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Revealing the Frank–Evans "Iceberg" Structures within the Solvation Layer around Hydrophobic Solutes

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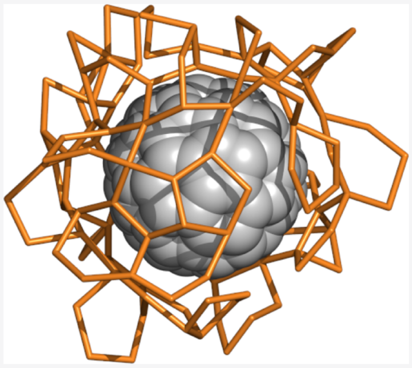
ABSTRACT: Using computer simulations, the structural properties of solvation water of three model hydrophobic molecules, methane and two fullerenes (C60 and C80), were studied. Systems were simulated at temperatures in the range of 250−298 K. By analyzing both the local ordering of the molecules of water in the solvation layers and the structure of hydrogen bond network, it is shown that in the solvation layer of hydrophobic molecules, ordered aggregates consisting of water molecules are formed. Even though it is difficult to define the exact structure of these aggregates, their existence alone is clearly noticeable. Moreover, these aggregates become more pronounced with the decrease of temperature. The existence of the ordered aggregates around the hydrophobic solutes complies with the concept of "icebergs" proposed by Frank and Evans.



■ INTRODUCTION

From the thermodynamic point of view, the hydrophobic effect manifests itself by the occurrence of significant unfavorable free energy of mixing of the hydrophobic substance with water. At moderate temperatures (close to the room temperature), the extent of this effect is determined by the entropic contribution to the free energy.[1]

The origins of hydrophobic effect are ascribed to many factors such as the tetrahedral geometry of the water molecule and its hydrogen bonding abilities (including formation of networks) and its small size,[2−5] which is responsible for small probability of formation of a cavity in the liquid that would be large enough to contain a solvated molecule.

Frank and Evans[6] tried to relate the observed loss of entropy upon mixing with the structural changes that occur in liquid water as a result of the presence of hydrophobic solutes. The authors proposed that around the molecule of the solute, a kind of "cage," consisting of the molecules of water, is formed. This ordered structure, similar in some regards to the structure of a clathrate, was referred to by Frank and Evans as an "iceberg." If the model of "icebergs" is correct, the solvation water of hydrophobic molecules should show a significant degree of some specific ordering. This ordering can be manifested by the enhancement of the hydrogen bond network, which can result from factors such as the increase of the number of hydrogen bonds between water molecules or the energy of the bonds or the increased tetrahedral ordering of water molecules. Some research[7−11] seem to suggest that this effect in fact occurs, but the extent of the observed changes (compared to bulk water) is in some cases relatively small. On the other hand, there are also studies arguing that the solvation water of hydrophobic molecules does not differ in terms of the structure or is even less ordered than bulk water.[12,13]

Some authors, in turn, indicate that the similarities between the solvation water of the hydrophobic solutes and the solid water lie in dynamic properties rather than structural ones. There are many reports[14−16] showing that the dynamics of the solvation water of hydrophobic solutes is slower than the dynamics of bulk water; however, there is no consensus on the extent of this effect. It was also showed that it can have nonmonotonic temperature dependence.[17] Moreover, this slowdown does not necessarily have to be attributed to the structural changes in water.[18]

Despite this, the concept proposed by Frank and Evans is still debated. It is considered incorrect by some researchers,[13,15,19,20] despite the fact that they noticed a slight increase in the ordering of water in the solvation shells of hydrophobic molecules (when compared to bulk water). It is because the term "iceberg" is sometimes interpreted in a quite literal sense, that is, as a solid or solidlike structure surrounding the hydrophobic solute. However, it is worth noting that Frank and Evans did not explicitly define the form of the "icebergs"; they only pointed out that their structure should not be identified with the structure of solid water.[6] In a less literal sense, "icebergs" can be regarded as a tendency of water

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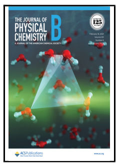

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molecules in the solvation shell of hydrophobic solutes to possess such structural features which show some similarities (to a lesser or greater extent) to the behavior of water molecules in the solid phase. In that sense, these structures will show a higher degree of ordering than bulk water, but—at the same time—will be also less defined and prone to change in time. This is the approach that we have adopted in our work.

