structure of the water in the proximity of the hole. This will depend upon the size (and shape) of the hole in some way. While the

CED of water might be a reasonable approximation for the pressure against which ΔV does work for a small hole, Archimedes principle tells us that the pressure must be much less for a large hole. Thus, the effective P for $P\Delta V$ work in water might be expected to vary with the size of the solute making the hole. As mentioned earlier, Lee has suggested that larger holes might lead to larger negative entropies due to the small size of molecular water relative to the hole made by the solute,[56] which differs from our conclusions.

Which pressure needs to be considered, atmospheric or that within the water?

If the work done by inserting the solute in the solvent to make a solute-sized hole is simply expansion against the atmospheric pressure in the laboratory, then the only work would be against this pressure and $\Delta H=q$. If that be the case, to what do the calculated energies of making the holes in the 50-water clusters correspond? The first law tells us that $U=q+w$. So the increase in the energy of the water cluster must correspond to a change in either q or w (or both). Since the $P\Delta V$ for making the hole in the water cluster increases the potential energy (the hole will spontaneously collapse if allowed to do so) it must correspond to (potentially reversible) work. As the calculated energy change is much too large to be attributed to work versus atmospheric pressure, clearly this must be work against the internal pressure of the solvent. From another perspective, making the same size hole in the atmosphere outside the water cluster would require much less work than making the whole inside the water cluster. In a useful analogy, the water cluster can be thought of as if it were a balloon, where the intermolecular attractions between the water molecules replaces the rubber interactions in the balloon. Blowing up the balloon requires work as does making the hole in the water cluster. The balloon will deflate and the hole in the water will collapse spontaneously if allowed to do so.

Entropy

The entropy of a system can be broken up into contributions from the number of configurations or configurational entropy (i.e., the number of local minima of equivalent energy) and the entropy calculated from the translational, rotational and vibrational entropies of the individual minima. The following development (taken from a 'white paper' [51] published on the Gaussian Inc., web site and based upon a development by McQuarrie[50]) shows how Gaussian 03 and Gaussian 09 calculate the vibrational entropy (S_V) from the vibrational analyses of the wavefunction.

$$\begin{aligned}
 S_V &= R \left(\ln(q_V) + T \left(\frac{\partial \ln q}{\partial T} \right)_V \right) \\
 &= R \left(\ln(q_V) + T \left(\sum_K \frac{\Theta_{v,K}}{2T^2} + \sum_K \frac{(\Theta_{v,K}/T^2) e^{-\Theta_{v,K}/T}}{1 - e^{-\Theta_{v,K}/T}} \right) \right) \\
 &= R \left(\sum_K \left(\frac{\Theta_{v,K}}{2T} + \ln(1 - e^{-\Theta_{v,K}/T}) \right) + T \left(\sum_K \frac{\Theta_{v,K}}{2T^2} + \sum_K \frac{(\Theta_{v,K}/T^2) e^{-\Theta_{v,K}/T}}{1 - e^{-\Theta_{v,K}/T}} \right) \right) \\
 &= R \left(\sum_K \ln(1 - e^{-\Theta_{v,K}/T}) + \left(\sum_K \frac{(\Theta_{v,K}/T) e^{-\Theta_{v,K}/T}}{1 - e^{-\Theta_{v,K}/T}} \right) \right) \\
 &= R \sum_K \left(\frac{\Theta_{v,K}/T}{e^{\Theta_{v,K}/T} - 1} - \ln(1 - e^{-\Theta_{v,K}/T}) \right)
 \end{aligned}$$

Where q_v is the vibrational part of the partition function, the subscript 'K' refers to the K^{th} vibration, and $\Theta_{v,K} = h\nu_{K}/k_b$

If we make the reasonable assumption that the number of low energy configurations for a given solute (i.e., Ne, Ar, or Kr) in a 50 water cluster be a constant, then the entropy of any one of the equivalent minima that we choose to examine will be its internal entropy plus a constant. As one would expect, the translational and rotational entropies will not vary significantly for the clusters with and without solute (the translation and rotational entropies increase with the mass of the solute but only by 0.3 and 0.1 cal/degree/mol, respectively). Thus, we expect the major contribution to ΔS for an *individual* low energy configuration with a noble gas solute compared to the pure water cluster to come from the vibrational entropy. Furthermore, any entropic contribution due to the reorganization of the aqueous solvent should come from ΔS_v for the 50 waters. ΔS for transfer of the noble gas from the gas phase to aqueous solution will also include an entropy of mixing term (which is always positive), the reduction in entropy upon going from two entities to one upon addition of the solute to the cluster, and an increase in entropy due to the formation of three additional vibrational modes. The first two of these contributions should be the same for all three noble gases and are not included in our analyses. However, the last will affect the calculated vibrational entropy. In order to keep the number of vibrations constant for the 50 water cluster alone and with the noble gas solute within the cluster, we must remove the contributions to the vibrational entropy from these three additional modes. We assume that the three additional vibrations will be very delocalized. Thus, to compare the vibrational entropies of the clusters including the solutes (with that of the pure water cluster) we have subtracted the vibrational contributions of the three lowest vibrations. We note that since the lowest vibrations contribute most to the overall vibrational entropy, the value that we calculate is lower limit to ΔS_v .

