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## **MOLECULAR DYNAMICS SIMULATIONS OF GUEST – HOST HYDROGEN BONDING IN STRUCTURE I, II, AND H CLATHRATE HYDRATES**

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### **ABSTRACT**

The standard picture is that clathrate hydrates form when hydrophobic guest molecules are compressed with water under high pressure-low temperature conditions. In the ice-like hydrate framework, water molecules form molecule-sized cavities that encapsulate the guests and minimize water-hydrophobic guest interactions. This picture, however, must be modified by observations that many water soluble, hydrogen-bonding molecules form hydrates under relatively mild pressure-temperature conditions as well. Furthermore, these hydrates form with the same canonical structures as hydrophobic guests. We recently performed a series of molecular dynamics simulations, single crystal X-ray crystallographic structural determinations, and NMR relaxation time experiments to explicitly study the presence of hydrogen bonds between the guest and host in clathrate hydrates. Systems studied include binary structure H hydrates of *tert*-butylmethylether and pinacolone, the binary structure II hydrates of tetrahydrofuran, tetrahydropyran, *tert*-butylamine, 1-propanol, 2-propanol, and ethanol and structure I hydrates of ethanol. These guests form hydrogen bonds of varying stability and lifetime which affect the hydrate structure and the dynamics of both the water host and the guests. Spectroscopic signatures of the guest-host hydrogen bonding are briefly discussed.

*Keywords:* clathrate hydrates, hydrogen bonding, kinetic inhibitors

### **INTRODUCTION**

Clathrate hydrates are usually considered to form when water and sufficiently hydrophobic molecular species are subject to high pressures and/or low temperatures.[1-3] To minimize the water-hydrophobic interaction, water molecules form networks of ice-like water-water hydrogen bonding frameworks with cages which encapsulate the guest molecules. This picture however, is somewhat incomplete since it is known that water-miscible substances such as tetrahydrofuran (THF) can also form clathrate hydrates. These latter guest molecules may have a hydrophilic functionality, but this must be

balanced by large hydrophobic moieties in the molecule.[4] The nature of hydrates of water-soluble guests or guests with strongly hydrophilic functional groups are the subject of this talk.[4,5]

The structure of the hydrate formed in the presence of water-soluble or molecules with hydrophilic functional groups depends on the size of these molecules and the nature of the helper gas. Structure I (sI), structure II (sII) and, structure H (sH) binary hydrates with water soluble guests are observed. The formation of hydrates in some of these cases depends on the

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presence of hydrophobic help gases like methane, H<sub>2</sub>S or Xe.

An interesting counterpoint is to view the formation of methane or carbon dioxide (help gas) hydrates as the driving force for hydrate formation in these cases. Addition of large hydrophilic molecules to the water-gas system shifts hydrate formation to lower pressures than required for the pure CH<sub>4</sub> or CO<sub>2</sub> hydrates. However, the large guests may lead to the formation of hydrate structures different from those of the pure small help gas. For example, ethanol, 1-propanol, and 2-propanol lead to the formation of a binary sII clathrate hydrates with the alcohol in the large cage (either in full or partial occupancy) and methane in the small cages of the hydrate. The alcohols reduce the pressure required for hydrate formation compared to the pressure required to form pure methane sI hydrate.

The effect of the water soluble solutes in reducing the pressure of the (aqueous solution + hydrate + gas) equilibrium phase boundary is partially understood in terms of the change in the thermodynamic activity of the aqueous solution compared to pure water.[3] The molecular level understanding of the water-guest interactions in hydrate cages is the subject of this talk. To achieve this, we performed molecular dynamics simulations, single crystal X-ray structural analysis, and NMR relaxation time studies of the clathrate hydrates of hydrophilic molecules (with proper help gases). In the studies, hydrogen bond formation between ketone, ether, alcohol, and amine guest molecules and water cages in the clathrate hydrates were observed.[5] Guest-host hydrogen bonding was found to affect guest and host static and dynamic properties.