■ METHODS

Computer Simulations. Computer simulations (in the all-atom version) of the selected molecules, methane, two fullerenes (C60 and C80) and lysozyme (PDB code: 193L), were conducted with the use of Amber16 package[21] in the *NpT* conditions. The parameters for the lysozyme and the carbon atoms of the fullerenes were taken from the ff03 force field, and the parameters for the methane molecule were taken from refs 22 and 23.

Every simulation system consisted of one molecule of the solute in a rectangular simulation box filled with liquid SPC/E water. Periodic boundary conditions were applied during all of the simulations. It was shown[24−26] that the SPC/E model can be successfully used in the studies of supercooled water, even though its properties may not be identical to the properties of real supercooled water in corresponding conditions. Its melting temperature was found to be equal to 215 K.[27] The number of water molecules in the simulation systems was equal to 2658 for the system with the methane molecule, 6952 and 7188 for the systems with the C60 and C80 fullerenes, and 31110 for the system with the molecule of lysozyme. Since the molecule of lysozyme is positively charged, eight chloride ions were also added to neutralize the system (see the Supporting Information for details).

Computer simulations for the analysis of the properties of solvation water of ice were carried out in the same conditions with the use of an ice block surrounded by about 22,000 water molecules. The block of ice consisted of 2090 water molecules. Two faces of the block that were selected for the analysis were basal planes of ice. Their size was equal to about 4 × 4 nm. In order to avoid the influence of the edges of the ice block on the results, only the central part of the solvation layer of ice was analyzed (the distance between the analyzed molecules of water and the edges of the ice block was equal to at least 1 nm).

The simulations were carried out at temperatures, 250, 258, 268, 278, 288, and 298 K, for about 20 ns (with the time step equal to 0.002 ps). The procedure of the equilibration of the systems, preceding the main simulations, was carried out for about 5 ns.

Analysis. *Concept of the Order Parameters.* The term "structure of water" can be understood as a certain average spatial arrangement of molecules as well as the mutual orientation of these molecules in water. In order to provide a quantitative characteristic of the structure of water defined in this way, we used the concept of the order parameter p, described in detail in our previous papers.[28,29]

To explain the physical background, we have to begin from the equation that describes the entropy (per molecule) of the system consisting of N particles, which can be expressed as a sum of the entropy of an ideal gas (s^{id}) and the contributions to the entropy originating from n-particle correlations ($s^{(n)}$)

$$\frac{S}{Nk} = s^{\mathrm{id}} + s^{(2)} + s^{(3)} + \ldots + s^{(N)} = s^{\mathrm{id}} + s^{(\mathrm{exc})} \quad (1)$$

where k is the Boltzmann constant and $s^{(\mathrm{exc})}$ is the excess entropy. Higher correlations become increasingly difficult to calculate; therefore, we limit ourselves to the $s^{(2)}$ term, describing two-particle interactions. The first step to calculate the order parameter is to determine a two-particle water−water correlation function (the definition of this function is given in the Supporting Information). Its values depend on the distance between pairs of water molecules (r), two angles in a spherical coordination system (ϕ and θ), and three Euler angles (α, β, and γ) describing the mutual orientation of the molecules (Figure S3).

