

ONIOM Method Characterization of Hydrogen Bonding Sites of Mycolactone A/B, a Buruli Ulcer Toxin

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Abstract

Mycolactone molecules are responsible of Buruli ulcer disease. In this work, we are interested in the geometric, energetic and spectroscopic characterization of the hydrogen bonding interactions in mycolactone A/B, using quantum chemical method, especially ONIOM(HF/6-311+G(d,p):AM1) and ONIOM(B3LYP/6-311+G(d,p):AM1) levels. ONIOM two layers method has been used because mycolactones compounds are very large, taking into account diffuse and polarization functions are important whenever the matter is intermolecular interactions. Geometric, energetic and spectroscopic parameters of hydrogen bonding reaction on each of the nine oxygen heteroatoms of mycolactone A/B have revealed that the O_{sp^2} heteroatom is far away the hydrogen bonding site. The identification of such a site constitutes a tool for working out a methodology for the annihilation of the destruction effects of mycolactones.

Keywords

Hydrogen Bonding, *Mycobacterium ulcerans*, Mycolactone, ONIOM, Quantum Chemistry

1. Introduction

Buruli ulcer is a disease caused by *Mycobacterium ulcerans*, a microorganism belonging to the family of bacteria responsible for tuberculosis and leprosy [1]. Longtime neglected, this disease that prevails in tropical and subtropical humid countries, has increased in West Africa since 1980 [2]. This situation led the World Health Organization (WHO) to classify this disease as emerging and to recognize it as a public health and development problem [3]. *Mycobacterium ulcerans* secretes a toxin called mycolactone, responsible for extremely deep tis-

sue damage, because of its cytotoxic and immunosuppressive properties. Nowadays, six (06) different natural molecular structures of mycolactones named A/B, C, D, E, F and G, have been isolated [4]. The mycolactone is constituted of a lactone ring linked to two lateral chains. Especially, the form A/B is the subject of this study (Figure 1).

Despite the progress in medical management, the therapeutic arsenal against Buruli ulcer remains limited [5]. Indeed, antibiotic therapy and restorative surgery remain the reference treatment, with high cost and numerous relapses (16% to 28%), in case of serious infection [6]. The mode of the toxin's action remains unknown. The relationship between mycolactone and the proteins responsible for the appearance of Buruli ulcer are related to the conformation of the molecules and their intermolecular interactions. Hydrogen bond is one of the most important inter-molecular interactions involved in supramolecular chemistry, protein-ligand interactions [7] [8] and especially crystal engineering [9] [10]. Polyfunctional molecules, generally, comprise several heteroatoms which are capable to receive Hydrogen bonds. This work, part of Buruli ulcer control program, focuses on mycolactones A/B. It aims to determine, by quantum chemical methods, some physicochemical properties of these mycolactone molecules, in particular, geometric and energetic parameters of the hydrogen bonds established on the heteroatoms, in order to determine hydrogen bonding site. Final aim is to propose an experimental methodology of the annihilation of the destructive effects of mycolactone A/B.

2. Experimentation Section

2.1. Computational Details

Mycolactone A/B possesses nine (09) heteroatoms, all those are sp^2 or sp^3 hybridized oxygen atoms, shown in red color at a 3D molecular structure of mycolactone A/B (Figure 2). Heteroatoms are numbered from 1 to 9 and these numbers will also correspond respectively to the names of the different hydrogen bond complexes.

ONIOM method, developed by Morokuma *et al.* [11], is used because of the

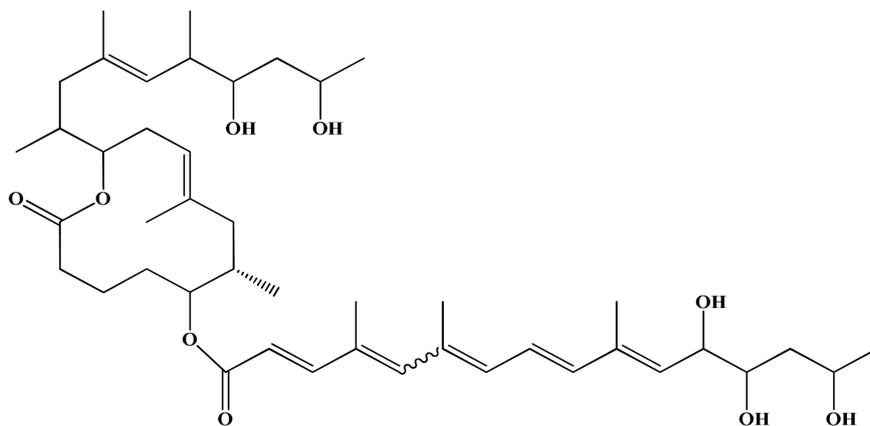


Figure 1. 2D structure of mycolactone A/B.