The vibrational ΔS 's calculated for Ne, Ar, and Kr (see table 1) vary from 1.5 to -2.0 cal/degree/mol including both B3LYP and X3LYP results. The vibrational ΔS 's can be seen to be close to zero and certainly not the values of ~ -30 cal/degree/mol reported by Frank and Evans. Since these values represent lower limits, they could be more positive, but certainly not more negative. Thus, reduced entropy due to increased ordering of the H-bonds in water does not appear to occur for these systems. Whatever entropy reduction observed for the hydrophobic effect on proteins must come from a different source. Garde's recent report[30] indicating increased mobility of water molecules near hydrophobic surfaces supports these conclusions. We note that the ~ 0 entropy changes that we calculate validate the $(\delta H/\delta P)_S = V$ relationship from which we derived the work term.

Nevertheless, the change in heat capacity, ΔC_p observed for protein unfolding does suggest a change in entropy for the folding/unfolding processes.[57] However, this ΔS could be due to the restricted internal motions within, and fewer equivalent states available to, the folded compared to the unfolded state of the protein.

Compressibility

The compressibility of a substance is defined as $(1/V)\delta V/\delta P$, which is the reciprocal of the bulk modulus. Since the compressibility generally is defined for a pure phase (liquid or solid) it would not be expected to apply to isolated solutes. Nevertheless, we note that the bulk moduli for the noble gases increase in the order $\text{Ne} < \text{Ar} < \text{Kr}$. [58] Long chain hydrocarbons, such as n-alkanes, have conformational flexibility that the noble gases and methane lack. As such, they can assume a minimum volume conformation in water, which might be considerably different from the conformations they assume when neat or dissolved in a nonpolar solvent. Abraham[3] and Cramer[59] showed that plots of the molecular

volumes vs. the ΔG 's of solvation for the noble gases and hydrocarbons produce linear relationships for the organic solvents benzene and octanol. In water, the noble gases and methane retained the linear relationship, but larger alkanes fell significantly off the line. On this basis, Abraham[3] suggested that the hydrophobic effect should be defined with respect to the difference in solvation between hydrocarbons and the noble gases. He suggested a value of 0.54 kcal/mole per $-\text{CH}_2-$ group for the hydrophobic effects of the n-alkanes. From the reports of Abraham,[3] and Cramer,[59] one recognizes the apparent volumes of n-alkanes must be somewhat smaller than their experimental molecular volumes to put the ΔG 's of aqueous solvation for the n-alkanes with at least two carbons on the same linear relationship with the noble gases and methane. These observations suggest that the hydrophobic effect could be due to the increased pressure within water as compared to benzene and octanol.

Ouellette has noted that the conformational equilibria of several organic molecules depend upon the internal pressure, with higher internal pressures (often used interchangeably with CED) favoring the conformations with the lower partial molar volumes.[60]

In addition, the compressibility of the neat phase can also be a factor, as once an n-alkane is compressed into a small volume, one might consider the internal interactions within the solute to resemble that of the neat phase. Furthermore, an aggregate of several compressible solutes should have a volume less than the sum of the isolated solute molecules. Assuming that our suggestions that the high pressure within the water compared to organic solvents leads to the hydrophobic effect, the effect should be larger for more compressible substances. Organic substances generally are more compressible than water at ambient temperatures. This effect might be operative in micelles or lipid bilayers, where the nonpolar ends of amphiphiles could be compressed into each other. Similarly, this pressure effect can lead to the folding of peptides and proteins to structures that occupy smaller volumes than their unfolded conformations.

The above implies that the volume of solutes such as n-alkanes, peptides, etc. (but not noble gases or methane) might decrease upon aqueous solution. If such be the case, the expression $dH = VdP$ (which is valid for constant V) should be modified to $dH = VdP + PdV$, which would lead to $\Delta H = V\Delta P + P\Delta V$ after integration between the original and final values of P and V. One might suppose that the entropy of a folded hydrocarbon such as those studied by Ouellette[60] would have more constrained vibrations as well as fewer possible equivalent states, both of which would lead to reduced entropy. Similar behavior of proteins could explain the entropy reductions noted for protein folding such as that noted previously[57].