Next, the integral is calculated in the space volume enclosing the nearest surrounding of individual water molecules. Its extent is determined by a cutoff value R_{cut}. If R_{cut} is sufficiently large, the values of the integral change slowly with increasing R_{cut}. For the purpose of determining the p parameter, the limit of the integration was chosen as the extent of the second solvation layer of water molecule, equal to 0.58 nm. As we showed before,[28] the order parameter p can be expressed as the sum of three terms

$$p = p_{\mathrm{tra}} + p_{\mathrm{con}} + p_{\mathrm{ort}} \quad (2)$$

where terms p_{tra}, p_{con}, and p_{ort} represent contributions originating from translational (r-dependent), configurational (r, ϕ, and θ-dependent), and orientational (r, ϕ, θ, α, β, and γ-dependent) ordering of molecules. We also showed that the values of the p_{con} and p_{ort} parameters are correlated, which allows for a significant simplification of the calculation procedures. By definition, the values of the order parameters are always nonpositive: equal to zero in the case of a complete disorder (for the ideal gas) and increasingly more negative with the increasing degree of order.

The values of $(p_{\mathrm{tra}})_{\mathrm{solv}}$ and $(p_{\mathrm{con}})_{\mathrm{solv}}$ characterize the structure of water that creates the solvation layer of the molecule of solute. However, it has to be noted that these values depend on multiple factors, including the thickness of the analyzed solvation layer, the shape of the solvated surface, the specific interactions of water molecules with the solvated molecule, and the interactions of water molecules with each other. The influence of the last two of these factors is the most interesting because they determine what we can call the "inner" structure of solvation water. In order to evaluate them (and exclude the influence of the geometry of the analyzed layer on the results), we created a "reference systems" by transferring the molecules of the analyzed solutes into separate simulation boxes filled with bulk water. After that, the molecules of water that overlap with the atoms of the molecules of the solutes were removed from the boxes. The criteria of the overlapping were the closest distances from the centers of mass of the water molecules from the atoms of the solutes (the cutoff distance was equal to 0.17 nm, as previously[30]). As a result, the systems in which the molecules of the solutes are solvated with water in which the structure is bulk-like were created. By determining the values of $(p_{\mathrm{tra}})_{\mathrm{bulk}}$ and $(p_{\mathrm{con}})_{\mathrm{bulk}}$ in these systems, reference points for the calculations were obtained. The difference between the values of the order parameters calculated for the real solvation shells of the molecules of solutes and the values corresponding to the "reference systems" $\Delta p_{\mathrm{tra}} = (p_{\mathrm{tra}})_{\mathrm{solv}} - (p_{\mathrm{tra}})_{\mathrm{bulk}}$ and $\Delta p_{\mathrm{con}} = (p_{\mathrm{con}})_{\mathrm{solv}} - (p_{\mathrm{con}})_{\mathrm{bulk}}$ reflect the changes in the structure of solvation water resulting from its specific interaction with the solvated surface.[29,31]

The calculations were performed for water molecules within the first solvation shell (0.5 nm). For justification of the thickness of the layer, see the Supporting Information.

The same procedure—the comparison with the structure of the bulk water that fills the same space as the real solvation layer—was also used in the case of other parameters that characterize the properties of water in the solvation shell of the molecules selected for our study.

Analysis of the Water–Water Hydrogen Bonds. Parameters δ and τ. In this work, the "conical" definition of the hydrogen bond is used.[32] Compared to other commonly used definitions, it reflects the real properties of hydrogen bonds relatively best.[33] The subject of our interest was the search for five- and six-membered rings formed by water molecules connected by hydrogen bonds and the analysis of their orientation in relation to the solvated surface as well as the tendency of the rings to connect and form more complex, spatial structures.

To identify the rings formed by water molecules, all hydrogen bonds between the water molecules in the selected solvation shell were analyzed (along with the hydrogen bonds with water molecules adjacent to the selected solvation shell but beyond its scope). Every water molecule can, potentially, participate in the creation of multiple rings. Each time, we looked for the shortest, closed path along hydrogen-bonded water molecules. For example, six water molecules can create two four-membered rings (two water molecules are shared between the rings), but in this case, there is also a hydrogen-bonded six-molecule-long, closed path. In such cases, it was assumed that there are two four-membered rings instead of one six-membered ring.