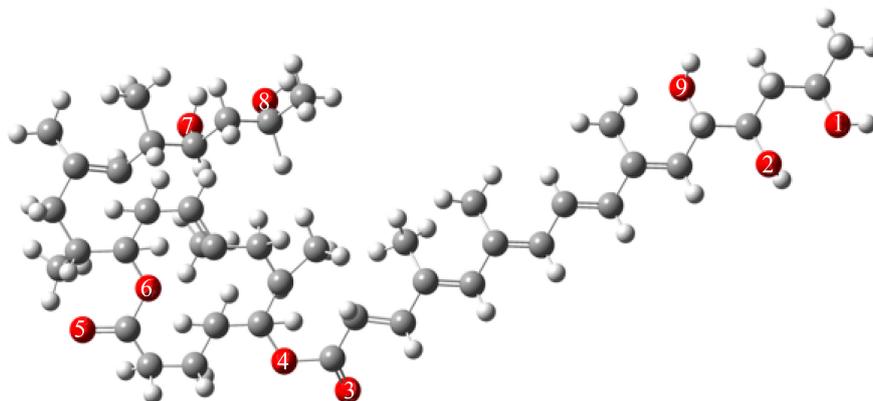


Figure 2. 3D Molecular structure of mycolactone A/B (visualized with *Gauss View 5.0* software).

high number of atoms in mycolactone A/B. It consists of cutting the studied system into several layers, each of the layers being treated at a different calculation level. It therefore allows to describe precisely the part of the system which has particular interest for the study, called the internal layer, and to describe in a less precise manner the rest of the system, called the outer layer or the environment. ONIOM method permits to obtain the energy of the real system at a high level of computation called high level, $E(\text{high, real})$, by means of extrapolation according Equation (1), where $E(\text{low, real})$ is the energy of the real system at the low calculation level, $E(\text{high, model})$ the energy of the model system at the higher calculation level, and $E(\text{low, model})$ the energy of the model system at the low calculation level. An example of description of the ONIOM two layers in mycolactone A/B is shown in **Figure 3**.

$$E(\text{high, real}) = E(\text{low, real}) + E(\text{high, model}) - E(\text{low, model}) \quad (1)$$

All calculations were performed, using Gaussian 03 software [12] at the ONIOM (HF/6-311+G(d,p):AM1) and ONIOM(B3LYP/6-311+G(d,p):AM1). The presence of diffuse and polarization functions in the basis sets is important in order to take into account the lone pairs of the heteroatoms, as well as intermolecular interactions.

2.2. Geometry Optimization

Nine hydrogen bond complexes were constructed on each of the oxygen heteroatoms, a water molecule being the probe, as Hydrogen Bonding Donor. Such hydrogen bond can be characterized by geometric parameters (**Figure 4**).

Before optimization, for all complexes, the angle of the *linearity* α has been set at 180° and the angle of the *directionality* β , at 109.5° for sp^3 hybridized oxygen and 120° for sp^2 hybridized oxygen. According to Gillespie's V.S.E.P.R (Valence Shell Electron Pair Repulsion) theory (**Figure 5**), the distance d between an oxygen atom of mycolactone and a hydrogen atom of the probe is set at 2 \AA . These values correspond respectively to the angles and the minimum approach distance of the hydrogen bond [14].

