Hydrogen Bonding Abilities of Thioamide

Ho-Jin Lee,[†,‡] Young-Sang Choi,*[,†] Kang-Bong Lee,[‡] Jeunghee Park,[§] and Chang-Ju Yoon*[,||]

Department of Chemistry, Korea University, 1 Anam-dong, Seoul, 136-701, Republic of Korea,
Advanced Analysis Center, Korea Institute of Science and Technology, Seoul 136-791, Republic of Korea,
Department of Chemistry, Korea University, 208 Seochang-dong, Jochiwon 339-700, Republic of Korea,
Department of Chemistry, The Catholic University of Korea, Pucheon, 420-743, Republic of Korea

Received: January 15, 2002; In Final Form: March 22, 2002

The strengths of hydrogen bonding interaction between formamide (FA) and thioformamide (TFA) were investigated at the B3LYP level with the 6-311G(d,p), 6-31+G(d,p), and 6-311++G(2d,2p) basis sets. The 18 minimum energy structures of FA-FA, TFA-TFA, and TFA-FA dimers were examined. The average strength of the OCN−H- - -O═C, SCN−H- - -S═C, OCN−H- - - S═C, and SCN−H- - -O═C hydrogen bonds at the B3LYP/6-311++G(2d,2p) level was −6.1 ± 0.3, −5.0 ± 0.1, −4.8 ± 0.3, and −7.3 ± 0.4 kcal/mol, respectively, when the basis set superposition error (BSSE) was corrected. The results show that TFA is a good hydrogen bond donor but a poor hydrogen bond acceptor as compared to FA. For the OC−H- - -O═C, SC−H- - -S═C, OC−H- - - S═C, and SC−H- - -O═C hydrogen bonds, the average strength has been predicted to be −2.2 ± 0.3, −2.2 ± 0.2, −1.0 ± 0.3, and −3.1 ± 0.3 kcal/mol, respectively. It is remarkable that the thioformyl hydrogen atom of TFA has a strong hydrogen bonding ability as compared to that of FA. The abilities of the hydrogen bond donor have a good correlation with the proton affinities of the deprotonated anion.

1. Introduction

The hydrogen bonding between peptide groups plays a crucial role in determining the conformational stability and binding affinity of peptide and protein structures. Because of its importance, the characteristics of N−H- - -O═C and C−H- - -O═C hydrogen bonds have been extensively investigated experimentally and theoretically.[1−4] The results have contributed to giving insights on understanding of the conformational stability of protein structure.

Thioamide is formed by the replacement of the carbonyl oxygen by sulfur in amide bond. This modification has been thought to have an enhanced or reduced effect on the conformational flexibility or binding affinity, depending on steric or hydrogen bonding force.[5−8] A number of studies have therefore focused on the synthesis of the biologically important thioamide-containing peptides.[5] The conformational properties of thioamide-containing peptide (thiopeptide) were also extensively investigated.[6−8] These studies led to the finding that the hydrogen bonding interaction between thioamide and amide would determine the conformational preference of thiopeptides. However, the hydrogen bonding strength of thioamides was scarcely investigated.[9−12] Laurence et al. have reported an experimental result that the hydrogen bonding formation constants of several thioamides with 4-fluorophenol are smaller than that of corresponding amide.[9] Our group investigated the hydrogen bonding abilities of thioacetamide with *N*,*N*-dialkylamides in a nonpolar CCl_4 solvent using near-IR, IR, NMR, and quantum mechanical calculations.[10] Recently, Alemán calculated the strength of amide−thioamide interactions, showing that thioamide is a weak hydrogen bond acceptor but a strong hydrogen bond donor as compared to amide, being explained in terms of the electronegativity.[11] In contrast, it was reported that the hydrogen bond acceptor ability of thioamide sulfur could be surprisingly equal to or exceed that of amide oxygen.[12]

