## Hydration of Adamantane Skeleton: Water Assembling around Amantadine and Halo-substituted Adamantanes

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Oxygen (a and b) and hydrogen (c and d) number density maps of solvent water molecules around adamantane (a and c) and perfluoroadamantane (b and d). For O number density, red (higher than 0.09 atoms Å<sup>-3</sup>) and blue (lower than 0.02 atoms Å<sup>-3</sup>) are plotted; for H number density, white (higher than 0.12 atoms Å<sup>-3</sup>) are plotted. Note that O number density of bulk water (1 g cm<sup>-3</sup>) is uniform and 0.033 atoms Å<sup>-3</sup>).

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We performed Monte Carlo simulations to reveal the water distributions around adamantane derivatives. Adamantane derivatives attract water molecules, and specific water distributions are observed around the skeleton. Perfluoroadamantane attracts water more than adamantane.

Adamantane ( $C_{10}H_{16}$ ) is a highly symmetric tricyclic aliphatic hydrocarbon that is the simplest of the diamondoids, with a dipole moment of 0 D. Adamantane is known as a valuable building block for polymers for the enhancement of their thermal stability or improvement of their physical properties.<sup>1,2</sup> Adamantyl-bearing compounds are also used in the field of medicinal chemistry and drug development, and some of them are in clinical use.<sup>3</sup> The adamantyl group is used to modify the water solubility and lipophilicity of an original compound that may be highly water soluble or poorly soluble. Through the incorporation of an adamantyl group into the structure, the membrane solubility can be changed to a value that may be clinically useful.

The octanol/water partition coefficient,  $\log P$ ,<sup>4</sup> is used as an index of the lipophilicity of a compound and is often used to evaluate the bioavailability of candidate molecules for therapy. A positive value of  $\log P$  indicates a preference of the compound for the lipid phase, and a negative value shows a preference for water. It is thought that a compound should have a reasonable value of  $\log P$  to be a good candidate for a new drug. The  $\log P$  value of adamantane is positive, yet lower than that of decane, which is also composed of ten carbon atoms.<sup>5</sup> This feature affords adamantylbearing compounds with more tractable solubility properties compared to decane-substituted analogs, which may be much less soluble in water.<sup>3</sup>

Amantadine (1-aminoadamantane) is known as a blocker of the M2 channel activity of the influenza A virus,<sup>6</sup> and also as an antagonist against Parkinson's disease.<sup>7</sup> The estimated  $\log P$  values of amantadine<sup>5</sup> and adamantane<sup>3</sup> are 2.22 and 4.24, respectively, indicating that the ratio of the water solubility to the lipophilicity of amantadine is roughly 100 times larger than that of adamantane.

Although the water solubility of adamantane is very low, it is still slightly "soluble" in water, which is related to hydrophobic hydration.<sup>8</sup> Previously,<sup>9</sup> we showed that the water molecules in the first solvent shell around adamantane are oriented in such a way that the dipole direction of water is tangential to the skeleton surface, and the hydrogen-bonding network is formed among the water molecules in the first shell as well as between the first shell and the outer shell.

For the development of new drugs and materials utilizing adamantyl groups, it is necessary to estimate how attractive the adamantane skeleton is for water. To this end, we have performed Monte Carlo (MC) simulations of some adamantane derivatives surrounded by water molecules, and show how the water distribution changes by a substituent group.

For the MC simulations, the molecular mechanics (MM) parameters of the solutes were created as follows. First, we optimized the geometries of the target molecules, using the ab initio molecular orbital (MO) method. The target molecules in this letter are adamantane, 1-chloroadamantane, 1-fluoroadamantane, amantadinium, and perfluoroadamantane. Adamantane, as well as perfluoroadamantane, has  $T_d$  symmetry. The other three adamantane derivatives have  $C_{3\nu}$  symmetry. The MP2/aug-ccpVDZ level of theory was used for the geometry optimization using the Gaussian09 program package.<sup>10</sup> The stationary structures of those molecules were confirmed by normal mode analysis. The optimized structural parameters were in excellent agreement with the experimental values.<sup>11,12</sup> Then, we calculated the atomic charges of the adamantane derivatives by using natural population analysis (NPA).13 The structural parameters and atomic charges obtained from the ab initio MO calculations are listed in the Supporting Information.<sup>20</sup> The Lennard–Jones parameters determined by Freindorf and  $Gao^{14}$  were applied to the atoms of the adamantane derivatives. The TIP3P water potential function<sup>15</sup> was employed for the solvent molecules.

