The Effect of Urea on the Structure of Water: A Molecular Dynamics Simulation

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This paper reports an analysis using molecular dynamics simulations of the effect of urea on the structure of water. Two definitions of the tetrahedral distributions are used to quantify this effect. The first one is sensitive to the mutual orientation between a reference water molecule and the water molecules forming the tetrahedron, and the second is sensitive to their radial distribution. The analysis shows that increasing urea mole fraction results in a reduction of the structured tetrahedral arrangement contribution in favor of an unstructured one. In order to understand this behavior, we used the nearest neighbor approach which allows us to get unambiguous information on the radial and orientation distributions of the water molecules around a probe one. The results indicate that the decrease of the tetrahedral arrangement of the nearest neighbors around a probe water molecule is associated with both the increase of the fluctuation in their radial distances as well as with the loss of their mutual orientations with respect to those observed in pure water. The tetrahedral distribution of water in the hydration shell of urea as well as that around its carbonyl and amine groups is also discussed.

1. Introduction

The aqueous solutions of urea are known for their macroscopic properties such as protein denaturation,[1] solubilization of hydrocarbons,[2] and slowing down of the micellar aggregation.[3] When theoretical interpretations are sought for these macroscopic properties of urea aqueous solutions, one must consider the urea–urea, urea–water, and water–water interactions. The last term addresses the manner in which urea solute may alter the structure of water. To explain how the urea affects the structure of water, Frank et al.[4] assume that the liquid water exists in an equilibrium between two states, open or ordered vs dense or disordered, and that the hydrogen bonds between water molecules are destroyed by introducing urea solute. This concept becomes essential to describe phenomena of fundamental and practical importance in aqueous solutions ranging from the change in the conformation of proteins (denaturation process), the bioprotection in drying and freezing processes, to hydrophobic/hydrophilic interactions and intermolecular forces.

There is a long-standing controversy regarding the effect of urea on the three-dimensional H-bond network of water because of the difficulty to define quantitatively the structure of water. Indeed, several published experimental (vibrational spectroscopy, NMR, neutron scattering, dielectric relaxation, and thermodynamic data) and computer simulation studies clearly differ in their conclusion about the effect of urea on the structure of water. Infrared studies of urea aqueous solutions led to the conclusion that urea slightly alters the structure of water, and therefore urea cannot be described as a "structure" breaker.[5] In recent work, using infrared spectroscopy, Panuszko et al.[6] show that the oxygen–oxygen distances between two water molecules in urea aqueous solutions are very similar to those in pure water, suggesting that urea has a slight effect on the water structure. The structure breaking of urea was suggested by Walrafen[7] from the effect of urea on the intermolecular Raman band of water between 152 and 175 cm^{-1}. The chemical shift of water measured by NMR spectroscopy is not altered significantly, even at higher concentration.[8] The authors interpret the result as an indication that urea mixes freely with water, leaving the structure of water as structured as in pure water. NMR analysis of the diffusion coefficient in the urea/water system indicates that urea is a structure breaker.[9] The spin–lattice relaxation times T_1 of the ^{17}O nucleus of a water molecule in urea at 25 °C were measured by NMR spectroscopy.[10] It was found that urea has no significant effect on the water structure. This result was established by following the variation of the ratio $(1/T_1)/(1/T_1^0)$, where $1/T_1$ is the spin relaxation rate of the ^{17}O nucleus of water molecule in urea and $1/T_1^0$ is that in pure water. From pressure and temperature effects on the ^2H spin–lattice relaxation times and ^1H chemical shifts in urea/D_2O solutions, it was concluded that it is difficult to classify urea as either a structure-maker or a structure-breaker.[11] Soper et al.[12] using a neutron scattering experiment conclude that urea mixes in well with the water molecules but in doing so has a drastic effect on the water–water second neighbor shell.

Ultrasonic attenuation measurements on urea aqueous solution[13] conclude that urea acts as a structure breaker of the water network. An ultrahigh frequency dielectric constant experiment also leads to the conclusion that urea acts as a structure breaker of water. Recent dielectric measurements show that urea is not a strong breaker of water.[14]

The differential approach in solution thermodynamics used by Koga et al.[15] confirms the thermodynamic data obtained earlier by Egan et al.[16] and leads to the physical picture that urea affects the nature of the hydrogen bond network of water by forming a hydrogen bond directly to the network, reducing the degree of fluctuation characteristic to liquid water. The authors also conclude that, from the behavior of the urea−urea excess enthalpy, it is not possible to provide a clear-cut answer on the nature of the effect of urea on the water structure.

Several molecular-dynamics simulations have been tried to provide a microscopic picture to analyze the effect of the solute on the structure of water. Tsai et al.[17] found that urea preserves the water distribution by dispersing evenly in the water structure. Tovchigrecho et al.[18] show that the water−water interaction energy per water molecule in urea solutions is almost the same as that in neat water (-0.0499 and -0.0489 kcal·mol^{-1}). This result indicates that urea can be inserted in the hydrogen-bond network formed by water molecules without appreciably disturbing it.[18] The simulation results of Weerasinghe et al.[19] suggest that, because of the similarity between the water−water and water−urea interaction energies, urea aqueous solutions may be considered as ideal and, incidentally, urea has almost no effect on the structure of water. On the basis of the calculated values of the Kirkwood−Buff integrals, Chitra et al.[20] designated urea as a slight water structure maker. Wallqvist et al.[21] using the radial distribution function concluded that it induces a minimum disruption of the overall hydrogen bonding of the aqueous solution. Kuharsky et al.[22] showed that there are only small differences between water in the vicinity of urea and bulk water. Smith et al.[23] using molecular dynamics simulation concluded that urea is not a structure breaker; instead, urea can fit into the water structure without greatly disturbing the overall hydrogen bond network of water. Hua et al.[24] found that urea does not disrupt the water structure or its hydrogen-bonded network. On the basis of the calculated values of the activity coefficients of urea, the average number of hydrogen bonds, and their lifetime, Kokubo et al.[25,26] concluded that urea solutions have a near ideal character which incidentally implies a lack of water perturbation. Das et al.[27] conclude from the change in water−water hydrogen bond angle and distance that urea is a breaker of water structure. Yamzaki et al.[28] using the reference interaction site model (RISM) integration equation found that water molecules are a bit more structured than pure water. Vanzi et al.[29] concluded from the calculated hydration heat capacities of urea that this solute appears to structure water.