## COMPUTATIONAL METHODS

The initial coordinates of the water oxygen atoms in the sI, sII, and sH clathrate unit cells are taken from clathrate X-ray crystallography [6] and the positions of the water hydrogen atoms in the unit cells are determined by a Monte Carlo procedure which determines the proton configuration of the unit cell consistent with the Bernal-Fowler ice rules [7] with the lowest energy and dipole moment. The SPC/E and TIP4P models [8] were used for water. 3×3×3, 2×2×2, and 3×3×3 replicas of the sI, sII, and sH unit cell, respectively, were used in the simulations. Guest

molecules were initially placed in cage centres and allowed to equilibrate during the simulations.

The intermolecular van der Waals potentials between atoms *i* and *j* on different molecules are taken as a sum of Lennard-Jones (LJ) and electrostatic point charge interactions. The Lennard-Jones  $\sigma_{ij}$  and  $\epsilon_{ij}$  parameters for atoms of organic guest alcohol molecules are generally taken from the general AMBER force field (GAFF).[9] Small helper gas molecules such as CH<sub>4</sub>, CO<sub>2</sub>, Xe, and H<sub>2</sub>S are modelled custom designed potentials.[10] Partial electrostatic point charges on the atoms of the guest molecules were determined from charges from electrostatic potential grid (CHELPG) calculations.[11] Partial electrostatic point charges on the polar functional groups in the guest molecules are generally higher than the organic moiety and this provides a large driving force for the hydrogen bonding with water in the hydrate cages in the MD simulations.

Isotropic constant pressure-temperature *NpT* molecular dynamics simulations [12] on periodic simulation cells are performed using the DL\_POLY 2.20 program.[13] A time step of 1 fs is used. Cutoffs were used for short-ranged potentials and Ewald sum methods for long-range electrostatic potentials. The dynamics and hydrogen bonding calculations at each temperature and pressure were studied with constant energy, constant volume (*NVE*) simulations.

## RESULTS AND DISCUSSION

To quantify hydrogen bonding in the simulations, guest positions in hydrate cages are inspected at 0.25 ps intervals during the *NVE* simulation trajectory. At each discrete sampling time, hydrogen-bond indices for each guest *i*,  $b_i(X-H_W, t)$  and  $b_i(H_X-O_W, t)$  are assigned values of either 1 or 0 depending on whether the  $X-H_W$  or  $H_X-O_W$  distances were less than 2.1 Å. In these variables,  $H_W$  and  $O_W$  are cage water hydrogen and oxygen atoms, respectively. The *X* represents an electronegative atom of the guests which forms hydrogen bonds with water H atoms and  $H_X$  represents guest H atoms connected to the electronegative *X* atoms. The total probability of H-bond formation was determined by,

$$P(X-H_W) = \frac{1}{N_{tot\ i,t}} \sum b_i(X-H_W, t) \quad (1)$$

with a similar relation for  $P(\text{H}_\text{X}-\text{O}_\text{W})$ .  $N_\text{tot}$  is the total number of sampling points. The sampling time,  $t$ , corresponds to  $t = 0.25j$  (in ps) where  $j$  is the particular discrete sample time step.

Snapshots of hydrogen bonding guests in sI, sII, and sH large cages are shown in Figure 1. The  $\text{X}-\text{H}_\text{W}$  guest–host hydrogen bonds form when a water molecule rotates from the cage lattice to orient an OH bond towards a guest proton acceptor X atom. Bjerrum defects form in the clathrate hydrogen bonding network as a result of the guest–water hydrogen bonding and the cage faces can be somewhat distorted.