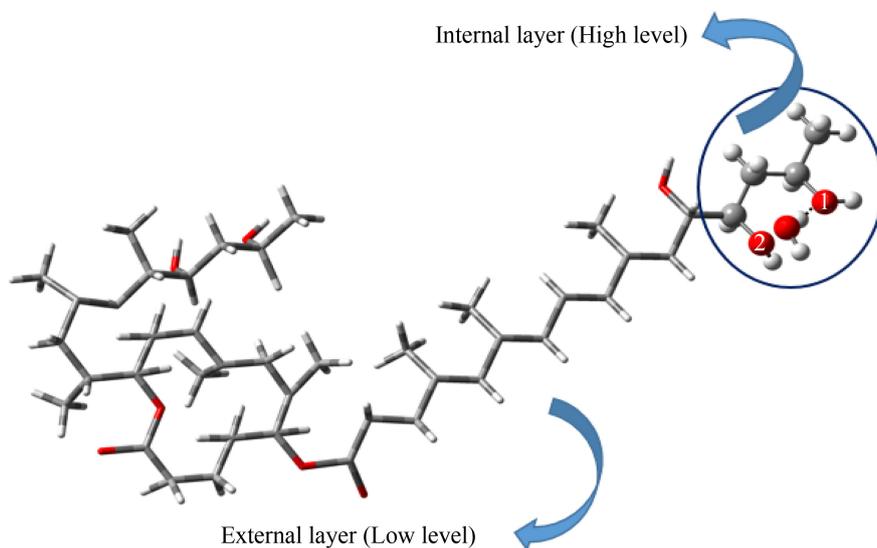


Figure 3. Description of a model for cutting a complex of mycolactone A/B according to ONIOM method (Figure from gaussview software).

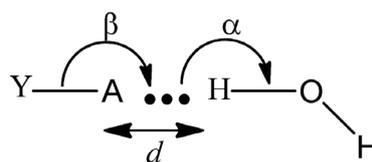


Figure 4. Geometric parameters α , β and d describing hydrogen bond [13].

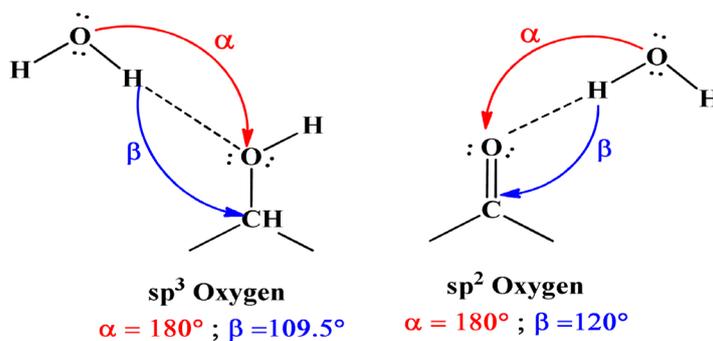
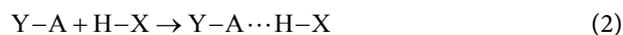


Figure 5. Definition of *linearity* and *directionality* angles describing hydrogen bond.

2.3. Energetic Parameters

Hydrogen bonding between a donor molecule H-X and an acceptor molecule Y-A occurs according to reaction 2. The hydrogen bond complex $\text{Y-A}\cdots\text{H-X}$ is the product. The variation in electronic energy, at 0 K, is given by Equation (3):



$$\Delta E_{\text{elec}}^0 = E_{\text{elec}}^0(\text{Y-A}\cdots\text{H-X}) - [E_{\text{elec}}^0(\text{Y-A}) + E_{\text{elec}}^0(\text{H-X})] \quad (3)$$

The internal energy, at 298.15 K, corresponds to the sum of the electronic, ro-

tational, translational and vibrational contributions, so that its variation can be written according to Equation (4):

$$\Delta E_{298}^0 = \Delta E_{\text{electronic}}^0 + \Delta E_{\text{rotation}}^0 + \Delta E_{\text{translation}}^0 + \Delta E_{\text{vibration}}^0 \quad (4)$$

Geometry optimization of both reactants and products, gives access to all contributions (including nuclear repulsion energies). In ideal gas approximation, rotational and translational contributions are given according to Equation (5):

$$\Delta E_{\text{translation}}^0 = \Delta E_{\text{rotation}}^0 = -\frac{3}{2}RT \quad (5)$$

$\Delta E_{\text{vibration}}^0$ includes ZPVE (Zero Point Vibrational Energy) energy, *i.e.* lowest vibrational level energy, due to $3N-6$ normal vibrational modes ($3N-5$ for the linear molecules), each with frequency ν_i , up to N kernels at 0 K. Taking into account the extra energy due to vibrational levels population during temperature rising from 0 to 298.15 K, leads to Thus, Equation (6), from which the term $\Delta E_{\text{vib.thermal}}^0$ can be drawn:

$$E_{\text{vib.thermal}}^0 = R \sum_{i=1}^{3N-6} \frac{h\nu_i/k}{e^{h\nu_i/298\text{ K}} - 1} \quad (6)$$