In the present work, we select a simplest thioamide, thioformamide (TFA), as a proton donor or acceptor to elucidate the hydrogen bonding strength of thioamide. The hydrogen bonding interaction of TFA with TFA and formamide (FA) has been thoroughly examined by using the density function theory (DFT) with the three basis sets, 6-311G(d,p), 6-31+G(d,p), and 6-311++G(2d,2p).[13,14] The chemical structure of TA and TFA is given in Figure 1. The strength of the OCN−H- - -X═C, SCN−H- - -X═C, OC−H- - -X═C, and SC−H- - -X═C hydrogen bonding interaction in FA-FA, TFA-TFA, and TFA-FA dimers was estimated, where X represents an oxygen or sulfur atom. The quantitative information on the hydrogen bonding abilities of thioamide and amide would eventually shed light on understanding the biochemical processes and also aid to parametrize the molecular mechanic force fields.[8]

2. Computational Methods

All calculations were performed using the GAUSSIAN program.[15] The energy minima of FA-FA, TFA-TFA, and TFA-FA dimers are computed at the B3LYP/6-31G(d) level.[2a,13,14] The B3LYP/6-31G(d)-optimized structures were fully reoptimized at the higher 6-311G(d,p), 6-31+G(d,p), and 6-311++G-(2d,2p) basis sets.[13,14] The influence of the basis set superposition error (BSSE) has been evaluated with the aid of conventional counterpoise (CP) procedure including the influence of geometry relaxation upon complex formation.[16]

---

* Authors to whom correspondence should be addressed. (Young-Sang Choi) Use current address: Department of Chemistry, Korea University, 1 Anam-dong, Seoul, 136-701, Republic of Korea. Fax: 82-2-3290-3121; Tel: 82-2-3290-3125; E-mail: yschoi@korea.ac.kr. (Chang-Ju Yoon) E-mail: cjyoon@www.cuk.ac.kr.

[†] Department of Chemistry, Korea University, 1 Anam-dong, Seoul, 136-701, Republic of Korea.

[‡] Advanced Analysis Center, Korea Institute of Science and Technology.

[§] Department of Chemistry, Korea University, 208 Seochang-dong, Jochiwon 339-700, Republic of Korea.

[||] Department of Chemistry, The Catholic University of Korea.

10.1021/jp025516e CCC: $22.00

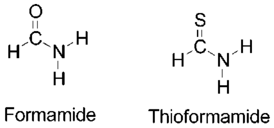

Figure 1. Chemical structures for model compounds, FA and TFA.

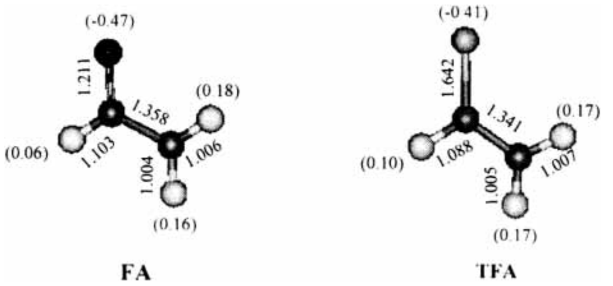

Figure 2. B3LYP/6-311++G(2d,2p)-optimized structures for FA and TFA. The atomic charges for the oxygen, sulfur, and hydrogen atoms are included in parentheses.

The proton affinity (PA) of a base B is defined as the negative value of the enthalpy change for the $B(g) + H^+(g) \rightarrow BH^+(g)$ reaction. The absolute PA value was calculated by the following equation:[17]

$$\mathrm{PA(B)} = -\Delta E^{o}_{\mathrm{elec}} - \Delta \mathrm{ZPE} + \Delta E_{\mathrm{vib}}(T) + {}^{5}/_{2}RT \quad (1)$$