Solute size

As noted above, thermodynamics considers matter to be continuous. However, matter (i.e., water) is structured and granular. The work done by making a hole of volume V against a pressure, P is simply $P\Delta V$ in a continuous system. In water, this may not be true. A small hole might require more work per unit volume than a large one. The pressure within the water would be some function of the volume (and perhaps the shape) of the hole since the work done to make the hole involves weakening, breaking, and/or reorganizing individual H-bonds. If the solute became compressed due to one or both of the factors mentioned (compressibility or folding to a conformation of lower partial molar volume), V would not be constant (as assumed in the preceding discussion). To go from a state at P_1 and V_1 to another at P_2 and V_2 , where both V and P can change, we must integrate over P and V:

$$Work(hole) = \int_{P_1}^{P_2} V dP + \int_{V_1}^{V_2} P dV$$

In the cases considered here, the holes made weakened several H-bonds, but the holes are sufficiently small that the number of H-bonds remained constant. Small holes create strongly concave surfaces (within the hole) inside the cluster, which allows the waters at the surface of this hole to keep their complement of (albeit strained) H-bonds. As holes become larger, the surfaces of the water around them become less concave rendering the formation of the full complement of H-bonds more difficult, leading to a reduction in the number of H-bonds within the water. If the hole became sufficiently large in a large volume of water, the water surface at the hole would resemble that at the air/water interface at the exterior of the entire volume of the water. If one considers the familiar sight of gas bubbles rising from an aqueous solution such as a carbonated beverage, the rate at which they rise appears to be consistent with a pressure gradient due to atmospheric pressure plus the weight of the water above the bubble. Thus, the pressure within the visible (hence large) hole in the solvent must be much less than the CED of water, consistent with the suggestion the pressure within the hole decreases as the hole gets larger, but seems inconsistent with the suggestion made by Lee.[56]

Distinction between aqueous (hydrophobic) solvation and the hydrophobic effect

As we have seen from the above discussion, Abraham found a hydrophobic effect for hydrocarbons, but none for the noble gases.[3] Cramer suggested that the hydrophobic effect does not exist.[59] The hydrophobic 'effect' can be divided into two different phenomena: 1) hydrophobic solvation, and 2) hydrophobic effects upon dynamics and reactivity. The work that we have described in this paper is directed toward the first of these. The Diels-Alder reaction and protein-folding provide examples of the second. The water clusters that we have employed are not large enough to study either the Diels-Alder reaction or protein folding. However, the calculations can provide an important insight. If reaction (in the case of the Diels-Alder) or folding (in the case of proteins) can reduce the size of the hole in the aqueous solvent, the potential energy will be appreciably lowered. The observation by Abraham that long hydrocarbons show this effect, but noble gases and methane do not,[3] as well as Ouelette's observation that hydrocarbons fold to reduce their partial molar volumes in aqueous solution[60] could be explained in this way.

Henry's law

Henry's law can be used to determine the chemical potential of a dilute solute in a two component system. The Henry's law constant, K_H , can be expressed as a pressure, in which case Henry's law can be written:

$$\mu_{solute}^{*H} = \mu_{solute}^* + RT \ln \frac{k_H^{solute}}{P_{solute}^*}$$

so K_H can be thought of as the partial pressure of the gas that would be in equilibrium with the dilute solution. The $K_H/10^4$ values for He and Ne are 14.97 and 12.30 respectively, which are of similar magnitude to the CED of water. The value for Ar decreases to 3.96 which reflects its larger stabilizing interaction with water and the (possibly) lower energetic

cost per unit volume to make a larger hole. One should note that the K_H 's can be derived from and are in perfect agreement with the published ΔG 's of solution.

Problems with the Entropy of the aqueous solvent argument for protein folding

The interpretation of the hydrophobic effect as being driven by the change in *entropy of the aqueous solvent* derives primarily from the work of Frank and Evans[1] who showed that transfer of nonpolar solutes to water has $\Delta G > 0$, but that q (heat, confused with ΔH) < 0 . [1] The problems with another report invoking a similar interpretation of urea dimerization[61] in water fails due to some erroneous assumptions, as has been discussed in detail elsewhere. [62]

Many arguments against this interpretation come directly from the literature.