It would seem that the controversy on the effect of urea on the structure of water pointed out previously is due to the fact that the connection between the infrared and Raman spectra (position, width, and intensity of the vibration bands) and the structure of water is usually unknown and consequently only approximate hypotheses could be used for this purpose.[30] Furthermore, in the case of neutron scattering, the majority of the observed signals arise from bulk water, masking the structural change contributions from water in the first hydration shell of the solute molecule. The controversy in the molecular dynamics simulations may be biased by both the potential models of urea and water used in each simulation and/or also to the particular choice of the statistical property used to quantify this effect. Indeed, in their first reported results, Das et al.[31] conclude from the behavior of the radial distribution function of water molecules that urea has no significant deformation on the structure of water. However, in the second reported paper,[27] these authors show using hydrogen bond angle behavior that urea acts as a structure breaker.

Although the radial distribution function is a central statistical parameter in the analysis of the structure, many molecular dynamics simulations[17,27,32–37] indicate that the radial distribution functions of water molecules and related properties undergo a little change and are not sufficient to characterize the effect of urea on the structure of water. Mehrotra et al.[38] introduced the idea of a structural analysis of the statistical state of solutions based on the proximity criterion which provides detailed interpretation of the local structure, particularly around sub-structures (i.e., atoms, functional groups, or subunits) of the solute. Kuharsky et al.[22] applied this idea to the analysis of the local structure in infinite diluted urea aqueous solution. The results show that the pair interaction energies, as well as the total number of hydrogen bonds, undergo small changes with respect to those in pure water and are then not sufficient to clarify the effect of urea on the structure of water. However, recent studies pointed out that the analysis of the angular distributions is a more sensitive indicator of structural perturbations of water molecules belonging to the hydration shell of urea.[17,24,29,39,40] This also leads us to consider the angular distribution of water molecules in the neighborhood of amine and carbonyl groups in urea. Several definitions of the angular distributions were considered: the distribution of cos θ, where θ is the angle between the OH axis and the one joining oxygen atoms of two hydrogen-bonded water molecules,[29] or the angle between three water oxygen atoms[24,27,39] and in terms of the angle between molecular axes of two water molecules.[40] Although these definitions of the mutual orientation between two water molecules are not complete,[41] the results converge to show that qualitative changes in the structure of water in the vicinity of urea occur, and particularly, Vanzi et al.[29] showed that the predominantly linear H-bond network of water molecules around the amine groups in urea is maintained and even enhanced, while it is distorted around the carbonyl group. In a previous work,[42] we showed using both free energy perturbation and the method of thermodynamic integration that amine groups of the urea molecule have a strong synergetic effect on the thermodynamics of urea hydration. Following this line of approach, we analyze in this paper the effect of increasing urea mole fraction, X_U, on the tetrahedral local structure of both bulk water molecules and of those belonging to the hydration shell of urea. This effect is quantified through the extent to which a given water molecule and its surrounding neighbors adopt a tetrahedral arrangement. To characterize the tetrahedral arrangement around a reference water molecule, we used two widely used definitions, the first one being sensitive to the mutual orientation of water molecules forming the tetrahedron[43–47] and the second one being sensitive to their radial distribution.[48–57] In order to understand the effect of urea on the tetrahedral arrangement of water molecules; we used the nearest neighbor approach[58–63] to get information on the radial and mutual orientation of the water molecules around a reference one. We also investigated the effect of adding urea on the tetrahedral local structure of water molecules in the first hydration shell of urea as well as in the vicinity of the amine and carboxyl groups of urea.

Accordingly, the paper is organized as follows: First, details of the simulation are given; second, the parameters connected to various aspects of the tetrahedral local structure of water and the nearest neighbor approach are introduced. In the third part, the evolution of these parameters as a function of the mole fraction of the solute is presented. Finally, these results are analyzed and discussed.

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TABLE 1: Nonbond Parameters for Urea and Water Potential Models

	atom	ε (kcal/mol)	σ (Å)	charge q (|e|)
urea[67]	C	0.10485	3.750	0.142
	O	0.20971	2.960	−0.390
	N	0.16979	3.250	−0.542
	H_U	0	0	0.333
water[68]	O_W	0.1548	3.154	0.000
	H_W	0.000	0.000	0.520
	S_F	0.000	0.000	−1.040

TABLE 2: Bond Parameters, Angles, and Dihedral Force Constants for Urea[66]

	bonds		
	C=O	C—N	N—H
r_0 (Å)	1.2770	1.3800	0.9896
k_b (kcal/mol/Å²)	500.0	376.0	438.0

	angles			
	O—C—N	N—C—N	C—N—H	H—N—H
k_θ (kcal/mol/rad²)	80.0	80.0	30.0	35.0
θ (deg)	122.9	114.2	120.0	120.0

	dihedral			
	x—C—N—x	O—C—N—H	x—x—C—O	x—x—N—H
k_ψ (kcal/mol)	2.5	2.5/2.0	10.5	1.0
δ (deg)	180.0	180.0/0.0	180	180
m	2	2/1	2	2