As a result, internal energy variation at 298.15 K is given by Equation (7):

$$\Delta E_{298\text{ K}}^0 = \Delta E_{\text{elec}}^0 + \Delta \text{ZPVE} + \Delta E_{\text{vib.thermal}}^0 - 3RT \quad (7)$$

Enthalpy and free enthalpy variations, At 298.15 K, enthalpy and free enthalpy are respectively given by Equations (8) and (9), and entropy variation, by Equation (11):

$$\Delta H_{298\text{ K}}^0 = \Delta E_{298\text{ K}}^0 - RT \quad (8)$$

$$\Delta G_{298\text{ K}}^0 = \Delta H_{298\text{ K}}^0 - T \cdot \Delta S_{298\text{ K}}^0 \quad (9)$$

where

$$\Delta S_{298\text{ K}}^0 = \Delta S_{\text{trans}}^0 + \Delta S_{\text{rot}}^0 + \Delta S_{\text{vib}}^0 \quad (10)$$

2.4. Spectroscopic Parameters

Spectroscopic descriptors can serve as Hydrogen bond scale. The X-H bond linking the donor atom X and the hydrogen atom H increases or decreases according to Hydrogen bond's strength. Therefore the stretch vibration wave-number can be measured. When the donor is a water molecule, the displacement $\Delta \nu(\text{O-H})$ is the scale, and respectively for sp^2 and sp^3 oxygen atoms, this scale is defined according to Relations (11) and (12):

$$\Delta \nu(\text{O-H}) = \nu_s(\text{O-H})_{\text{free}} - \nu(\text{O-H} \cdots \text{O}_{\text{sp}^2})_{\text{complex}} \quad (11)$$

$$\Delta \nu(\text{O-H}) = \nu_s(\text{O-H})_{\text{free}} - \nu(\text{O-H} \cdots \text{O}_{\text{sp}^3})_{\text{complex}} \quad (12)$$

At ONIOM(HF/6-311+G(d,p):AM1) and ONIOM(B3LYP/6-311+G(d,p):AM1) levels, frequencies of vibrator $\nu_s(\text{O-H})_{\text{free}}$ equal respectively, 4242.25 cm^{-1} and 3923.88 cm^{-1} .

3. Results and Discussion

3.1. Geometric Parameters

All geometry optimizations succeeded at the two levels of computation. Examples of initial guess geometry and then optimized geometries of two hydrogen bond complexes are shown in **Figure 6**. Geometric parameters are given in **Table 1**.

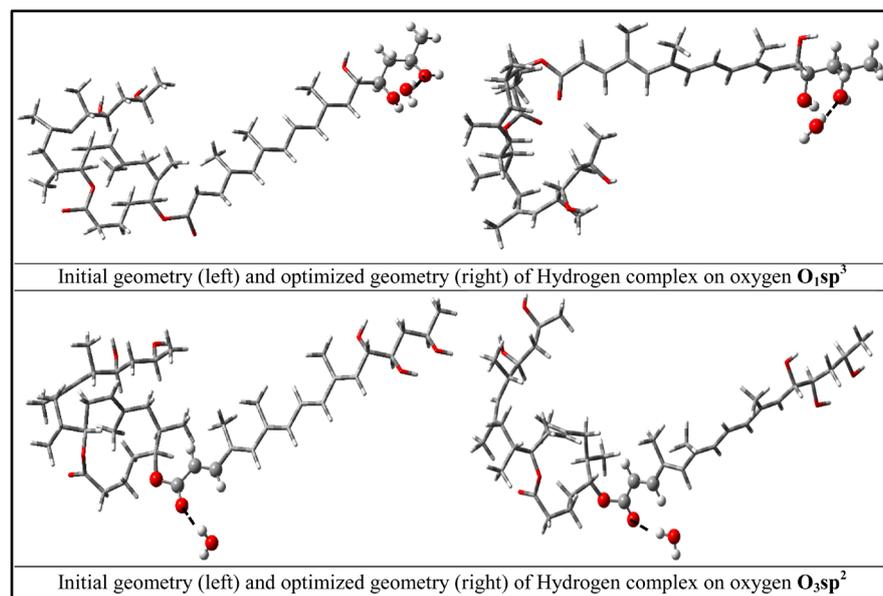


Figure 6. Examples of non-optimized and optimized geometries of Hydrogen bond complexes computed at ONIOM(B3LYP/6-311+G(d,p):AM1) level.

