

# Secondary Interaction Contribution in Hydrogen-Bonded Complex: Theoretical Model Study in Hydrogen Fluoride Trimer

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The secondary interaction contribution in complexation *via* multiple hydrogen bonds was estimated using model complexes. Based on the results of hydrogen fluoride complexes, proton donor (D) - proton acceptor (A) type secondary interaction was attractive, and the total stabilization energy should be increased about 25-35%, based on hydrogen bond interaction, by the D-A type secondary interaction. The D-D type secondary interaction was very small. The A-A type secondary interaction was repulsive, and the total stabilization energy should be decreased about 10-20% based on hydrogen bond interaction, by the A-A type secondary interaction.

**Keywords:** *ab initio*, Density functional theory, Hydrogen bond, Secondary interaction, Hydrogen fluoride

## 1 Introduction

Molecular recognition using a plurally hydrogen-bonded complex, for example, base pair formation in a nucleic acid duplex (Figure 1) [1], is an important topic in supermolecular chemistry [2]. It has been widely studied theoretically [3]. In such complexes, the arrangement of the proton donor (D) -acceptor (A) orientation has an important role in the total stability of the complex. Jorgensen *et al.* proposed secondary interactions in plurally hydrogen-bonded complexes [4,5]. The secondary interactions are defined as follows. The D-A type secondary interaction: an interaction between an acidic proton, forming a hydrogen bond, and a neighboring proton acceptor heavy atom. For example, an interaction between the 1-position proton of guanine and the *exo*-cyclic 2-position oxygen of cytosine. The A-A type secondary interaction: an interaction between a proton acceptor heavy atom and a neighboring proton acceptor heavy atom. For example, an interaction between the 1-position nitrogen of adenine and the *exo*-cyclic 4-position oxygen of uracil. The D-D type secondary interaction: an interaction between an acidic proton, forming a hydrogen bond, and a neighboring acidic proton. For example, an interaction between the 3-position proton of uracil and the *exo*-cyclic

6-position amino proton of adenine. Whether or not the neighboring hydrogen bond site forms a hydrogen bond, the secondary interaction should be considered; the A-A type secondary interaction should be considered to be between the *exo*-cyclic 2-position oxygen of uracil and the 1-position nitrogen of adenine, for example.

According to Jorgensen's proposal, the total hydrogen bond should be more stable when all the proton donor-acceptor pairs are arranged in the same direction as in Figure 1 I: DD-AA type complex, for example, the arrangement of the hydrogen bonds B and C in a guanine - cytosine base pair. On the other hand, the total hydrogen bond should be less stable when the proton donor-acceptor pairs are arranged alternately as in Figure 1 II: DA-AD type complex, for example, the arrangement of the hydrogen bonds A and B in guanine - cytosine and adenine - uracil base pairs. As a result, the adenine - uracil base pair is considered to have two hydrogen bonds and two repulsive secondary interactions (A-A and D-D type), and the guanine - cytosine base pair is considered to have three hydrogen bonds, two attractive secondary interactions (D-A type), and two repulsive secondary interactions (A-A and D-D type) [6]. We already reported the importance of secondary electrostatic interactions in hydrogen-bonding complexes [7], and we

report herein the contribution of the secondary interactions to the whole hydrogen bond formation energy, using hydrogen fluoride dimer/trimer as the models of the hydrogen bond site of a plurally hydrogen-bonded complex.

## 2 Computational Methods

The molecular interaction energies were evaluated by a supermolecular method. The basis set superposition error (BSSE) for hydrogen bond energies was corrected by using the counterpoise method [8]. In the supermolecular method, only total interaction energy can be calculated, and it is difficult to distinguish between the hydrogen bond energy and secondary interaction. A molecule, which has plural hydrogen bond sites (see formamide in Figure 2, for example), should be divided into each hydrogen bond site. Hydrogen fluoride was employed as a model of the divided hydrogen bond sites.

For the estimation of the molecular interaction, B3LYP/6-311+G\*\*, MP2/aug-cc-pVTZ, and QCISD(T)/aug-cc-pVTZ levels of the calculations were applied. The structure of the hydrogen fluoride was optimized in B3LYP/6-311+G\*\* for the DFT calculations ( $R_{HF} = 0.9222 \text{ \AA}$ ) and in QCISD(T)/aug-cc-pVTZ ( $R_{HF} = 0.9190 \text{ \AA}$ ) for the MP2 and QCISD(T) calculations.