Because of the relatively small thickness of the first solvation shell (0.50 nm), we adopted the following criterion for whether the ring belongs to the layer: at least half (i.e., three) of the water molecules forming the ring must be present in the considered layer.

The determination of the spatial orientation of the rings in relation to the hydrated surface was performed as follows. The plane approximating the positions of oxygen atoms of water molecules forming the considered ring was determined (using the least-squares method). The geometrical center of the ring on this plane was the starting point of the vector whose end was at the geometrical center of the set of 10 atoms of the solvated molecule closest to that point (naturally, with the exception of the methane molecule and the chloride ion). The angle between this vector and the vector normal to the ring plane was used to determine the ring orientation (and was called δ, see also Figure S4).

The tendency for the rings to create more complex structures was measured with the use of the τ parameter, defined by us as the ratio of the total number of rings (five- and six-membered) present in the solvation layer to the number of water molecules involved in their formation. The higher the value of this parameter, the more compact the structure consisting of a certain number of interconnected rings (less water molecules are needed to form it). As a reference, the value of τ for bulk water is obtained, as described in the case of the order parameter p. When calculating the value of τ_{bulk}, we limit the number of rings by removing those water molecules whose positions "overlap" with the solvated molecule. Therefore, the specific values of this parameter are not particularly informative on their own. However, rather than in exact values, we are interested in how they change between the analyzed solutes and with temperature.

Parameters θ. We also analyzed the geometry of a set of hydrogen-bonded molecules consisting of a central water molecule and all molecules hydrogen-bonded to it. It was done by calculating the angles between all vectors connecting the centers of mass of the central water molecule and its hydrogen-bonded neighbors. These angles should reflect the tendency of these sets of water molecules to adopt a tetrahedral configuration (with the reservations discussed when describing the order parameter Δp and applying the same procedure of subtracting the values obtained for bulk water). The results are presented as histograms $\Delta P(\theta) = P(\theta_{\text{solv}}) - P(\theta_{\text{bulk}})$.

■ RESULTS AND DISCUSSION

For the water contained in the first solvation layer of the tested molecules and for the solvation water of the *basal* plane of the ice crystal, we determined the values of the parameters $\Delta p_{\text{tra}} = (p_{\text{tra}})_{\text{solv}} - (p_{\text{tra}})_{\text{bulk}}$ and $\Delta p_{\text{con}} = (p_{\text{con}})_{\text{solv}} - (p_{\text{con}})_{\text{bulk}}$. These parameters allow for a clear illustration, in the form of an "ordering map,"of changes in the structure of solvation water as the temperature lowers. The obtained results are presented in Figure 1.

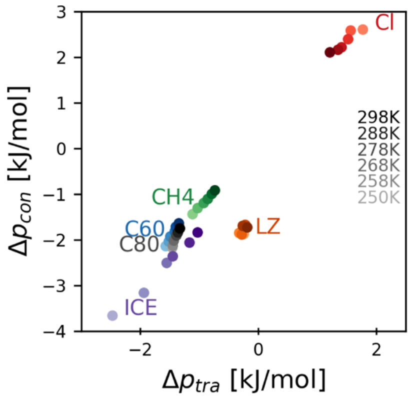

Figure 1. Ordering map illustrating the temperature changes of the degree of structural order of the solvation water of the studied solutes: the *basal* plane of ice, fullerenes C60 and C80, methane, lysozyme, and chloride ions. The color gradient indicates the direction of the temperature change (the lighter the color, the lower the temperature).