Table 1. Geometric parameters of Hydrogen bond complexes of mycolactone A/B.

	ONIOM (HF/6-311+G(d,p):AM1)			ONIOM (B3LYP/6-311+G(d,p):AM1)		
	α ($^{\circ}$)	B ($^{\circ}$)	d (\AA)	α ($^{\circ}$)	B ($^{\circ}$)	d (\AA)
O ₁ sp ³	135.90	92.80	4.10	132.70	94.58	3.86
O ₂ sp ³	161.97	109.04	2.02	163.30	108.40	1.88
O ₃ sp ²	163.20	115.00	2.09	162.10	127.00	1.91
O ₄ sp ³	129.71	68.08	4.67	126.30	131.77	2.73
O ₅ sp ²	169.78	120.10	2.00	162.90	117.09	1.93
O ₆ sp ³	146.94	78.67	4.84	159.30	102.15	2.86
O ₇ sp ³	153.45	141.20	2.12	145.50	123.09	1.86
O ₈ sp ³	161.31	112.93	2.07	171.40	111.41	1.99
O ₉ sp ³	152.61	118.67	2.06	169.50	115.23	1.93

At level ONIOM(HF/6-311+G(d,p):AM1), value of the linearity angles α on the O₅sp² heteroatom equals 169.78 $^{\circ}$ and is the closest angle to the ideal value of 180 $^{\circ}$, the directionality angle β equals 120.10 $^{\circ}$ and is the closest to the ideal angle of 120 $^{\circ}$, the hydrogen bond length d equals 2.00 \AA and is the smallest (**Table 1**). Indeed, as far as the lengths of the H bonds (distance d) are concerned, the prac-

tice is to consider a contact as a real H bond if the distance d is less than the sum of the Van der Waals radius, taking 1.52 Å [15], and 1.2 Å [16], respectively for a contact with the oxygen and hydrogen atoms; meaning that $d \leq 2.72$ Å. It is also known that the shorter the H bond length is, the stronger it is. So, according geometric parameters, O_5sp^2 heteroatom is the major hydrogen bonding site. At level ONIOM(B3LYP/6-311+G(d,p):AM1), the closest angle α , 171.40°, rather concerns the O_8sp^3 heteroatom, the closest angle β , 108.40°, is found on O_2sp^3 (the ideal β angle for sp^3 oxygen equals 109.5°), and the shortest length d , 1.86 Å, is found for O_7sp^3 . Values of geometric parameters computed at ONIOM (B3LYP/6-311+G(d,p):AM1) level don't allow an undoubtedly conclusion about the major hydrogen bonding site.

3.2. Energetic Parameters

All values of enthalpy $\Delta_r H_{298}^\circ$ are negative, whatever the calculation level, meaning that all hydrogen bonding process are exothermic (Table 2). However, the lowest values are computed in the case of heteroatom O_5sp^2 , respectively -62.24 kJ/mol and -37.32 kJ/mol at ONIOM(HF/6-311+G(d,p):AM1) and ONIOM(B3LYP/6-311+G(d,p):AM1) levels. In the same way, negative values of free enthalpy $\Delta_r G_{298}^\circ$ are computed for $O_2sp^3O_3sp^2$, O_5sp^2 and O_8sp^3 at both two levels. Both at ONIOM(HF/6-311+G(d,p):AM1) and ONIOM(B3LYP/6-311+G(d,p):AM1), these values equal respectively -3.33 kJ/mol, -18.82 kJ/mol, -19.53 kJ/mol and -13.02 kJ/mol. So, onthespecificheteroatoms, Hydrogen bonding is spontaneous.