$\Delta E^{o}_{\mathrm{elec}}$ represents the difference between the electronic energies of the products and the reactants at 0 K, ΔZPE is the difference in the zero-point energies of BH^+ and B, $\Delta E_{\mathrm{vib}}(T)$ accounts for the change in the population of vibrational levels at a temperature T, and the last term incorporates the classical correction for translation (${}^{1}/_{2}RT$ per degree of freedom), rotation (${}^{1}/_{2}RT$ per degree of freedom), and the conversion factor of energy to enthalpy (ΔnRT). Similarly, the PA of an anion A^- is defined as the enthalpy associated with the reaction $AH(g) \rightarrow A^-(g) + H^+(g)$ reaction.[3a] The PA values were calculated at the B3LYP/6-31G(d) level of theory. [13,14]

3. Results and Discussion

3.1. Molecular Geometries of the Monomers and the Hydrogen-Bonded Dimers. The B3LYP/6-311++G(2d,2p)-optimized structures of FA and TFA monomers are displayed in Figure 2. As a sulfur atom replaces the carbonyl oxygen atom, the C−S bond of TFA is longer than the C−O bond of FA, and the C−N bond of TFA is shorter than that of FA.[18] This structural difference may be responsible for a restriction of conformational preferences in thioamide-containing peptides.[6,7]

As expected, the atomic charge of oxygen (−0.47) of FA is more negative than that of the sulfur atom (−0.41) of TFA, indicating that TFA is a weaker hydrogen bond acceptor than FA.[9,11] The amide hydrogen atoms of FA (+0.16 or +0.18) and TFA (+0.17) have similar positive charges, which would indicate no different ability of FA and TFA. The thioformyl hydrogen (+0.10) of TFA shows slightly more positive charge than the formyl hydrogen (+0.06) atom of FA (see Figure 2). This implies that the thioformyl hydrogen of TFA might be a good hydrogen bond donor, which is discussed in the following sections.

The resulting 18 minimum energy structures of FA-FA, TFA-FA, and TFA-FA dimers at the B3LYP/6-311++G(2d,2p) level are displayed in Figures 3−5. The dimers **1**, **6,** and **7** have two N−H- - -O═C (or N−H- - - S═C) hydrogen bonds with a head-to-tail cyclic structure. The **2**, **7**, **12,** and **13** have one N−H- - -O(S)═C and one C−H- - -O(S)═C hydrogen bond. The **3**, **4**, **8** and **9**, **14−17** have one N−H- - -O(S)═C hydrogen bond. The dimers **5**, **10,** and **18** have two C−H- - -O(S)═C hydrogen bonds.

When FA and TFA form the hydrogen-bonded dimers, the length of C═O(S) and N−H bonds increases and that of C−N bond decreases by about 0.02 Å, respectively (Table S1). The change of C−H bond length is negligibly small. The detailed analysis is the following.

FA-FA Dimers. The optimized intermolecular parameters of FA-FA dimers **1−5** were calculated with the 6-311G(d,p), 6-31+G(d,p), and 6-311++G(2d,2p) basis sets and listed in Table 1. The distance of H- - -O and N- - -O show similar values regardless of the basis sets. The distances of H- - -O, N- -O, and C- - -O bonds for **1−5** are slightly longer by about 0.03 Å than those of the reported MP2/aug-cc-pVDZ-optimized geometries.[2a] Our DFT results are consistent with the available X-ray crystallographic data that the mean N−H- - - O═C hydrogen bond length is 2.00 ± 0.04 Å.[7] At the B3LYP/6-311++G(2d,2p) level, the lengths of the N−H- - -O═C hydrogen bond for **1−4** are found in the range 1.87−2.01 Å and of the C−H- - -O═C hydrogen bonds for **2** and **5** are 2.33 and 2.42 Å, respectively (see Figure 3).

TFA-TFA Dimers. The intermolecular parameters of TFA-TFA dimers **6−10** are listed in Table 1. The length of the N−H- - -S hydrogen bond is similar for three basis sets. The optimized structures at the B3LYP/6-311++G(2d,2p) level (see Figure 4) reveals that the SCN−H- - -S═C hydrogen bond lengths of **6−9** are in the range from 2.42 to 2.47 Å and the SC−H- - -S═C bond distances of **7** and **10** are 2.72 and 2.81 Å, respectively. The lengths of the SCN−H- - - S═C and SC−H- - - S═C bonds are longer than those of the OCN−H- - - O═C and OC−H- - -O═C bonds, implying that the hydrogen bonding strength of TFA dimers would be weaker than those of FA dimers. To our best knowledge, the calculation of TFA dimers is the first report.