Main conclusion that can be drawn from this figure regards the characteristic direction of the temperature changes in the solvation water of hydrophobic molecules—the values of both Δp_{tra} and Δp_{con} parameters become more and more negative as the temperature decreases. This means that—as the temperature decreases—the order of the solvation water around the hydrophobic molecules increases faster than it does in bulk water. It is striking that the nature of these structural changes closely resembles changes occurring in the solvation water of ice (purple line in Figure 1)—the only difference is that the extent of these changes is clearly smaller, that is, the rate of increase in the degree of order around hydrophobic molecules is smaller than in the vicinity of the ice surface.

We also analyzed the properties of water contained in the first solvation layer of a frequently studied, model globular protein, lysozyme. The lysozyme was chosen to represent a "typical" protein molecule, with the surface covered with mixed (hydrophobic and hydrophilic) groups. In the case of the lysozyme, these groups are scattered across the surface, and no

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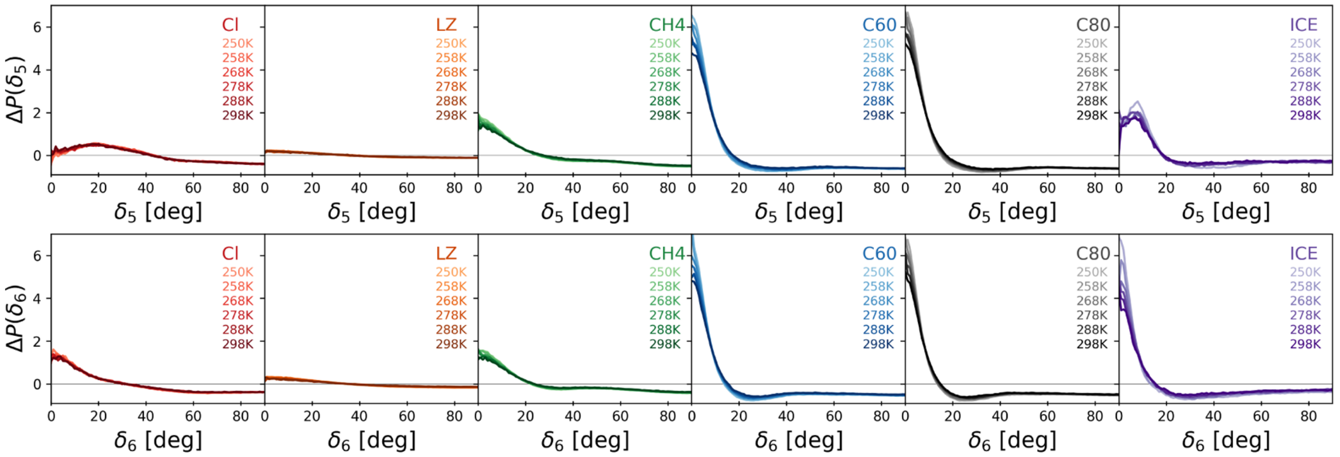

Figure 2. Histograms illustrating the orientation of five- and six-membered rings formed in the solvation layers of the molecules of the analyzed solutes and ice (presented as differences relatively to the bulk water filling these layers) at the studied temperatures. Color scheme is the same as in Figure 1.

large patches of uniform chemical character are visible. As it can be seen in Figure 1, the results clearly differ from the ones obtained for the analyzed hydrophobic molecules. The temperature changes are less pronounced. Some additional comments on the interpretation of the values of the order parameters can be found in the Supporting Information.

To complete the picture, we note that the direction of the temperature change observed in the solvation shell of chloride anions (present in the simulation box with lysozyme) is opposite to the one found for the solvation water of hydrophobic molecules. With the decrease of temperature, the difference in structural ordering between solvation water and bulk water also increases. However, this time, the values of the Δp_{tra} and Δp_{conf} parameters are positive, indicating increasing disorder (relatively to bulk water) with decreasing temperature. Chloride ion is said to be able to participate in creating a hydrogen bond network in aqueous solution.[34] On the other hand, it forces the surrounding water molecules to achieve the most favorable electrostatic orientation with respect to the ion.[35,36] The structural changes in water caused by the addition of sodium chloride have been observed to be similar to the change in structure of pure water because of increasing pressure.[36] The influence of ions on water is temperature-dependent. For example, at low temperatures, the presence of sodium chloride increased the water self-diffusion coefficient beyond the corresponding values for bulk water.[37]