We coded our own program to create the configuration of water molecules so as to form the NVT ensemble (at constant number *N*, volume *V*, and temperature *T*) using the MC method based on the Metropolis–Hastings algorithm.<sup>16</sup> For each system, 500 water molecules were distributed around a solute molecule in a solvation sphere with a radius of 15.4 Å. The density of a solute molecule with 500 water molecules in this sphere was  $1 \text{ g cm}^{-3}$ . The temperature was set at 300 K.

For each system, the simulation was performed with the following procedure. First, a simulation with  $10^8$  MC steps was performed for equilibrium. Afterward, a simulation of  $2 \times 10^{10}$  MC steps was performed and used for the analysis.

The number density of an oxygen atom of solvent water is expressed as

$$n_{\rm O}(x, y, z) = \frac{\langle N_{\rm O}(x, \delta x, y, \delta y, z, \delta z) \rangle}{\delta x \delta y \delta z} \tag{1}$$

The numerator on the right side of eq 1 denotes the count average of a solvent O atom in  $x \approx x + \delta x$ ,  $y \approx y + \delta y$ , and  $z \approx z + \delta z$ . This was sampled each time all the water molecules had moved. The number density is in units of atoms Å<sup>-3</sup>. The number density of the solvent H atom,  $n_{\rm H}(x, y, z)$ , was defined similarly.

It should be noted that the O number density,  $n_O(x, y, z)$ , of bulk water (1 g cm<sup>-3</sup>) is uniform at 0.033 atoms Å<sup>-3</sup>. In Figure 1, red points are plotted where the O number density is higher than 0.09 atoms Å<sup>-3</sup>.

It is remarkable that the distribution is not uniform in either the O distribution (Figure 1) or the H distribution (Figure 2) for

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Figure 1. Oxygen number density of solvent water molecules around adamantane derivatives: (a) adamantane, (b) 1-chloroadamantane, (c) 1-fluoroadamantane, (d) amantadinium, and (e) perfluoroadamantane. Threshold to plot is 0.09 atoms Å<sup>-3</sup>.

each of the adamantane derivatives. The "front," "side," and "back" are indicated in Figure 3. The water distribution is affected by the interaction between the solute and the surrounding water molecules, so that the water distribution possesses a similar symmetry to the solute. These characteristics cannot be seen in the radial distributions of the O number density (Figure S2)<sup>20</sup> or the H number density (Figure S3),<sup>20</sup> since a radial distribution gives an averaged view around the solute.

As listed in Table 1, for each of the adamantane derivatives, the position of the first peak of the H distribution is close to that of the O distribution, indicating that the water molecules in the first hydration shell are tangential to the skeleton surface. This is one of the characteristics of hydrophobic hydration.<sup>17</sup> Here, the first hydration shell is defined as the inside of the first minimum of the radial distribution of the O number density. For each of the 1-substituted adamantane derivatives, the actual hydration pattern in the first hydration shell is not just "hydrophobic," as will be discussed below.

**Figure 2.** Hydrogen number density of solvent water molecules around adamantane derivatives: (a) adamantane, (b) 1-chloroadamantane, (c) 1-fluoroadamantane, (d) amantadinium, and (e) perfluoroadamantane. Threshold to plot is 0.12 atoms Å<sup>-3</sup>.



Figure 3. Molecular structure of adamantane derivative. "Front" and "back" are viewed along the  $C_3$  axis of the molecule.

The three-dimensional water distribution around adamantane is shown in Figure 1a for oxygen and Figure 2a for hydrogen. The first solvation shell is observed to be composed of "patches" of solvent water molecules that are laid over the adamantane surface. The O number density around the region of highest population is almost three times higher than that of bulk water. It is noteworthy that the O density of the first hydration shell is higher than that of bulk water (Table 1), indicating that water molecules assemble around adamantane.