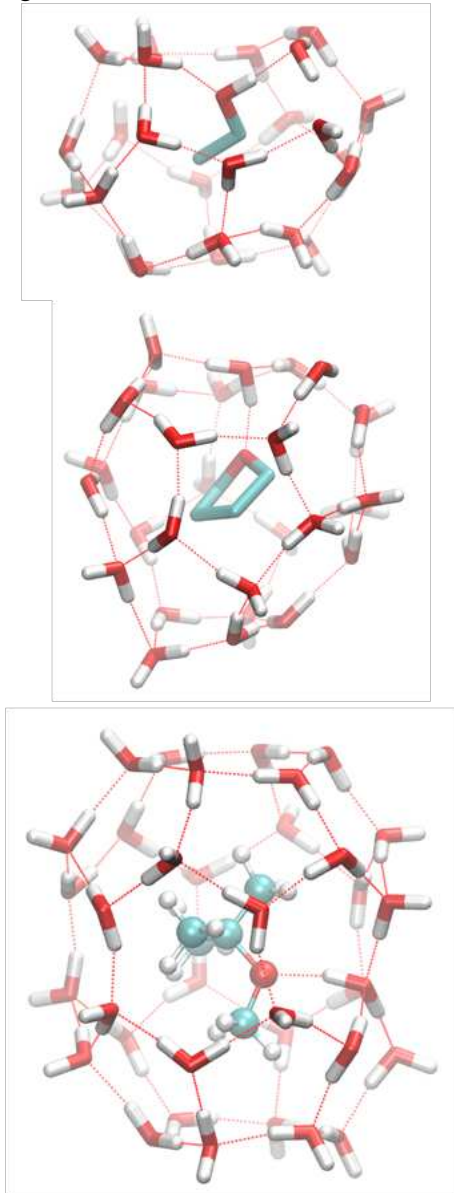


Figure 1. Hydrogen bonding of (a) ethanol in sI large cage (b) THF in sII large cage (c) tert-butylmethylether in sH large cage.

The hydrogen bond formation index of a THF guest to cage water molecules at 200 and 250 K are shown in Figure 2.

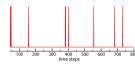


Figure 2. Guest-host hydrogen bond formation index,  $b_i(\text{O}\cdots\text{H}_\text{W}-\text{O}_\text{W})$ , for a THF guest in a sII clathrate large cage from a simulation trajectory at 250 K (top) and 200 K (bottom). At the higher temperature, hydrogen bond formation occurs more frequently.

The total probability of hydrogen-bond formation given in Eq. (1) does not give information about the lifetime of the hydrogen bond. To study the lifetime of hydrogen bonds,  $\tau(\text{X}-\text{H}_\text{W})$  and  $\tau(\text{H}_\text{g}-\text{O}_\text{W})$  we count the number of consecutive sampling points for which the hydrogen-bond remains intact. The average lifetime of hydrogen bonds at each temperature is defined as

$$\langle \tau \rangle (\text{X}-\text{H}_\text{W}) = \frac{1}{N_\text{HBOND}} \sum_i \tau_i(\text{X}-\text{H}_\text{W}) \quad (2)$$

where  $N_\text{HBOND}$  is the number of H-bonding events during the trajectory. The lifetimes of individual hydrogen bonds as defined in the Eq. (2) are shown in Figure 3. In addition to the inherent stability of the  $\text{X}\cdots\text{HOH}$  hydrogen bonds, the long lifetime of the hydrogen bond can be due to the relaxation of neighbouring water molecules of the cage in the vicinity of the hydrogen bonding water. The lifetime of these hydrogen bonds is determined to be between 1 – 10 ps.

Depending on the nature of the guest–water hydrogen bonding, the probability of hydrogen bonding can either increase or decrease at higher temperatures. For cases where the guest–water hydrogen bond is weaker than the water–water hydrogen bond (such as the case of THF in sII hydrate shown in Figure 2, and pinacolone and

tert-butylmethylether in sH hydrate), the thermal vibrations of the water molecules in the lattice facilitate the water-water bond breaking and lead to enhanced probabilities of THF-water hydrogen bonding. In cases where the guest-host hydrogen bonding is strong (in the alcohol + methane binary sII hydrates), higher temperatures lead to breaking of guest-water hydrogen bonds and smaller probabilities of hydrogen bond formation.

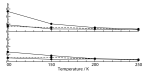


Figure 3. The lifetimes (ps) of (a)  $O_H-H_W$  hydrogen bond formation, (b)  $H_O-O_W$  hydrogen bond formation, and (c) simultaneous  $O_H-H_W$  and  $H_O-O_W$  hydrogen bond formation for 1-propanol, 2-propanol, and ethanol at temperature between 100 – 250 K.

The radial distribution functions (RDFs) for the guest electronegative atom ( $X$ ) and hydrogen ( $H_X$ ) atoms and the cage water atoms ( $H_W$  and  $O_W$ ) can be used to identify hydrogen bonding between the guests and host water molecules. Some sample RDFs are shown in Figure 4. The RDF plots show that first peaks for the  $O_H-H_W$  interactions are at distances  $\sim 1.8$  Å which are within the range of hydrogen bonding. The  $O_H-O_W$  RDFs in Fig. 4(a) show a peak at  $\sim 2.8$  Å which is consistent with hydrogen bonding. The proximity of the  $O_H$  atoms to the cage  $O_W$  atoms is due to hydrogen bonding and not the encapsulation of the guests in the large cages.