In this context, it is worth to recall the results of analogical studies carried out for the solvation water of antifreeze proteins. The surface of such a protein molecule consists of two areas: the one capable of binding to the ice surface and the remaining part that does not display affinity to ice. The specificity of the ice-binding area lies both in its geometry (the area is usually flat) and in its hydrophobic character.[38] In the vicinity of the ice-binding area,[29,31] the direction of temperature changes in the degree of ordering of solvation water was very similar to the ones observed in the case of the hydrophobic solutes. On the other hand, in the vicinity of the remaining (non-ice-binding) surface fragments, the degree of order of solvation water (relatively to bulk water) changed in the opposite direction[29,31] it decreased as the temperature decreased.

Therefore, in our opinion, the effect of increasing of the degree of order of solvation water (relatively to bulk water) with decreasing temperature characterizes the hydrophobic hydration process. Moreover, the far-reaching similarity of the changes in the structure of the solvation water of the studied hydrophobic molecules to the changes observed in the ice solvation water prompts us to possibly explain these changes by referring to the well-known concept of Frank and Evans's "icebergs." In liquid water, we can encounter not only pairs of hydrogen-bonded water molecules but also more extended structures, such as compatible with the structure of ice six-membered rings and octameric units, but also not compatible with the structure of ice five-membered rings,[39,40] responsible for the phenomenon of supercooling.[41,42]

These aggregates of water molecules, when adjacent to the surface of the hydrophobic molecule, would perhaps be able to associate with one another. If so, formation of such an extended structure entwining a molecule of a hydrophobic substance—although not necessarily in the form of a closed cage—is essentially in line with the idea of Frank and Evans.

To verify this view, we looked for five- and six-membered rings in the solvation layer of the selected hydrophobic molecules. Moreover, we compared the obtained results with those for the solvation layer of the *basal* surface of the ice crystal, the lysozyme molecule, and the chloride ion. Two parameters are of most interest to us: the orientation of the ring plane in relation to the hydrated surface (characterized by angles δ) and the value of the parameter τ, which is a measure of the tendency of the rings to connect into larger structures. The results of these calculations are presented in Figure 2.

The results show a strong preference for the "parallel" arrangement of the rings in relation to the hydrophobic surface, as is in the case of the surface of ice. We observe a different picture for the lysozyme, where this distribution is close to random—in this case we have to note, however, that in the case of the protein, the angles δ may be a little troublesome to obtain and interpret due to the rough surface of the protein. The "parallel" arrangement of the rings in the vicinity of the hydrophobic surface suggests the possibility of creating a hydrogen-bonded net enclosing the hydrophobic molecule. This effect is also clearly temperature-dependent in the case of the hydrophobic solutes. The tendency for parallel orientation of the rings increases with decreasing temperature, in accordance with the results concerning the order parameters.

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The measure of the tendency for rings to connect to each other are the values of the τ parameter (see Methods section). By examining the changes of the value of the ratio $\tau_{\text{solv}}/\tau_{\text{bulk}}$ as a function of temperature (Figure 3), one can conclude about the tendency to form the above-mentioned aggregates. For all studied systems, except from the chloride ions, the ratios $\tau_{\text{solv}}/\tau_{\text{bulk}}$ are greater than one. Moreover, as the temperature is lowered, this ratio clearly increases, which indicates an increasing tendency to form the described aggregates in the solvation layer of the studied molecules (again, except from the chloride ion). Interestingly, there is no difference in the behavior of solvation water of hydrophobic molecules and lysozyme. We interpret these results as follows.