2. Methods

In contrast to previous studies,[64,65] the MD simulations were performed here with a potential function that represents intermolecular Lennard-Jones and Coulombic interactions, as well as intramolecular interactions. Thus, it is given by

$$V_{total} = \sum_{i<j} 4\varepsilon_{ij}\left[\left(\frac{\sigma_{ij}}{r_{ij}}\right)^{12} - \left(\frac{\sigma_{ij}}{r_{ij}}\right)^{6}\right] + \frac{q_i q_j}{r_{ij}} +$$
$$\sum_{bonds} k_b(r_{ij} - r_{eq})^2 + \sum_{angles} k_\theta(\theta - \theta_{eq})^2 +$$
$$\sum_{improprer} k_\omega(\omega - \omega_{eq})^2 + \sum_{dihedral} k_\psi(1 + \cos(m\psi - \delta))^2$$

(1)

where r_{ij} is the distance between atoms i and j of different solute molecules. The equilibrium bond lengths are given by r_{eq}, the angles by θ_{eq}, and the improper angles by ω_{eq}. k_b is the elongation constant, k_θ is the valence angle, k_i ($i = \omega, \psi$) is the barrier height, m is the multiplicity that determines the number of energy minima during a full rotation, and δ is the phase factor that determines where the torsion passes through energy minima. The corresponding force constants are those proposed by Kallies[66] for urea. The Lennard-Jones parameters ε_{ii} and σ_{ii} and the atomic charges q_i of Jorgensen for urea[67] have been employed here. For water, the rigid TIP4P potential model was used.[68] The van der Waals interactions between urea and water molecules were modeled with the use of the Lorentz−Berthelot combination rules. The values of the force field parameters are specified in Tables 1 and 2. The simulations have been performed using the DL_POLY program.[69] They were performed on the isothermal isobaric ensemble at 300 K and 1 atm. A weak coupling scheme with relaxation times of 0.1 ps (temperature) and 0.5 ps (pressure) was used. All site−site

TABLE 3: The System Simulated in This Work[a]

N_U	N_W	X_U	C_U (M)	V_{UW}^b (nm³)	ρ_{UW} (g/cm³)	T_{sim} (ns)
0	864	0.0	0.0	26.03	0.9929	4
18	846	0.02	1.116	26.77	1.0124	4
43	821	0.05	2.569	27.81	1.0374	4
61	803	0.07	3.547	28.55	1.0544	4
86	778	0.10	4.824	29.61	1.0758	4
104	760	0.12	5.689	30.34	1.0911	4
130	734	0.15	6.864	31.45	1.1104	4
156	708	0.18	7.963	32.56	1.1284	4
172	692	0.20	8.601	33.21	1.1400	4
199	665	0.23	9.622	34.34	1.1572	4

[a] N_U is the number of urea molecules, N_W is the number of water molecules, X_U is the urea mole fraction, V_{UW}^b is the simulation box, C_U (mol/L) is the concentration, ρ_{UW} is the solution density, and T_{sim} is the total simulation time.

interactions have been truncated to zero beyond the center−center cutoff of 15 Å. The long-range part of the electrostatic interactions has been accounted for using the Ewald sum method. The three variables, the real space cutoff, the convergence parameter α, and the largest reciprocal space, controlling the Ewald sum procedure are 15 Å, 0.3 Å^{-1}, and 7, respectively. The equations of motion were integrated with the aid of the leapfrog algorithm and a time step of 1 fs. The simulations were performed on pure water and on solutions of solute mole fractions (X_U) of 0.02, 0.05, 0.07, 0.10, 0.12, 0.15, 0.18, 0.20, and 0.23. These compositions are specified in Table 3. For each mole fraction, the system was equilibrated for 4 ns. The production stage lasts 400 ps (400 000 configurations). The coordinates of molecules were stored each 0.4 ps and are used to calculate the relevant statistical properties.

3. Local Tetrahedral Distribution

The local structure of liquid water is classified as tetrahedral because its coordination number (defined as the area under the first peak of the oxygen−oxygen radial distribution function) is above 4 and less than 5. Indeed, if one looks at the oxygen−oxygen radial distribution function, the position of the first peak is associated with the distance between the two oxygen atoms involved in a hydrogen bond and the position of the second peak is related to the distance between the oxygen atoms located at the vertices of the tetrahedron. However, as it was outlined by J. C. Dore,[70] the position of the second peak cannot be unequivocally taken as evidence of the tetrahedral structure, as the trigonal arrangement of oxygen atoms produces a very similar peak.[70,71] Furthermore, a recent study using the reverse Monte Carlo modeling technique demonstrates the no exclusivity of the tetrahedral model to explain the new synchrotron radiation experiments.[72]

In order to quantify the effect of a urea molecule on the structure of water, the tetrahedral local structure of water is used in this paper as an observable which characterizes the extent to which a given water molecule and its surroundings adopt a tetrahedral arrangement. Two definitions of the tetrahedral distributions of water are used.