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**Table 1.** The positions (in Å) of the first maximum and of the first minimum for each of the radial distributions of O and H number densities (Figures S2 and S3),<sup>20</sup> the hydration number, and the O number density (in atoms Å<sup>-3</sup>) of the first hydration shell for each of the adamantane derivatives: (a) adamantane, (b) 1-chloroadamantane, (c) 1-fluoroadamantane, (d) amantadinium, and (e) perfluoroadamantane tane

	First maximum		First minimum		Hydration	Number
	Н	0	0	Η	number	defisity
(a)	5.05	5.15	6.65	6.95	36.7	0.037
(b)	5.15	5.15	6.65	7.05	35.6	0.036
(c)	5.15	5.15	6.65	6.95	36.6	0.037
(d)	5.15	5.15	6.65	6.95	36.4	0.036
(e)	5.45	5.55	7.05	7.15	43.6	0.040

<sup>a</sup>The hydration number of a target molecule is defined as the number of O atoms in the first hydration shell, which is inside the first minimum of the radial distribution of O number density.

The water distribution around perfluoroadamantane is shown in Figure 1e for oxygen and Figure 2e for hydrogen. Since the C– F bond in perfluoroadamantane is around 0.25 Å longer than the C–H bond in adamantane (Tables S1a and S2a), the molecular diameter of perfluoroadamantane is larger than that of adamantane. Note that the atomic charges of perfluoroadamantane and adamantane are "inside out," as shown in Tables S1b and S2b. The carbon atoms of adamantane are negative, while those of perfluoroadamantane are positive. In spite of the reversed charge distribution, the first solvation shell of perfluoroadamantane looks like a cage composed of patches in which solvent water molecules are laid over the molecular surface. The O number density of the first hydration shell of perfluoroadamantane is higher than that of adamantane. Therefore, perfluoroadamantane attracts water molecules more strongly than adamantane.

For hydrophobic hydration, the hydration free energy change of the alkane can be decomposed into the free energy of the cavity formation and the free energy change due to attractive van der Waals and electrostatic interactions.<sup>18</sup> The former (cavity component) is large and positive, and the latter is large in magnitude and negative, being dominated by the attractive component of the solute–solvent energy change. Generally, for the alkane, the attractive component is slightly smaller in magnitude than the cavity component, resulting in a positive but small hydration free energy. Comparing perfluoroadamantane with adamantane, the cavity component of the former is larger than the latter because the molecular skeleton of the former is larger in magnitude than the latter because the former attracts more water molecules than the latter.

The water distribution around 1-chloroadamantane is shown in Figure 1b for oxygen and Figure 2b for hydrogen. The atom at the center in the front view is chlorine. A circular distribution of water O atoms is observed around the Cl atom, yet no specific H distribution is observed around Cl. This indicates that the Cl atom is not strong enough to fix the positions of the water H atoms through hydrogen bonding.

The water distribution around 1-fluoroadamantane is shown in Figure 1c for O and Figure 2c for H. The atom at the center in the front view is fluorine. The distribution of water H atoms around F is divided into two layers, indicating that the two hydrogen atoms of a water molecule are distributed separately. One of the H atoms of a water molecule is strongly hydrogen-bonded to the F atom, and the other H atom points in the outer direction. This is a characteristic of hydrophilic hydration, in contrast to the water distribution around perfluoroadamantane. It is notable that the F-substitution effect on the hydration pattern may depend on the number of the substitution.

The water distribution around amantadinium is shown in Figure 1d for O and Figure 2d for H. The characteristics of the water distribution around amantadinium are similar to those around 1-fluoroadamantane. The H atoms of the ammonium cation attract water molecules, which is a characteristic of hydrophilic hydration, although the first hydration shell around the adamantane skeleton exhibits a hydrophobic character similar to that of adamantane.

These 1-substituted adamantane derivatives (1-chloroadamantane, 1-fluoroadamantane, and amantadinium) can be regarded as amphiphilic molecules. Adamantane and perfluoroadamantane are hydrophobic molecules. Because of the significant increase in water density near the cavity, each of these adamantane derivatives can be said to be wet in a microscopic aspect.<sup>19</sup> The visualization of the number density around a solute molecule makes it possible to show clearly the hydration pattern and substitution effect around a large molecule such as adamantane.

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