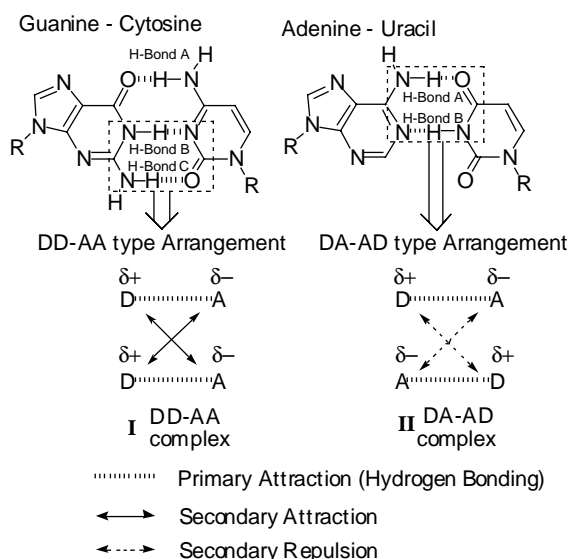


Figure 1. Watson-Crick type base pair and hydrogen bond arrangement in a plurally hydrogen-bonded complex.

The hydrogen bond lengths in B3LYP (2.800 Å), MP2 (2.800 Å), and QCISD(T) (2.900 Å) studies were determined by the potential energies calculated at the levels of B3LYP/6-311+G\*\* and QCISD(T)/aug-cc-pVTZ using the linear ( $C_{\infty v}$ ) structure [9]. Only in the MP2 study, the basis set limit was estimated with Feller's procedure [10] using aug-cc-pVDZ, aug-cc-pVTZ and aug-cc-pVQZ basis sets. The distance between the hydrogen fluorides was fixed to 2.25 Å (Figure 2), considering the distance between the hydrogen bond sites of the typical molecules forming a plurally hydrogen-bonded complex, *e. g.*, formamide dimer and nucleic acid base pairs.

We evaluated the secondary interactions using two types of models: hydrogen fluoride dimer models, and hydrogen fluoride trimer models. In the hydrogen fluoride dimer systems, hydrogen bond energy and secondary interaction energies were evaluated by the arrangement of the hydrogen fluorides: Figure 2 I; for the hydrogen bond energy, Figure 2 II; for the D-A type attractive secondary interaction, Figure 2 III; for the D-D type repulsive secondary interaction and Figure 2 IV; for the A-A type repulsive secondary interaction.

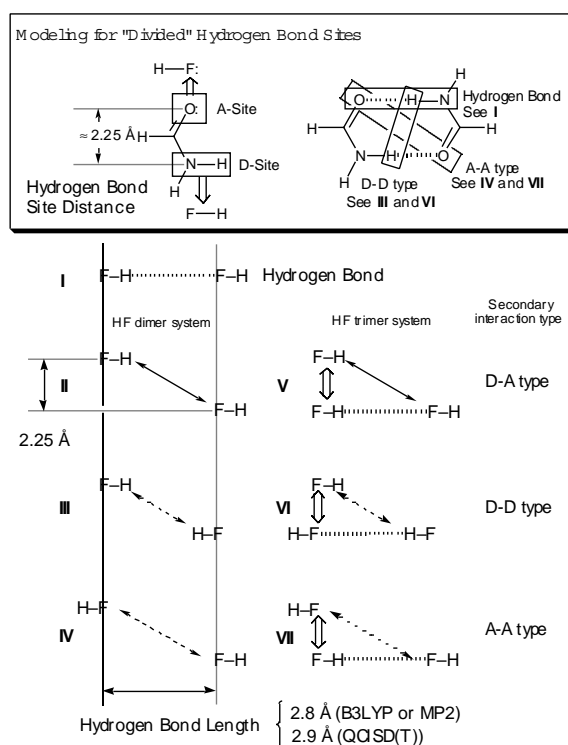


Figure 2. Modeling for divided hydrogen bond sites of plurally hydrogen-bonded complex by the arrangement of the hydrogen fluoride dimers/trimers.