- 1) Abraham showed that transfers of rare gas solutes to water behaves differently from nonpolar organic solutes, which is not consistent with the entropic model.
- 2) Diels-Alder reactions have ΔV_{act} 's < 0 from measurements under applied pressure (rates increase with pressure) and they behave similarly in water, which implies that there be pressure applied by water upon the solutes. Furthermore their rates correlate with the CED's of solvents, in general.
- 3) Constricting salts (such as LiCl) increase the Diels-Alder rates in water and increase the CED (volume of water decreases but ΔH_{vap} is constant).
- 4) Henry's law constants for helium and neon are the same order of magnitude as CED of water, which implies that partial pressures of these gases similar to the CED of water would be required to reduce ΔG to zero (maintain an equilibrium).

The current report adds several other arguments against the argument that entropy dominates the hydrophobic effect:

- 5) DFT calculations show that substantial work is required to make holes in water.
- 6) These calculations are in general agreement with the VAP interpretation of the hydrophobic effect.
- 7) Vibrational analyses show that there are negligible changes in the vibrational entropies in the water clusters upon insertion of a rare gas atom.
- 8) Using the calculated values for the work involved in making the holes to modify the reported ' ΔH 's' reported by Frank and Evans[1] by setting $\Delta H = q + w$ (rather than $\Delta H = q$) no longer requires the large entropy changes reported by them.

Conclusions

The evidence we present suggests that the internal pressure interpretation of the hydrophobic effect generally used or implied by organic chemists is preferable to the interpretation that this effect be due to a negative entropy of solvation of non-polar solutes in water. We believe it to be important to distinguish between hydrophobic *solvation* and the hydrophobic *effect*. Hydrophobic *solvation* applies to any nonpolar solute in aqueous solution including the rare gases studied here. The hydrophobic *effect* causes changes in conformations and/or reactivities. The rare gasses have no capacity for either conformational change or reactivity, so they feel hydrophobic solvation, but are not subject to the hydrophobic 'effect'. The foregoing agrees with Abraham's observations that noble gases do not have a hydrophobic

effect, as well as, that large hydrocarbons, proteins and other large nonpolar molecules will favor more compact conformations or associate in aqueous solution and that reactions that result in a reduction of volume will be accelerated both kinetically and thermodynamically in water. The folding of proteins to achieve smaller molecular volumes in water will be accompanied by a decrease in entropy due to the additional constraints upon the folded vs. unfolded structures. Thus, a lower entropy for a folded protein in water can be consistent with negligible entropy change in the aqueous solvent, itself.

We show that internal pressure is largely responsible for hydrophobic solvation. Work is required to make a hole in a large water droplet. This work had not been accounted for in the interpretation usually used by biochemists. When included, it negates the need for an entropy argument.

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Figure 1.

The effect of the cohesive energy density (CED) upon the endo/exo ratio¹⁷ for three Diels-Alder Reactions.

Figure 2. Inner Solvation shell taken from 50 waters + neon. The outer waters have been removed for clarity. The dashed lines indicate H-bonds. Note that each water near the neon participates in four H-bonds (two as donor and two as acceptor).

Table 1

Calculated properties for noble gases in a 50 water cluster and reported experimental values for aqueous noble gas solutions. See text for explanations.

	Ne	Ar	Kr
$\Delta E_{\text{transfer from gas}}$ (kcal/mol)	7.5 (7.6)	12.3 (11.6)	14.6 (14.1)
$\Delta H_{\text{transfer from gas}}$ (kcal/mol)	9.2 (9.4)	13.8 (13.6)	16.3 (15.9)
ΔS_{vib} (cal/degree/mol) ^a	1.5 (−0.1)	−0.1 (−2.0)	−0.2 (−0.6)
van der Waals radius ^b (Angstroms)	1.54	1.88	2.02
Volume cm ³ /mol (sphere)	9.2	16.8	20.8
Volume cm ³ /mol (cube)	17.6	32.0	39.7
Volume (liquid) in cm ³ /mol (T) experiment ^c	16.8 (25 K)	24.2 (84 K)	32.2 (116 K)
Heat (ΔH in literature) kcal/mol ^d	−1.88	−2.73	−3.55
ΔS (literature) cal/degree/mol ^d	−28.8	−30.2	−32.3
ΔE (hole) kcal/mol	7.0 (7.8)	7.7 (8.4)	8.2 (9.1)
−T (298) ΔS (literature) ^d kcal/mol	8.6	9.0	9.6
ΔH (using $\Delta E_{\text{hole}} + q$)	5.2 (5.9)	5.0 (5.7)	4.6 (5.5)
K_H (atm/10 ⁴) ^e	12.30	3.96	2.23
ΔG (literature) ^f	6.94	6.27	5.93
Effective CED's kcal/cm ³ from ΔE	0.82, 0.43	0.73, 0.38	0.70, 0.37

^aLess three lowest vibrational contributions. Does not account for six equivalent states.

^bref. 22.

^cref.24.

^dref. 1.

^eref 23.

^fref.3.