Spontaneity is much greater with the O_5sp^2 heteroatom, since the corresponding values are the lowest, *i.e.* -19.53 kJ/mol at both ONIOM (HF/6-311+G(d,p):AM1) and ONIOM(B3LYP/6-311+G(d,p):AM1) levels. Therefore, the O_5sp^2 heteroatom gives the most stable complexes. Values of $\Delta_r G_{298}^\circ$ computed for O_3sp^2 are the closest to those computed for O_5sp^2 . Those two heteroatoms, seem to be subject to mesomerism, which enhances their hydrogen bonding ability. In the other hand, O_1sp^3 , O_4sp^3 , O_6sp^3 , O_7sp^3 and O_9sp^3 heteroatoms have

Table 2. Energetic parameters of Hydrogen bond complexes of mycolactone A/B. (Entropy, in J/mol.K).

	ONIOM(HF/6-311+G(d,p):AM1)			ONIOM(B3LYP/6-311+G(d,p):AM1)		
	$\Delta_r H_{298}^\circ$	$\Delta_r S_{298}^\circ$	$\Delta_r G_{298}^\circ$	$\Delta_r H_{298}^\circ$	$\Delta_r S_{298}^\circ$	$\Delta_r G_{298}^\circ$
O_1sp^3	-19.46	-0.12	16.98	-26.20	-014	16.98
O_2sp^3	-17.74	-0.04	-3.33	-28.30	-0.08	-3.33
O_3sp^2	-29.83	-0.03	-18.82	-36.63	-0.06	-18.82
O_4sp^3	-28.21	-0.11	5.52	-10.61	-0.05	5.52
O_5sp^2	-62.24	-0.14	-19.53	-37.32	-0.06	-19.53
O_6sp^3	-23.65	-0.19	35.04	-23.67	-013	35.04
O_7sp^3	-26.14	-0.12	10.07	-4.16	-0.04	10.04
O_8sp^3	-29.57	-0.05	-13.02	-4.16	-0.05	-13.02
O_9sp^3	-18.18	-0.12	19.70	-4.26	-0.08	19.70

Table 3. Frequency displacements $\Delta\nu(\text{O-H})$ (cm^{-1}) of Hydrogen bond complexes of mycolactone A/B.

	ONIOM(HF/6-311+G(d,p):AM1)	ONIOM(B3LYP/6-311+G(d,p):AM1)
O ₁ sp ³	107.33	222.64
O ₂ sp ³	127.29	222.71
O ₃ sp ²	145.32	231.57
O ₄ sp ³	26.19	195.15
O ₅ sp ²	159.68	233.20
O ₆ sp ³	117.22	223.10
O ₇ sp ³	154.20	228.35
O ₈ sp ³	113.56	198.89
O ₉ sp ³	156.55	223.26

positive values of free enthalpies, meaning that there is no possibility of spontaneous reaction for these different sites. It's noticeable that all the latter heteroatoms are sp³ hybridized. It seems that sp³ hybridized oxygen cannot be hydrogen bond major site.

3.3. Spectroscopic Parameters

All frequency shifts are positive (Table 3), corresponding to a decrease in the bond O-H vibration frequency, under hydrogen bonding process. The higher the shift $\Delta\nu(\text{O-H})$ is, the stronger the Hydrogen bond will be. Highest values correspond to O₅sp² heteroatom, *i.e.* 159.68 cm^{-1} and 233.20 cm^{-1} respectively at ONIOM(HF/6-311+G(d,p):AM1) and ONIOM(B3LYP/6-311+G(d,p):AM1) levels. Spectroscopic parameters designate then the O₅sp² oxygen atom as the major Hydrogen bonding site.

4. Conclusion

ONIOM two layers method has been successfully used to identify mycolactone A/B hydrogen bonding major sites. This compound possesses up to nine oxygen heteroatoms, all sp² or sp³ hybridized. Geometric, energetic and spectroscopic parameters have been computed at both ONIOM(HF/6-311+G(d,p):AM1) and ONIOM(B3LYP/6-311+G(d,p):AM1) levels. Results show that sp² hybridized oxygen is the major hydrogen bonding site and then sp³ hybridized oxygen is unlikely subject to hydrogen bonding. Two sp² oxygen atoms, O₃sp² and O₅sp², involved in mesomerism process are the very major sites. Our analysis has permit to undoubtedly designate the major site as O₅sp² atom. Annihilating such a site would render the action of *Mycobacterium ulcerans* ineffective, assuming that all intermolecular interactions will occur on the same site as Hydrogen bonding.

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