Figure 2 V-VII show the arrangement of three hydrogen fluorides for the D-A type attractive secondary interaction (Figure 2 V), the D-D type repulsive secondary interaction (Figure 2 VI) and the A-A type repulsive secondary interaction (Figure 2 VII). The magnitude of each interaction was evaluated as follows. The hydrogen fluorides were named as shown in Figure 3. D-A type arrangement of three hydrogen fluorides (Figure 2 V) is shown for example. Three molecular interaction energies should be considered in the system:  $x$  = hydrogen bond interaction between  $\text{HF}^A$  and  $\text{HF}^B$  ( $E_{HB}$ ),  $y$  = repulsive interaction between  $\text{HF}^A$  and  $\text{HF}^C$  ( $E_{rep}$ ), and  $z$  = secondary interaction between  $\text{HF}^B$  and  $\text{HF}^C$  ( $E_2$ ). However, these interactions could not be calculated directly by the supermolecular method; thus, to determine these three interactions, three interaction energies, *i. e.*,  $l$ : total stabilization energy of  $(\text{HF}^A-\text{HF}^C)+\text{HF}^B$  (interaction energy between  $(\text{HF}^A-\text{HF}^C)$  and  $\text{HF}^B$ , here,  $\text{HF}^A-\text{HF}^C$  were dealt as one part. See also Figure 3),  $m$ : interaction energy of  $(\text{HF}^B-\text{HF}^C)+\text{HF}^A$  and  $n$ : interaction energy of  $(\text{HF}^A-\text{HF}^B)+\text{HF}^C$  were calculated. The interaction  $l$  is considered to include the interactions  $x$  and  $z$ , the interaction  $m$  is considered to include the interactions  $x$  and  $y$ , and the interaction  $n$  is considered to include the interactions  $y$  and  $z$ ; thus,  $l = x + z$ ,  $m = x + y$ , and  $n = y + z$ . D-D and A-A type secondary interactions were also calculated as above, using the corresponding trimer complex (Figure 2 VI and VII, respectively).

All molecular orbital calculations were carried out using a Gaussian 94 program [11].

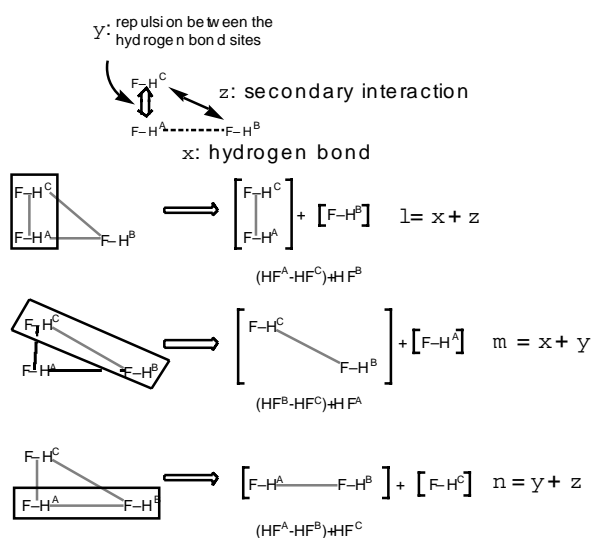


Figure 3. Estimation of the hydrogen bond ( $x$ ), the repulsion of neighboring HF ( $y$ ) and the secondary interaction ( $z$ ) for the model of neighboring hydrogen bond sites by the combination of hydrogen fluoride trimer division ( $l$ ,  $m$  and  $n$ ).

### 3 Results and Discussion

Tables 1 and 2 show the hydrogen bond energies and three types of secondary interaction energies, using the hydrogen fluoride dimer systems (Figure 2 I-IV) and the hydrogen fluoride trimer systems (Figure 2 V-VII), respectively, in the B3LYP/6-311+G\*\* level of the calculation. Similar results, the ratio of the secondary interaction based on the hydrogen bond, were observed in both dimer systems and trimer systems. The D-A type attractive secondary interaction was evaluated as 20-30% of the hydrogen bond (I in the dimer system and  $x$  in the trimer system). Unexpectedly, the D-D type secondary interaction was evaluated as weakly (4-5%) attractive in this level of theory. The A-A type repulsive secondary interaction is about 20% of the hydrogen bond. Similar results were observed based on the hydrogen fluoride dimer systems and the hydrogen fluoride trimer systems in the DFT calculations.

Table 1. Molecular interaction (the hydrogen bond and the secondary interaction) energies (kcal/mol) and the ratio of the secondary interaction based on the hydrogen bond stability by use of hydrogen fluoride dimer models, in B3LYP/6-311+G\*\*.