Many of the guest molecules have strong hydrogen bonding probability while maintaining the local cage form of the clathrate hydrate. The stability of the cage and hydrate structure can be due to the presence of the help gas or the hydrophobic moieties of the large guest.

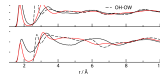


Figure 4. The  $O_H-H_W$ ,  $H_O-O_W$  and  $O_H-O_W$  RDFs for atom pairs on the 1-propanol (top) 2-propanol (middle) and ethanol (bottom) hydroxyl groups with lattice water atoms. The first peaks at  $< 2$  Å shows the occurrence of hydrogen bonding.

Dynamics of rattling motions and rotations of the guests in the clathrate cages were extracted from *NVE* simulations. Hydrogen bonding tethers guests to cage water molecules and greatly reduces their translational and rotational mobility. To determine the effect of tethering on the guest rotations in the cages, we calculate rotation angle,  $\cos\theta(t) = \boldsymbol{\mu}(t) \cdot \boldsymbol{\mu}(t)$  of the guests at different times  $t$ , where  $\boldsymbol{\mu}(t)$  is a unit vector which defines a fixed direction inside each guest molecule. The correlation function  $M_2(t)$  related to second-order Legendre polynomial  $P_2(\cos\theta) = 3\cos^2\theta - 1$  characterizes the guest rotation and correlates with NMR relaxation times,[14]

$$M_2(t) = \langle 3 \cos^2 \theta(t) - 1 \rangle \quad (3)$$

where the brackets represent an ensemble average over all guests and time origins. The motion of the vector  $\boldsymbol{\mu}(t)$  is affected by the tethering of guests to the cage water molecules such that tethered guests retain their orientations for longer times than guest molecules not hydrogen bonded to the cage waters.

The  $M_2(t)$  autocorrelation functions for the guest molecules are plotted in Figure 5. By virtue of their larger size, larger guest molecules will have slower  $M_2(t)$  decay rates. The effect of hydrogen bonding on slowing the decay of  $M_2(t)$  is particularly noticeable at higher temperatures. This is observed by comparing the decay of  $M_2(t)$

for butane with hydrogen-bonding 1-propanol and 2-propanol.

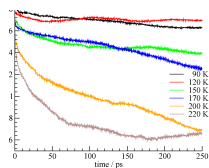


Figure 5. The decay of the  $M_2(t)$  function with time at temperatures for 90 K to 220 K for the ethanol guest molecules in the sI binary hydrate.

## CONCLUSIONS

In clathrate hydrates of guests with hydrophilic functional groups, hydrogen bonds between the guest and the water molecules can be observed. In the MD simulations, the hydrogen bonding is the result of large partial charges on the X and  $H_X$  atoms and their geometric positioning at the end of the alcohol molecules. The hydrogen bonds have finite lifetimes and are accommodated while maintaining the cage structures. The guests detach from the water molecules, rotate in the cage, and form new hydrogen bonds with other cage water molecules.

The presence of a helper gas is required for the formation of the water-miscible guest clathrate hydrates. The hydrophobicity of these help gases stabilizes the clathrate hydrate phase.

Hydrogen bonding tethers guest molecules to the cage wall and affects the rotational dynamics of the guests in the large cages. Furthermore, the hydrogen bonding leads to the formation of Bjerrum L-defects that allow greater rotational freedom for neighbouring water molecules. The rotation of water molecules into the L-defects adjacent to the alcohol guest prolongs the lifetime of the guest-host hydrogen bond by blocking the simple rotation of the guest-bonded water molecule into its original water lattice site.

Hydrogen bonds decrease the stability clathrate hydrate framework and push the stability zone of the binary helpgas + guest clathrates into higher pressures regions of the phase diagram than their non-hydrogen bonding analogs. The lattice defects and water relaxation around them caused by guest-water hydrogen bonding severely distort the faces of the clathrate hydrate cages and may lead to enhanced diffusion of guests between the hydrate cages.

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