TFA-FA Dimers. The intermolecular parameters for TFA-FA dimers **11−18** are listed in Table 2 and the structures optimized at the B3LYP/6-311++G(2d,2p) level are displayed in Figure 5. The OCN−H- - -S═C hydrogen bond length of **14** and **16** are 2.55 and 2.52 Å, respectively, which is longer than the OCN−H- - -O═C bond length of **3** and **4** (in Figure 3) by about 0.5 Å. Tran et al. reported that the average OCN−H- - -S═C hydrogen bond distance is 2.52 ± 0.06 Å and the average OCN−H- - -S═C angle is 169° ± 8°, which agree excellently with our data.[7a] For **15** and **17**, the hydrogen bond lengths of the SCN−H- - -O═C interaction are 1.95 and 1.94 Å, respectively, which are shorter than those of the SCN−H- - -S═C for **8** and **9** (in Figure 4) by about 0.5 Å. These suggest that the carbonyl oxygen of FA would be a better hydrogen bond acceptor than the sulfur of TFA as previous reports.[9,11] The length of the SCNH- - -O═C hydrogen bond of **17** is shorter than that of the OCNH- - -O═C of **4**, implying a good hydrogen bond donating ability of TFA relative to that of FA.[11]

The SC−H- - -O═C hydrogen bond length of **12** and **18** are 2.19 and 2.25 Å, respectively. The OC−H- - -O═C bond lengths are 2.33 and 2.41 Å for **2** and **5**, respectively (see Figure 3). The result indicates that the thioformyl hydrogen atom of TFA would be a good hydrogen bond donor as compared to that of FA. This will be fully discussed in a following section in detail.

3.2. Hydrogen Bonding Abilities of Amide and Thioamide. The association energies without and with correcting the BSSE for **1−18** are listed in Table 3. We analyzed the hydrogen bonding abilities of thioamide and amide as a proton donor or

TABLE 1: Structural Parameters for the Hydrogen Bonds in Dimers 1−10

	OCN−H- - -O═C bond			OC−H- - -O═C bond		
	H- - -O	N- - -O	N−H- - - -O	H- - - -O	N- - -O	C−H- - -O
1						
6-311G(d,p)	1.872	2.893	172.4			
6-31+G(d,p)	1.875	2.898	172.3			
6-311++G(2d,2p)	1.873	2.892	172.6			
ref 2[a]	1.836	2.863	174.2			
2						
6-311G(d,p)	1.906	2.911	166.4	2.284	3.223	141.8
6-31+G(d,p)	1.906	2.916	167.1	2.317	3.246	140.7
6-311++G(2d,2p)	1.908	2.915	167.8	2.329	3.260	141.3
ref 2[a]	1.876	2.891	168.8	2.274	3.231	143.6
3						
6-311G(d,p)	1.990	2.960	158.2			
6-31+G(d,p)	2.004	2.974	158.0			
6-311++G(2d,2p)	2.005	2.980	160.1			
ref 2[a]	1.976	2.939	156.0			
4						
6-311G(d,p)	1.957	2.948	164.1			
6-31+G(d,p)	1.977	2.993	176.1			
6-311++G(2d,2p)	1.984	2.995	175.1			
Aug-cc-pVDZ	1.940	2.929	162.7			
5						
6-311G(d,p)				2.377	3.281	138.0
6-31+G(d,p)				2.400	3.304	138.1
6-311++G(2d,2p)				2.421	3.323	138.3
ref 2[a]				2.355	3.301	142.3