The first one, $f(q_1, X_U)$, associated with the orientational parameter, q_1, introduced initially by Matubayasi[46] and Chau et al.[43] and rescaled by Errington et al.,[44] as given by

$$q_1 = 1 - \frac{3}{8}\sum_{j=1}^{3}\sum_{k=j+1}^{4}\left(\cos\psi_{jk} + \frac{1}{3}\right)^2$$

(2)
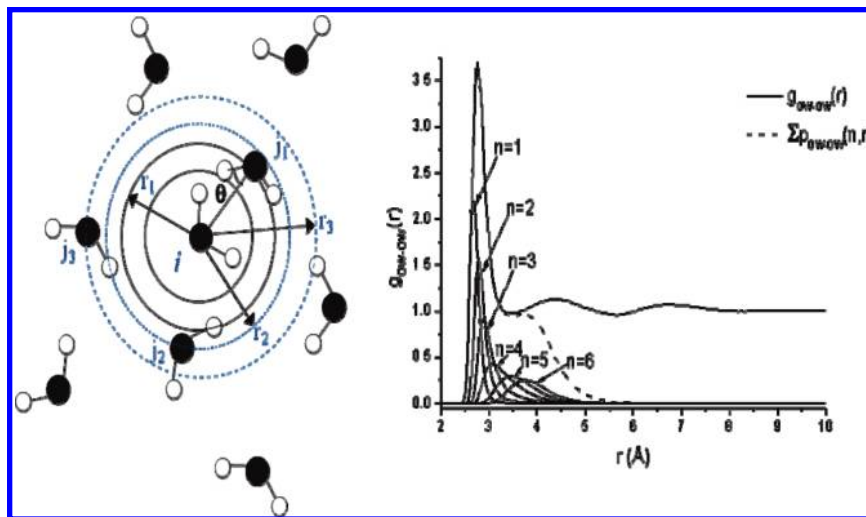
Figure 1. Two dimensional schematic representation for the calculation of the nearest neighbor radial and angular distributions. Separate radial distribution functions are defined for each set of nearest neighbor oxygen atoms O_W (indicated by n), at distance r from a reference oxygen atom O_W. θ is the angle between the axis joining the two oxygen atoms and the OH axis. On the right side, the oxygen−oxygen radial distribution $g_{O_W-O_W}(r)$ as well as the nearest neighbor distributions, $P_{O_W-O_W}(n,r)$ for $n = 1-6$ and $\sum_{n=1}^{6} P_{O_W-O_W}(n,r)$ are presented.

where ψ_{jk} is the angle formed by joining the oxygen atom of the central molecule and those of its four nearest neighbors, j and k (≤ 4). The value of this parameter is equal to 1 for a perfect tetrahedral arrangement.

The $f(q_1,X_U)$ distribution is bimodal, and as pointed out by these last authors, this suggests that the transient arrangement adopted by a molecule and its four nearest neighbors can be described as being predominantly "ice"-like structured (high-q peak) or unstructured (low-q peak). Many other terms are used in the literature to characterize the arrangement associated with these two peaks. Indeed, the high-q peak is associated with either a low density local structure (LD)[73] or hydrogen-bonded water molecules.[74]

The second definition of the tetrahedral distribution $f(q_2,X_U)$ is associated with the parameter q_2 suggested by Medvedev et al,[52] viz.,

$$q_2 = \sum_{i>j}^{15} \frac{(l_i - l_j)^2}{15\bar{l}^2} \qquad (3)$$

where l_i is the length on the ith edge of the tetrahedron formed by the four nearest neighbors of a given water molecule and $\bar{l}$ is their average value. The value of this parameter is equal to 0 for a perfect tetrahedron.

To calculate these tetrahedral distributions, we consider water molecules as belonging to the tetrahedron if their distances with respect to a reference water molecule are lower than $R = 3.35$ Å. This distance corresponds to the position of the first minimum in the oxygen−oxygen radial distribution function in pure water, and the coordination number at this distance is around 4. One may notice that the first definition of the tetrahedral distribution is written explicitly in terms of the orientation of water molecules forming the tetrahedron, while, in the second definition, the tetrahedral distribution is written in terms of the radial distance between the water molecules forming the tetrahedron (more precisely between oxygen atoms which are almost the center of mass of water molecules). This means that the first definition is sensitive to the mutual orientation of water molecules forming the tetrahedron while the second one is sensitive to their radial distance. This allows us to get information on the effect of

urea on the radial as well as mutual orientation of the water molecules forming the tetrahedron.

The average values of q_i ($i = 1, 2$) associated with the distribution $f(q_i,X_U)$ were obtained from the expression

$$\langle q_i \rangle = \frac{\int_0^1 q_i f(q_i,X_U)\, dq_i}{\int_0^1 f(q_i,X_U)\, dq_i} \qquad (4)$$

The effect of each solute on the structure of water is thus analyzed through the behavior of the average value $\langle q_i$ ($i = 1, 2$)$\rangle$ as a function of the solute mole fractions.

4. Nearest Neighbor Approach

It is important to clarify the mechanism of distortion of the tetrahedral arrangement of water molecules when X_U increases. To achieve this goal, it is essential to understand how urea affects the radial and mutual orientation of water molecules around a reference one. The information on these parameters is unambiguously obtained using the nearest neighbor approach.[58–63] This approach consists of ranking the instantaneous neighbors according to their distance from a reference water molecule. More precisely, the oxygen atom neighbors of a reference oxygen atom are sorted by distance into the first neighbor, second neighbor, etc. (see Figure 1). Separate nearest neighbor radial distribution functions, $P_{O_W-O_W}(n,r)$, may be defined for each set of nearest neighbor oxygen atoms (indicated by n), and at distance r from the central oxygen atom. It is obvious to mention that an average is done over all choices of central oxygen atom and that the corresponding radial distribution $g_{O_W-O_W}(r)$ is equal to $\sum_{n=1}^{6} P_{O_W-O_W}(n,r)$ (see Figure 1). The average distance between the oxygen of the probe water molecule and that of its nearest neighbors was calculated as a function of the solute mole fraction, X_U, using the following equations:

$$\langle r_{O_W-O_W}(n,X_U) \rangle = \int_0^{+\infty} P_{O_W-O_W}(n,r')r'\, dr' \qquad (5)$$