	Energy	Ratio	Model in Figure 2
$E_{HB}$	-3.82	—	I
$E_2$ D-A	-1.07	<b>0.28</b>	II
$E_2$ D-D	-0.14	<b>0.04</b>	III
$E_2$ A-A	+0.77	<b>0.20</b>	IV

Table 2. Molecular interaction (the hydrogen bond and the secondary interaction) energies (kcal/mol) and the ratio of the secondary interaction based on the hydrogen bond stability by use of hydrogen fluoride trimer models, in B3LYP/6-311+G\*\*.

	Interaction Energy			Interaction in Figure 3	Ratio ( $z/x$ )
$E_{HB}$	-3.52	-3.85	-3.85	$x$	—
$E_{rep}^\dagger$	+11.64	+5.13	+5.13	$y$	
$E_2$ D-A	-0.79			$z$	<b>0.22</b>
$E_2$ D-D		-0.19		$z$	<b>0.05</b>
$E_2$ A-A			+0.72	$z$	<b>0.19</b>
$E_T$	-0.29	+0.05	+0.04	three-body interactions	
$E_{total}$	+7.04	+1.13	+2.04	total interaction	
	<b>V</b>	<b>VI</b>	<b>VII</b>	Model in Figure 2	

$^\dagger$ Repulsive interaction between  $\text{HF}^A$  and  $\text{HF}^C$  in Figure 3. See the computational method in the text.

In the trimer systems, three-body interaction should be considered [12]; however, three-body interactions in the D-A type, the D-D type and the A-A type trimer ( $E_T = E_{total} - (E_{HB} + E_2 + E_{rep})$ ) were all small, comparing total interaction energies of the complexes ( $E_{total} = E_{HFtrimer} - 3E_{HFmonomer}$ ). Rincón *et al.* reported hydrogen bond cooperativity in the hydrogen fluoride clusters. The stabilization energy per one hydrogen bond in the cluster significantly arises from the tetramer, but it is not remarkably changed between the dimer and the trimer [13]. Our results were in good agreement with the results of Rincón *et al.* [13]; thus, we can safely deal with these trimer systems as the model of hydrogen bond sites without consideration of three-body interaction. Taking account of these results, MP2 and QCISD(T) studies were carried out based on the hydrogen fluoride dimer systems. Table 3 shows the hydrogen bond energy and three types of secondary interaction energies in various methods using the hydrogen fluoride dimer systems. The basis set effect in the MP2 method was small. The D-A type secondary interaction was estimated to be about 30%. The result of D-A type attractive secondary interaction was similar to that of DFT. The D-D type secondary interaction was evaluated to be about 10% (QCISD(T)) or about 15% (MP2) attractive. The A-A type repulsive secondary interaction was about 10-15% of the hydrogen bond. Thus, DFT estimated D-A type secondary interaction in high accuracy, but it underestimated the contribution of the D-D type and overestimated the A-A type secondary interaction.

Figure 4 shows the change in the secondary interaction depending on the distance between the hydrogen fluorides, which corresponds to the hydrogen bond length, in DFT (A) and QCISD(T) (B) methods. The trend of these two figures is similar: all interactions in DFT are a parallel shift of the results in QCISD(T). The D-A type and the A-A type interactions were quite insensitive to the hydrogen bond length. In contrast to these two interactions, the D-D type interactions were sensitive to the hydrogen bond length. It was repulsive when the dis-

tance between the hydrogen fluorides was long, and it was attractive when the distance between the hydrogen fluorides was short. As the result, it was weakly attractive in the range of normal hydrogen bond length. From the result of this potential energy study, Figure 5 is considered to be the reason why the D-D type secondary interaction was evaluated as attractive: there are two tertiary attractive interactions between the proton and the fluorine atom of the opposite side, and these two interactions overcome the repulsive interaction between two protons (Figure 5A) [14]. In the case of the D-D interaction, tertiary interaction is 52 degrees bent hydrogen bond-like interaction. The atom distance between the hydrogen and the fluorine ( $R_{HF} = \text{ca. } 2.2 \text{ \AA}$ ) was comparable with the atom distance in the hydrogen bond ( $1.8 \text{ \AA}$ ). On the other hand, the  $R_{HF}$  in A-A type arrangement (Figure 5B) was much longer (ca.  $4.0 \text{ \AA}$ ). The fluorine-hydrogen-fluorine bent angle (ca. 149 degrees) is too highly bent to form the hydrogen bond-like interaction. Thus, tertiary interaction in A-A type arrangement is considered to be negligible.