	SCN−H- - -S═C bond			SC−H- - -S═C bond		
	H- - -S	N- - -S	H- - -S═C	H- - -S	N- - -S	C−H- - -S
6						
6-311G(d,p)	2.424	3.445	173.7			
6-31+G(d,p)	2.426	3.448	173.6			
6-311++G(2d,2p)	2.417	3.435	173.2			
7						
6-311G(d,p)	2.440	3.463	179.9	2.716	3.756	158.9
6-31+G(d,p)	2.447	3.472	179.4	2.725	3.766	158.6
6-311++G(2d,2p)	2.433	3.454	178.9	2.722	3.761	159.2
8						
6-311G(d,p)	2.495	3.448	155.1			
6-31+G(d,p)	2.501	3.459	155.9			
6-311++G(2d,2p)	2.488	3.455	158.4			
9						
6-311G(d,p)	2.468	3.431	157.5			
6-31+G(d,p)	2.482	3.479	165.3			
6-311++G(2d,2p)	2.470	3.463	165.5			
10						
6-311G(d,p)				2.816	3.857	159.2
6-31+G(d,p)				2.821	3.861	158.8
6-311++G(2d,2p)				2.808	3.844	159.0

acceptor and summarized the average hydrogen bond strengths of TFA and FA in Table 4.

FA-FA Dimers. For the most stable cyclic dimer **1**, the association energy is −15.95, −13.62, and −13.12 kcal/mol at the B3LYP level with the 6-311G(d,p), 6-31+G(d,p), and 6-311++G(2d,2p) basis sets, respectively. The BSSE-corrected association energy (E_{ass}) for **1** has been calculated as −12.56, −13.18, and −12.82 kcal/mol with the 6-311G(d,p), 6-31+G(d,p), and 6-311++G(2d,2p) basis sets, respectively. The contribution of the BSSE to the association energies calculated with the 6-31+G(d,p) and 6-311++G(2d,2p) basis sets is very little. The E_{ass} value of **1** is lower than the one calculated using the MP2 method at the complete basis set (CBS) limit which currently provide a best estimate of hydrogen bond energies.[2a] The underestimating effect of the DFT method also holds for **2**−**5** (see Table 1).[3a] The DFT method yields systematically a low association energy on average by 1.3 kcal/mol.

The strength of one OCN−H- - - O═C hydrogen bond could be estimated by dividing the E_{ass} value of **1** by 2, and directly from the E_{ass} values of **3** and **4**. The average values of the OCN−H- - -O═C strength are −6.0 ± 0.3, −6.3 ± 0.3, and −6.1 ± 0.3 kcal/mol with the 6-311G(d,p), 6-31+G(d,p), and 6-311++G(2d,2p) basis sets, respectively, as shown in Table 4. The OC−H- - -O═C hydrogen bond strength was calculated from the E_{ass} value of dimers **2** and **5**. The mean value of the H- - -O═C hydrogen bond strength is −1.9 ± 0.3, −2.4 ± 0.3, and −2.2 ± 0.3 kcal/mol for the 6-311G(d,p), 6-31+G(d,p), and 6-311++G(2d,2p) basis sets, respectively. The average values of the OCN−H- - -O═C and OC−H- - -O═C strength are usually smaller than those estimated at the MP2/CBS level, −7.1 ± 0.2 kcal/mol and −2.6 ± 0.3 kcal/mol, respectively.[2a] However, the difference is less than 1 kcal/mol, suggesting that the DFT calculation could be a suitable method to predict the hydrogen bond strength with a reasonable accuracy.[19]

TFA-TFA Dimers. The association energies with and without correcting the BSSE are very close for the three basis sets. Using the data of **6**, **8,** and **9**, the strength of a SCN−H- - -S═C hydrogen bond was calculated by the same procedure used for