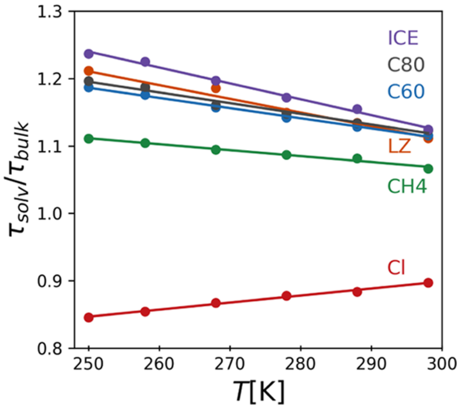

Figure 3. Dependence of the $\tau_{\text{solv}}/\tau_{\text{bulk}}$ ratio on the temperature, determined for the water contained in the solvation layer of the molecules of the studied solutes and ice. Regression lines that approximate the data are also shown.

Liquid water has a natural tendency to form structurally ordered aggregates. By interacting with the surface of the solute, these aggregates are either repelled from that surface (if it is a hydrophobic surface) or they are anchored on it at the points where there are atoms capable of hydrogen bonding with the water molecules. In both cases, it results in a specific change of the structure of the entire aggregate—to preserve it in a form that fits to the type of surface to be hydrated (hydrophobic or hydrophilic). As shown by the results presented in Figures 1 and 2, in the case of the lysozyme, this structural change appears to be smaller, while it is greater (and is strongly temperature-dependent) in the case of the hydrophobic surface. The results for chloride ions correspond well with the results presented in Figure 1. As we can see in Figure 3, the values of ratio of $\tau_{\text{solv}}/\tau_{\text{bulk}}$ are less than one. With decreasing temperature, the aggregates become less interconnected relatively to bulk water, which agrees with the observed temperature dependence of the order parameters Δp (Figure 1).

Grdadolnik *et al.*,[9] using IR spectroscopy and molecular dynamics, concluded that in the solvation layer of methane, there are strengthened, more numerous, and more tetrahedrally oriented hydrogen bonds than in bulk water, resembling those in ice and clathrates. As an origin of this phenomenon, they pointed the absence of intercalating water molecules that cause the electrostatic screening of hydrogen bonds in bulk water.

Although our results may confirm some increase of tetrahedral ordering of water around methane, the same is not true for the fullerenes (we observe increase and decrease, respectively, of the histogram values for angles around 109° in Figure 4).

It is known that what is called a hydrophobic effect can manifest differently when hydrophobic solutes of different sizes and surface topography are concerned.[1,43,44] The decrease of tetrahedral ordering that we observe in the case of the fullerenes corresponds, for example, with our previous results concerning purely hydrophobic protein-shaped solute.[45] It does not contradict the results concerning the local ordering (p parameter) or the connectivity parameter τ. The net of hydrogen bond, while trying to encircle the hydrophobic molecule (as we conclude from Figure 2), becomes a little strained because of the significant size of the solute and lack of possible acceptors or donors of hydrogen bonds at its surface. This parameter is also strongly temperature-dependent. As the temperature lowers, the histograms deviate from the bulk water more and more analogically as the ordering parameters Δp. In the case of the solvation water of ice, it indicates increasing resemblance to the solid phase, while in the case of the fullerenes, it characterizes the solute-specific net of hydrogen bonds encircling the molecules. The case of methane indeed resembles more the case of solvation water of ice; with lowering temperature, the tetrahedral ordering seems to increase a little (Figure 4), although the effect is relatively small.