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The corresponding fluctuation $\Delta r_{O-O}(n,X_U)\Delta r_{i-j}(n,X_s)$ was estimated using the following equations:

$$\langle r_{O_W-O_W}{}^2(n,X_U) \rangle = \int_0^{+\infty} P_{O_W-O_W}(n,r')r'^2 \, dr' \qquad (6)$$

and

$$\Delta r_{O_W-O_W}(n,X_U) = [r_{O_W-O_W}{}^2(n,X_U) - \langle r_{O_W-O_W}(n,X_U)\rangle^2]^{1/2} \qquad (7)$$

This parameter quantifies the radial fluctuation of the nearest neighbors.

The nearest neighbor approach is also used to get information on the mutual orientation between a reference water molecule and its nearest neighbors. Although the complete description of the orientation of two water molecules requires six variables,[75] we found that the mutual orientation described by the angle θ between the axes joining the oxygen atom of a reference water molecule and the one belonging to the nearest neighbor water and its OH axis (see Figure 1) was sufficient to analyze the effect of increasing X_U on the mutual orientation between two water molecules. The nearest neighbor mutual orientation, $q(\theta,n,X_U)$, between a reference water molecule and its nth neighbors ($n < 6$) as a function of X_U was then calculated.

5. Results and Analysis

The results obtained here for the tetrahedral distribution functions $f(q_1,X_U)$ and $f(q_2,X_U)$ and the corresponding average values $\langle q_1 \rangle$ and $\langle q_2 \rangle$ are given for different X_U in Figures 2 and 3. As X_U increases, $f(q_1,X_U)$ exhibits an appreciable decrease in the high-q peak with a corresponding increase of both the low-q peak and the low-q values laying between 0.1 and 0.4. The corresponding average value $\langle q_1 \rangle$ decreases with increasing X_U (see the inset of Figure 1). The existence of an isosbestic point (around 0.5) indicates that urea specifically reduces the predominantly tetrahedral structured water molecules in favor of the unstructured one.
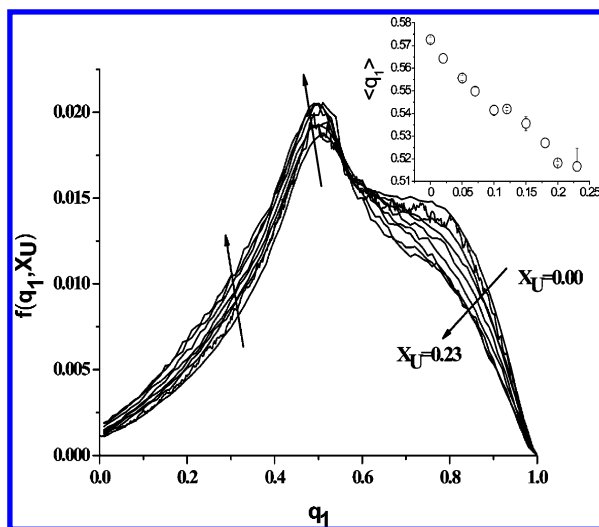

Figure 2. Tetrahedral distribution of water molecules, $f(q_1,X_U)$ (see eq 2) in aqueous urea solutions. In the inset are given the corresponding average values $\langle q_1 \rangle$ as a function of the urea mole fractions X_U. Arrows indicate the effect of increasing urea mole fractions.
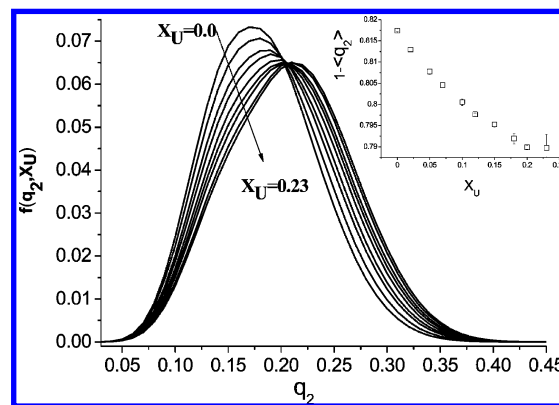
Figure 3. Tetrahedral distribution of water molecules, $f(q_2,X_U)$ (see eq 3) in aqueous urea solutions. In the inset are given the corresponding average values $1 - \langle q_2 \rangle$ (in order to compare directly with $\langle q_1 \rangle$) as a function of the urea mole fractions X_U.
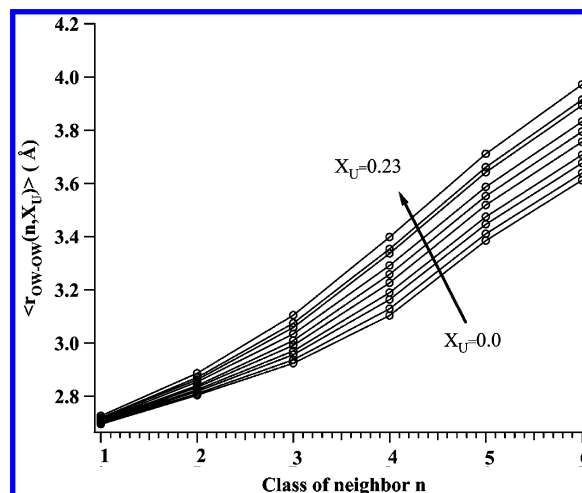