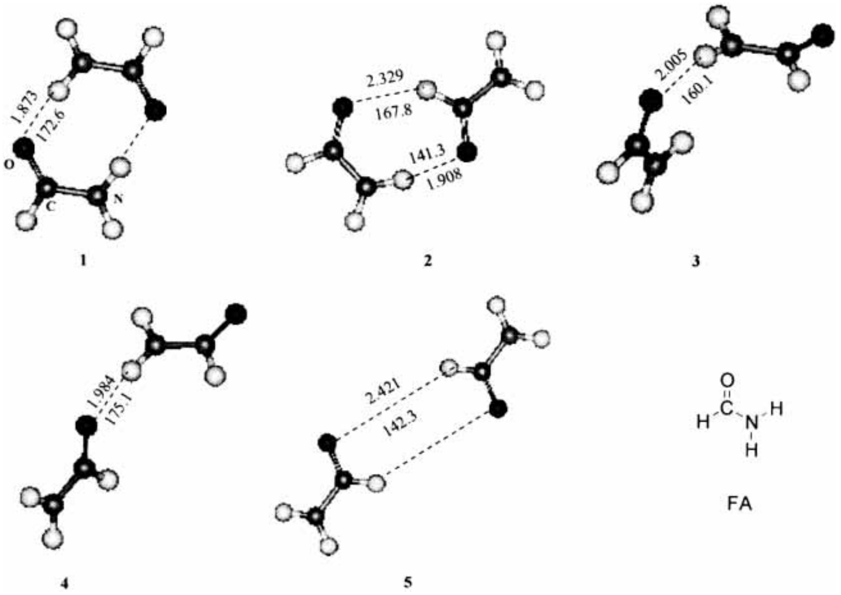

Figure 3. B3LYP/6-311++G(2d,2p)-optimized structures for FA-FA dimers **1**−**5**. The hydrogen bond distances (in Å) and angles (in degree) are displayed.

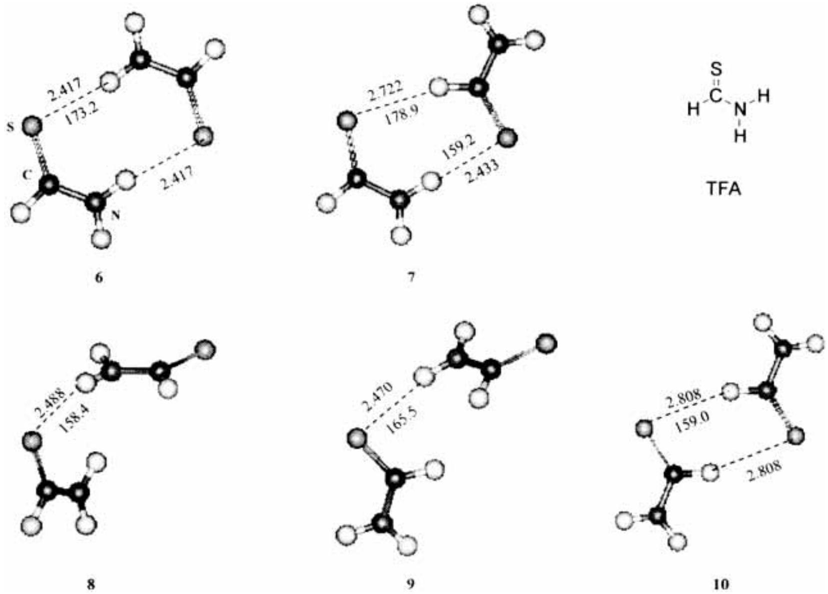

Figure 4. B3LYP/6-311++G(2d,2p)-optimized structures for TFA-TFA dimers **6**−**10**. The hydrogen bond distances (in Å) and angles (in degree) are displayed.

FA dimers. The average hydrogen bond strength is −5.0 ± 0.3, −5.2 ± 0.2, and −5.0 ± 0.1 kcal/mol with the 6-311G(d,p), 6-31+G(d,p), and 6-311++G(2d,2p) basis sets, respectively (see Table 4). This demonstrates that the replacement of the carbonyl oxygen of FA by sulfur atom results in reducing the hydrogen bonding ability by about −1.0 kcal/mol.