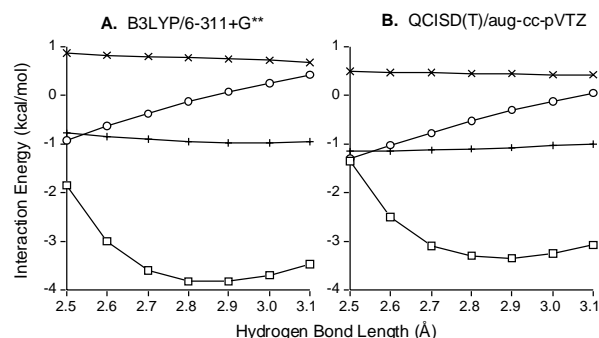


Figure 4. Potential energy curves of the A-A type (cross), DD type (circle), D-A type (plus) secondary interactions, and hydrogen bond (square) depending on the hydrogen bond length (between the heavy atoms). See also Figure 2.

Table 3. Molecular interaction (the hydrogen bond and the secondary interaction) energies (kcal/mol) and the ratio of the secondary interaction based on the hydrogen bond stability by use of hydrogen fluoride dimer models, in various calculation levels.

	B3LYP/6-311+G**		MP2/aug-cc-pVTZ		MP2/basis set limit <sup>†</sup>		QCISD(T)/aug-cc-pVTZ	
	Energy	Ratio	Energy	Ratio	Energy	Ratio	Energy	Ratio
H-Bond	-3.82	—	-3.24	—	-3.59	—	-3.35	—
2nd D-A	-1.07	<b>-0.28</b>	-1.08	<b>-0.33</b>	-1.08	<b>-0.31</b>	-1.07	<b>-0.32</b>
2nd D-D	-0.14	<b>-0.04</b>	-0.48	<b>-0.15</b>	-0.51	<b>-0.14</b>	-0.30	<b>-0.09</b>
2nd A-A	+0.77	<b>+0.20</b>	+0.47	<b>+0.15</b>	+0.43	<b>+0.12</b>	+0.44	<b>+0.13</b>

<sup>†</sup>: The values calculated based on the basis set limit, estimated by Feller's procedure [10].

From the results in Figure 4, both D-A type and A-A type secondary interaction energies were almost independent of the hydrogen bond length. In contrast to these two types of secondary interaction energies, D-D type secondary interaction energies were highly dependent on the hydrogen bond length. It was repulsive in the case of longer hydrogen bond length, and it was attractive in the case of shorter hydrogen bond length. Thus, the hydrogen bond length of the DA-AD type complex should be shorter than that of the DD-AA type, if the hydrogen bond capability of each hydrogen bond sites is the same. On the other hand, total hydrogen bond stabilization in the DD-AA type complex should be larger than that of the DA-AD type complex.

Next, a model study using a formamide-hydrogen fluoride complex was attempted. There are two proton donor (D1 and D2 in Figure 6) sites and acceptor (A1 and A2) sites in formamide. The hydrogen bond sites A1 and A2 are proton acceptor sites without and with D-D type secondary interaction. The hydrogen bond sites D1 and D2 are proton donor sites without and with A-A type

secondary interaction. The proton donatability of D1 and D2 sites, and acceptability of A1 and A2 sites without the secondary interaction should be similar, respectively. Thus, the contribution of the secondary interaction should be observed as the difference in the hydrogen bond stability.

Table 4 shows the results in B3LYP/6-311+G\*\* and MP2/aug-cc-pVTZ levels of the calculation. In both calculation levels, change in the stabilization energy with and without the secondary interaction was in good agreement with the results from the model complex using hydrogen fluorides (compare the ratio of the secondary interactions based on the hydrogen bond energy of Tables 3 and 4). D-D type secondary interaction was a very small attractive force; on the other hand, A-A type secondary interaction was a large repulsive force, and the ratio of the A-A type secondary interaction in the total interaction was 0.2-0.3. Thus, the secondary interaction contribution in a plurally hydrogen-bonded complex, shown in Table 3, is applicable for rough estimation of the trend in stabilization of the plurally hydrogen-bonded complex.