Figure 4. The average distance, $\langle r_{O_W-O_W}(n,X_U) \rangle$ (see eq 5), $\langle r_{W-W}(n,X_U) \rangle$, between a reference water molecule and its nearest neighbors. n indicates the number of the nearest neighbor distribution.
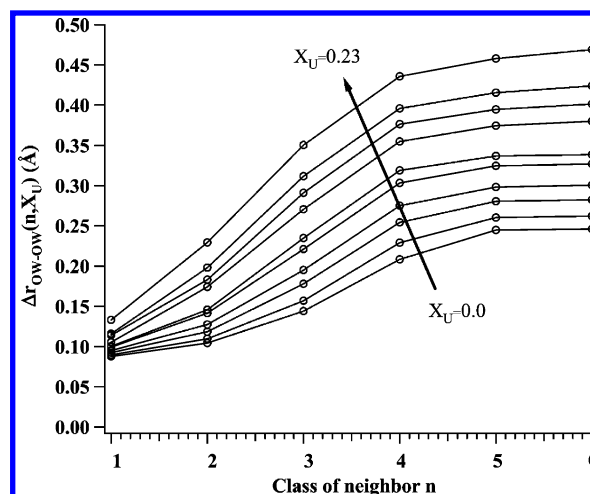
Figure 5. The fluctuation of the average distance $\Delta r_{O_W-O_W}(n,X_U)$ (see eq 7) between a reference water molecule and its nearest neighbors, n.

It should be mentioned that increasing the temperature has a similar effect on the behavior of the tetrahedral arrangement in pure water.[44,45]
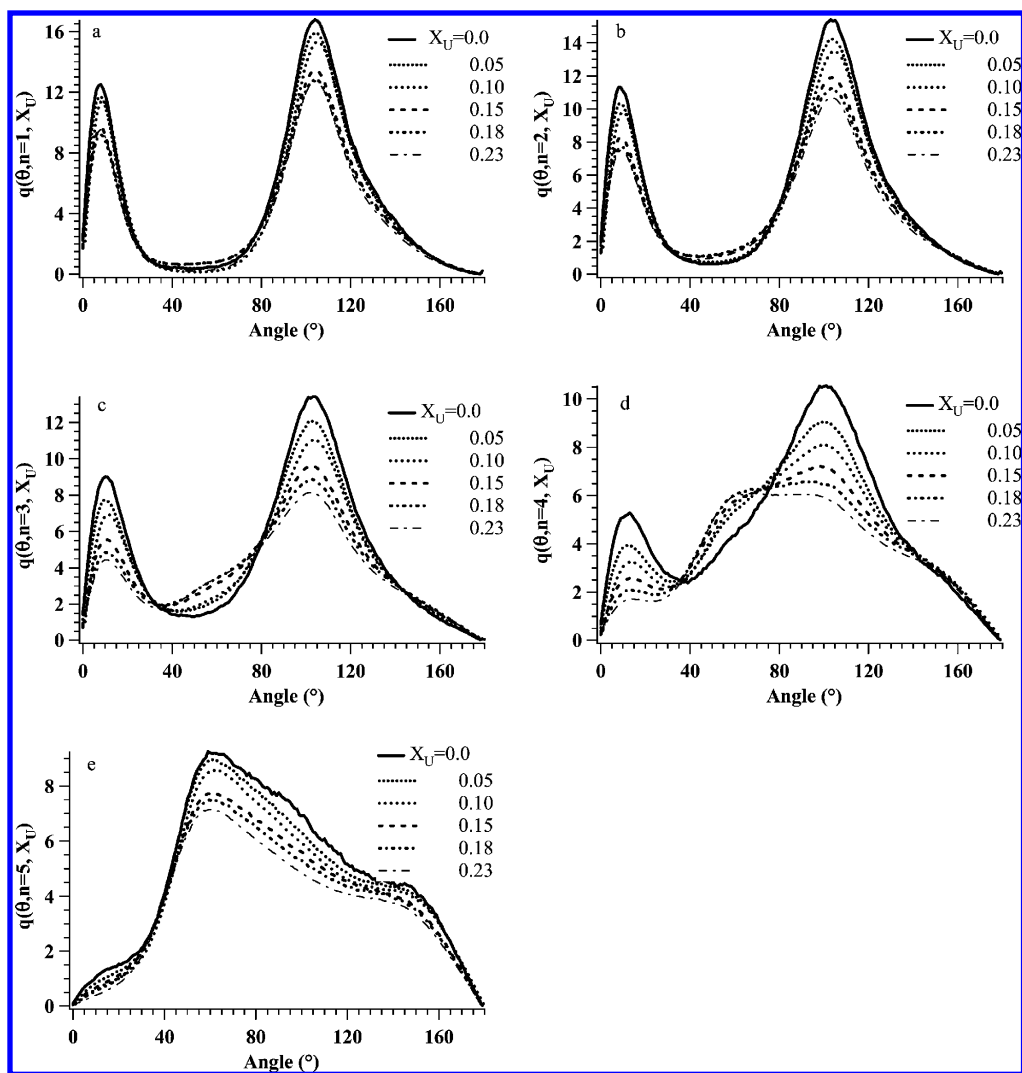
Figure 6. Nearest neighbor orientation distribution between a reference water molecule and its subsequent nearest neighbors. θ is the angle between the axes joining the two oxygen atoms and the OH axis (see Figure 1). X_U is the urea mole fraction. n indicates the number of the nearest neighbor distribution. $n = 1$ (a), $n = 2$ (b), $n = 3$ (c), $n = 4$ (d), and $n = 5$ (e).