The mean strength of a SC−H- - -S═C interaction, calculated by using the data of **7** and **10**, is about −2.2 kcal/mol, regardless of the basis sets. It is surprising that the strengths of the SC−H- - -S═C and OC−H- - -O═C bonds are very similar (see Table 4). This indicates that the thioformyl hydrogen atom of TFA is a good hydrogen bond donor as compared to that of FA, which is supported by the recent work of Borrmann et al. They reported the crystal and liquid structure of *N*,*N*-dimethylthioformamide(DMTF) and *N*,*N*-dimethylformamide (DMF), and suggested that the hydrogen bonding ability for C−H- - -S would be stronger than that for C−H- - -O bonds.[20]

TFA-FA Dimers. The strength of an OCN−H- - -S═C hydrogen bond was calculated using **11**, **14,** and **16**. The mean strength of the OCN−H- - -S═C bond is found in the range −3.8 to −4.8 kcal/mol depending on the basis sets. At the B3LYP/6-31+G(d,p) level, the energy difference between the OCN−H- - -O═C and OCN−H- - - S═C interactions is about 1.6 kcal/mol. This shows that the thiocarbonyl group (S═C) of TFA has the poor hydrogen bond accepting ability relative to the carbonyl group (O═C) of FA, which was consistent with the results of the atomic charges.[11,20] This also holds for the SCN−H- - -S═C in TFA-TFA dimers and the SCN−H- - -O═C interaction in TFA-FA dimers (see Table 3).

The strength of a SCN−H- - -O═C hydrogen bond could be calculated from the data of **11**, **15**, and **17**. The mean strength of the SCN−H- - -O═C interaction is in the range from −7.2 to −7.9 kcal/mol depending on the basis sets. Note that the SCN−H- - -O═C hydrogen bond is stronger than the

TABLE 2: Structural Parameters for the Hydrogen Bonds in Dimers 11−18

	OCN−H- - -S═C bond			SCN−H- - -O═C bond			OCN−H- - -S═C bond			SCN−H- - -O═C bond		
	H- - -S	N- - -S	H- --S═C	H- - -O	N- - -O	H- --O═C	H- - -S	C- - -S	C−H- - -S	H- - -O	C- - -O	C−H- - -O
11												
6-311G(d,p)	2.457	3.474	172.5	1.831	2.857	175.3						
6-31+G(d,p)	2.443	3.464	173.1	1.844	2.872	175.8						
6-311++G(2d,2p)	2.433	3.450	173.5	1.842	2.865	175.5						
12												
6-311G(d,p)	2.491	3.493	167.2							2.145	3.199	161.3
6-31+G(d,p)	2.481	3.488	167.8							2.174	3.223	159.8
6-311++G(2d,2p)	2.463	3.469	168.8							2.186	3.232	160.3
13												
6-311G(d,p)				1.847	2.874	178.7	2.900	3.779	136.8			
6-31+G(d,p)				1.864	2.893	178.3	2.867	3.761	138.2			
6-311++G(2d,2p)				1.867	2.891	178.9	2.866	3.765	139.0			
14												
6-311G(d,p)	2.571	3.495	150.7									
6-31+G(d,p)	2.568	3.498	151.4									
6-311++G(2d,2p)	2.548	3.488	153.6									
15												
6-311G(d,p)				1.922	2.912	162.3						
6-31+G(d,p)				1.948	2.957	169.9						
6-311++G(2d,2p)				1.951	2.955	169.0						
16												
6-311G(d,p)	2.546	3.487	154.0									
6-31+G(d,p)	2.530	3.517	163.7									
6-311++G(2d,2p)	2.517	3.499	163.2									
17				1.900	2.907	168.5						
6-311G(d,p)				1.935	2.954	177.0						
6-31+G(d,p)				1.940	2.955	176.4						
6-311++G(2d,2p)												
18												
6-311G(d,p)							3.114	3.944	132.5	2.195	3.244	160.3
6-31+G(d,p)							3.031	3.898	135.7	2.237	3.278	158.4
6-311++G(2d,2p)							3.001	3.887	137.0	2.252	3.300	158.7