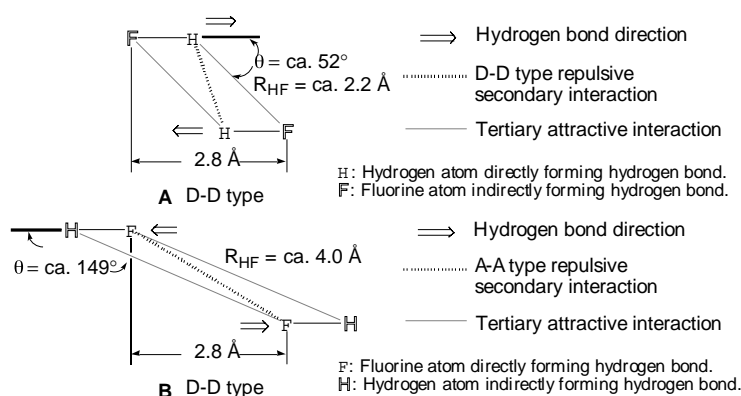


Figure 5. The tertiary interaction of D-D/A-A arrangement.

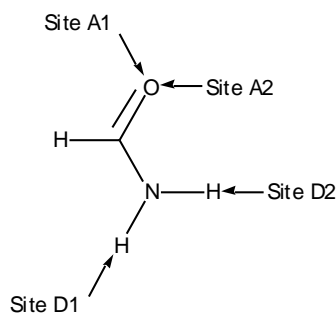


Figure 6. Hydrogen bond sites of formamide.

Table 4. Total interaction and the secondary interaction energy (kcal/mol) and the ratio of the secondary interaction in formamide-HF complex.

H-Bond Site	B3LYP/6-311+G**		MP2/aug-cc-pVTZ	
	Total Int.	2nd Int. (ratio/type)	Total Int.	2nd Int. (ratio/type)
D1	-2.37		-2.30	
D2	-1.70	0.67 ( <b>0.28</b> /A-A)	-1.76	0.54 ( <b>0.24</b> /A-A)
A1	-9.76		-9.68	
A2	-9.73	0.03 ( <b>0.003</b> /D-D)	-9.33	0.35 ( <b>0.04</b> /D-D)

## 4 Conclusion

The contribution of the secondary interaction in a plurally hydrogen-bonded complex was estimated using model complexes. Donor-acceptor type secondary interaction was attractive, and it had the largest (about 25-35% based on hydrogen bond interaction) contribution. Unexpectedly, donor-donor type secondary interaction was attractive, but the interaction was relatively small or, in some cases, negligible. Acceptor-acceptor type secondary interaction was strongly repulsive (about 10-20% based on hydrogen bond interaction). The estimation of the secondary interaction contribution was in good agreement with the change in hydrogen bond interaction energies in each formamide hydrogen bond site. Thus, the secondary interaction contribution in a plurally hydrogen-bonded complex, described here, is applicable for rough estimation of the trend in stabilization of the plurally hydrogen-bonded complex.

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# 水素結合錯体における二次的相互作用の寄与： フッ酸二量体、三量体によるモデル研究

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複数の水素結合形成時、隣り合った水素結合部位間に働く二次的相互作用をフッ酸二量体、三量体をモデルとして用い、*ab initio* 分子軌道法および密度汎関数法により考察した。二つの水素結合サイト間の二次的相互作用を考えた場合、水素結合の方向が揃っている DD-AA 型錯体 ( Figure 1 I ) で形成される、水素結合供与体 ( D ) -受容体 ( A ) 型の二次的相互作用により、水素結合錯体の安定性は 25-35% 増加する。一方、水素結合の方向が揃っていない DA-AD 型錯体 ( Figure 1 II ) で形成される、二種類の二次的相互作用の内、D-D 型二次的相互作用の影響は他の二次的相互作用よりも小さく、5-15% 増加する。D-D 型二次的相互作用で水素結合錯体の安定性が増加するというのは Jorgensen らによるモデルの説明と一致しないが、これは、本文 Figure 5 に示す三次的相互作用の影響と考えられる。一方、A-A 型二次的相互作用により水素結合錯体の安定性は 10-20% 減少する ( 本文 Table 3 参照 )。

上記のモデルによる結果を基に formamide の 4 つ ( 水素結合供与部位、水素結合受容部位ともに 2 つずつ ) の水素結合部位の水素結合能の違いをほぼ説明する事ができた。 ( 本文 Table 4 参照 )。

キーワード：非経験的分子軌道法, 密度汎関数法, 水素結合, 二次的相互作用, フッ酸