The same conclusion may be drawn from the behavior of $f(q_2, X_U)$ as a function of X_U (see Figure 2). These results stress the fact that increasing X_U results in the distortion of the tetrahedral arrangement of water molecules. Such observations would confirm the Frank et al. hypothesis.[4]

As pointed out previously, information on how the local tetrahedral structure of water is distorted may be obtained by analyzing the behavior of the average distance, the corresponding fluctuation, as well the mutual orientation between a reference water molecule and its first nearest neighbors. The average distance, $\langle r_{O_w-O_w}(n, X_U) \rangle$, as well as the corresponding fluctuation $\Delta r_{O_w-O_w}(n, X_U)$ of the sixth first nearest neighbors are then given in Figures 4 and 5, respectively. Figure 4 shows that the average distances between a reference water molecule and its two first nearest neighbors are slightly affected by increasing X_U. However, an appreciable increase of these distances is observed for the subsequent nearest neighbors. The behavior of $\Delta r_{O_w-O_w}(n, X_U)$ indicates that this parameter is more sensible to the effect of increasing X_U than the corresponding $\langle r_{O_w-O_w}(n, X_U) \rangle$. Indeed, starting from the second nearest neighbor, we can observe an obvious increase of the fluctuation in their radial distance and resulting in an increase of the overlap between the successive nearest neighbors, particularly between the fourth nearest neighbor and the fifth one. This suggests that
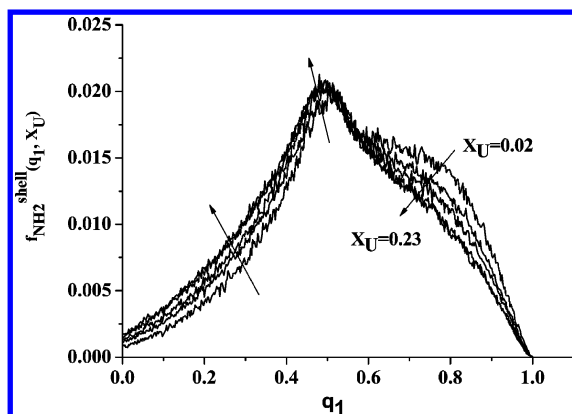
the distortion of the tetrahedral is associated precisely with this large radial fluctuation of these neighbors.

The nearest neighbor mutual orientation distributions are given in Figure 6, for different X_U. In the case of pure water, this distribution has two peaks, one around 12° and the second one around 110°. Figure 6 shows that, with increasing X_U, the orientation of the first and second nearest neighbors does not change with respect to their orientation in pure water; however, there is a decrease in the intensity of the two contributions around 12 and 110°. As X_U increases, an orientation contribution around an angle of 65° starts to increase between a reference water molecule and the third and fourth nearest neighbors. These results indicate that the distortion of the tetrahedral arrangement of the nearest neighbors around a probe water molecule is associated also with the loss of the mutual orientation occurring at a level of the third and particularly the fourth nearest neighbors (which may be associated with a weakening of hydrogen bonding involving these water molecules).[60,74]

A question arises then about the validity of the previous conclusions if a distinction is made between bulk water molecules and those in the hydration shell of a urea. To respond to this question, we consider water molecules as belonging to the hydration shell of urea if the distance between the center of mass (CM) of water and that of urea is less than 5.72 Å. This

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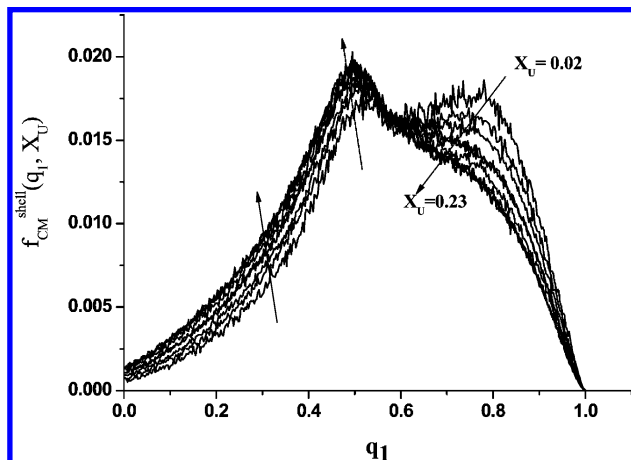
Figure 7. Hydration shell tetrahedral distribution $f_{CM}^{shell}(q_1, X_U)$ of water molecules.