It is also worth comparing some of the results obtained for methane with an analytical theory of hydrophobic hydration of Urbic and Dill.[46] According to this theory, the population of water molecules can be divided into a couple of states according to their interactions with other water molecules: hydrogen-bonded state, van der Waals state (molecules close to each other but not hydrogen-bonded), and nonbonded state. Additionally, the total energy of interactions in the system also includes cooperativity energy, when 6 water molecules form a full hexagonal cage[46] or 12 water molecules form a full cage of 15 hydrogen bonds.[47] For example, the model predicts that in the temperature range investigated by us, water molecules from the first solvation shell create more

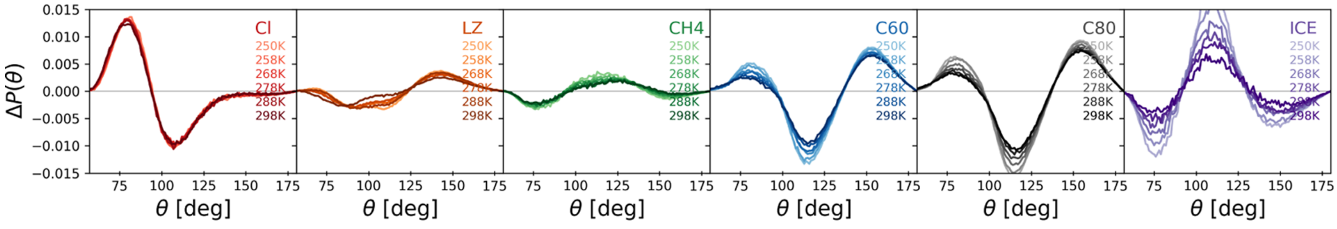

Figure 4. Dependence of $\Delta P(\theta) = P(\theta_{\text{solv}}) - P(\theta_{\text{bulk}})$ on the temperature, determined for the water contained in the solvation layer of the molecules of the studied solutes and ice. Color scheme is the same as in Figure 1.

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hydrogen bonds than bulk water and have low-variance, well-defined HB angles.[46] We observed, that in the case of methane molecule (which size is in the range of the solute sizes investigated by the authors in the mentioned paper), the mean number of hydrogen bonds in the first solvation shell indeed exceeds the mean number of hydrogen bonds found in the bulk liquid (Figure 5) a little. The authors concluded that they are able to see a stochastic version of the "iceberg" proposed by Frank and Evans.[46] The size of the fullerenes is above the upper limit of the sizes for which the results are reported; therefore, we cannot directly compare the results for these solutes.

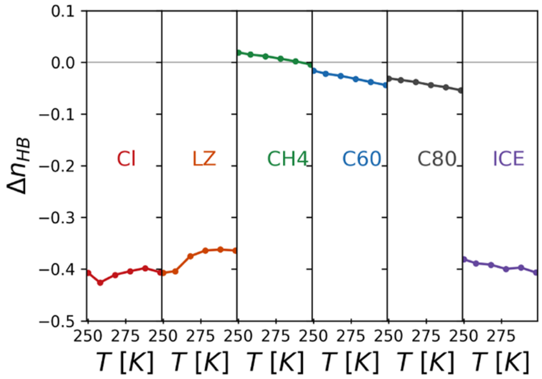

Figure 5. Dependence of the mean number of hydrogen bonds on the temperature, determined for the water contained in the solvation layer of the molecules of the studied solutes and ice. The results are presented as differences between the mean number of hydrogen bonds created by a water molecule with surrounding water molecules in the solvation layer and the mean number of hydrogen bonds created by a water molecule in bulk water (the water molecules in the ice block are not taken into account as hydrogen bond partners).

■ CONCLUSIONS

In the vicinity of the hydrophobic surface, we observe higher ordering of the solvation water (relatively to bulk water), regular arrangement of the rings created by hydrogen-bonded water molecules, and the tendency of these rings to connect with each other. It seems to be fully in line with the spirit of the Frank and Evans concept of "icebergs." The distinctness of the process of creating these "icebergs" increases with the lowering of the temperature. Although it is difficult to indicate what specific structural forms the postulated "icebergs" take, in our opinion, the fact of their existence is visible in the light of our results.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.jpcb.0c09489.

Details of the preparation of the systems and computer simulations and density distribution functions used to determine the extent of the solvation layer (PDF)

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Notes

The authors declare no competing financial interest.

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