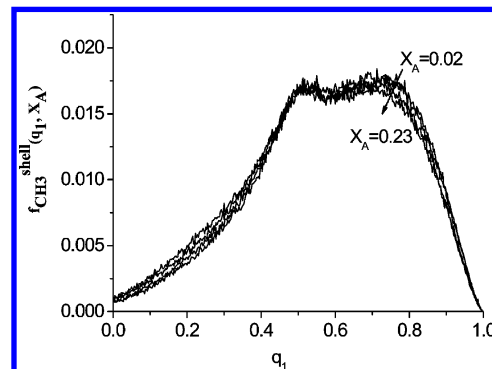**Figure 8.** Hydration shell tetrahedral distribution $f_{NH_2}^{shell}(q_1, X_U)$ of water molecules around the amine group.
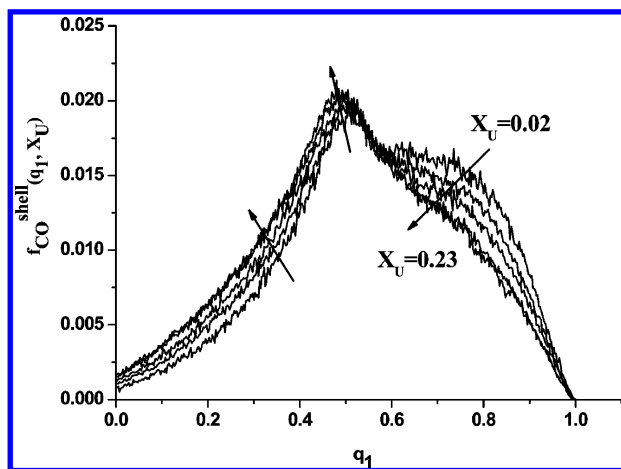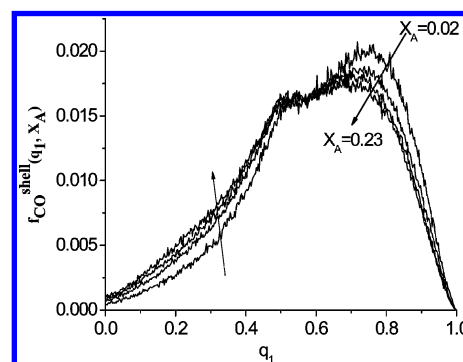

Figure 9. Hydration shell tetrahedral distribution $f_{CO}^{shell}(q_1, X_U)$ of water molecules around the carbonyl group.

Figure 10. Hydration shell tetrahedral distribution $f_{CH_3}^{shell}(q_1, X_A)$ of water molecules around the methyl group. X_A (=0.02, 0.12, 0.18, 0.23) are the mole fractions of acetone.

Figure 11. Hydration shell tetrahedral distribution $f_{CO}^{shell}(q_1, X_A)$ of water molecules around the carbonyl group. X_A (=0.02, 0.12, 0.18, 0.23) are the mole fractions of acetone.

distance coincides with the position of the first minimum of the urea−water radial distribution functions where the average number of water molecules around urea is 23. The hydration shell tetrahedral distribution $f_{CM}^{shell}(q_1, X_U)$ was then calculated as a function of X_U (see Figure 7). The shift from the structured high-q arrangement in favor of the low-unstructured arrangement with increasing X_U is clearly revealed in the behavior of $f_{CM}^{shell}(q_1, X_U)$. In order to get more insight into the effect of urea on the structure of water molecules belonging to its hydration shell, we calculated the tetrahedral distribution of water molecules surrounding amine, and carbonyl groups of

urea. We consider water molecules to be in the hydration shell of amine and carbonyl groups if the distance between the oxygen atom of water and that of nitrogen and oxygen atoms of urea are less than 4.425 and 3.325 Å, respectively. The corresponding tetrahedral distributions $f_{NH_2}^{shell}(q_1, X_U)$ and $f_{CO}^{shell}(q_1, X_U)$ are given in Figures 8 and 9, respectively. These results show that there is a concomitant shift of the tetrahedral distribution of water molecules around amine and carbonyl groups toward low-q values, inducing a distortion of the ideal tetrahedral arrangement of water molecules in the hydration shell of urea. For mole fractions higher than 0.18, no changes are observed in the shape and intensity of these tetrahedral distributions. This indicates that the distortion of the tetrahedral arrangement of water molecules is efficient in the low mole fractions. As a comparison, the tetrahedral distribution, $f_{CH_3}^{shell}(q_1, X_A)$ and $f_{CO}^{shell}(q_1, X_A)$, at different mole fractions of acetone, X_A (=0.02, 0.12, 0.18, 0.23), of water molecules around methyl and carbonyl groups in acetone were calculated and the results are depicted in Figures 10 and 11, respectively. In this case, the tetrahedral configuration of water molecules around the methyl group is slightly affected, while that around the carbonyl group is noticeably affected.

6. Conclusion

We performed molecular dynamics simulations of urea aqueous solutions at various urea mole fractions X_U ranging from 0.0 to 0.23 in order to quantify the effect of urea on the local structure of water. Two definitions of the tetrahedral distribution of water molecules, $f(q_1, X_U)$ and $f(q_2, X_U)$, were used. The first distribution $f(q_1, X_U)$ is explicitly written in terms of the mutual orientation between a reference water molecule and its neighbor forming the tetrahedron, while the second definition $f(q_2, X_U)$ is

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explicitly written in terms of their radial distance (distance between the oxygen atoms). The behavior of the average values associated with the two tetrahedral distributions clearly shows that urea induces a distortion of the tetrahedral arrangement of bulk water (radial and orientation). This result confirms Frank's hypothesis. In order to understand the mechanism of the distortion of the tetrahedral arrangement of water molecules, we used the nearest neighbor approach. The analysis of the nearest neighbor radial and orientation distributions with respect to a probe water molecule shows that the increase of the fluctuation in the radial distance as well as the loss of the mutual orientation of the nearest neighbor forming the tetrahedron (with respect to that in pure water) are behind the weakening of the tetrahedral arrangement of water molecules. The behavior of the tetrahedral distribution of water in the hydration shell of urea as well as around the amine and carbonyl groups reveals that increasing urea mole fraction induces a concomitant and strong shift of the tetrahedral arrangement of water molecules around amine and carbonyl groups toward low-q values, inducing a distortion of the ideal tetrahedral arrangement of water molecules. For mole fractions higher than 0.18, no changes are observed in the shape and intensity of these tetrahedral distributions.

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