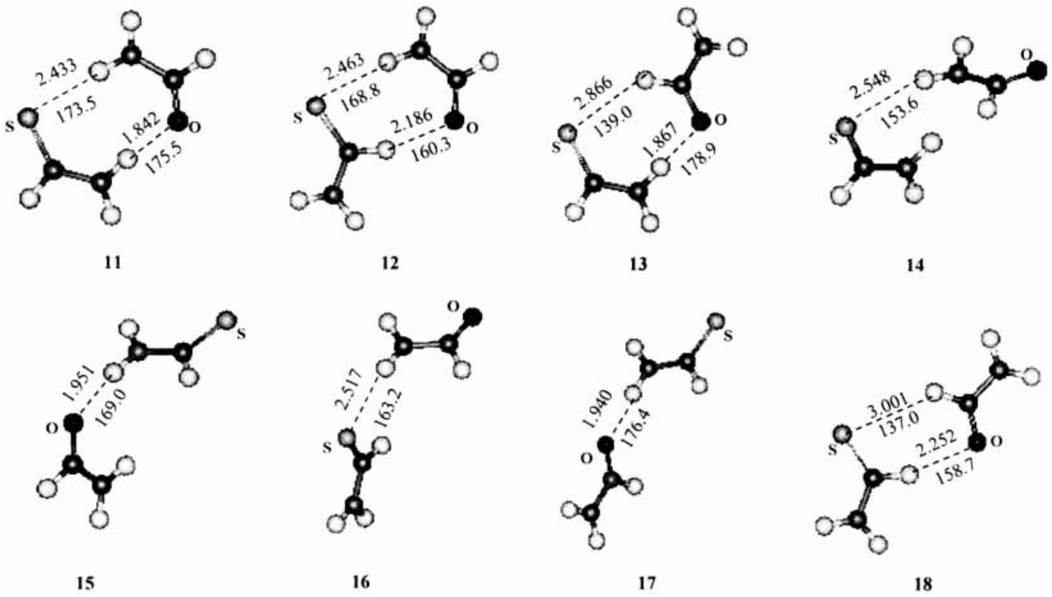

Figure 5. B3LYP/6-311++G(2d,2p)-optimized structures for TFA-FA or FA-TFA dimers **11**−**18**. The hydrogen bond distances (in Å) and angles (in degree) are displayed.

OCNH- - -O═C interaction. At the B3LYP/6-31+G(d,p) level, the energy difference between the SCN−H- - -O═C and the OCN−H- - -O═C bonds is about 1.9 kcal/mol. Remarkably, the B3LYP/6-31+G(d,p) and B3LYP/6-311++G(2d,2p) calculations predict the strength of the SCN−H- - -S═C and OCN−H- - -S═C hydrogen bonds to be similar. As shown in Table 4, the energy difference between two hydrogen bonds at the two levels of theory is in the range 0.2−0.5 kcal/mol. The B3LYP/6-311G(d,p) calculation predicts the more favorable SCN−H- - -S═C bond than the OCN−H- - -S═C bond by about 1.2 kcal/mol. The results indicate that TFA is the good hydrogen bond donor compared to FA.

Our results are consistent with a recent work of Alemán on the amide−amide and amide−thioamide interactions using model compounds, *N*-methylacetamide (NMA) and *N*-methylthioacetamide (NMTA).[11] At the MP2/6-311G(d,p)//MP2/6-31G(d) level of theory, the BSSE-corrected association energy of OCN−H- - -O═C in NMA-NMA, SCN−H-- -O═C in NMTA-NMA, and OCN−H- - -S═C in NMA-NMTA is −6.6 kcal/mol, −7.4 kcal/mol, and −4.6 kcal/mol, respectively,

TABLE 3: Electronic Association Energies (kcal/mol) for the Formation of FA and TFA Dimers as a Function of Basis Sets

	B3LYP/6-311G(d,p)		B3LYP/6-31+G(d,p)		B3LYP/6-311++G(2d,2p)		MP2/aug-cc-pVDT [a]	
	w/o BSSE	w/BSSE	w/oBSSE	w/BSSE	w/o BSSE	w/BSSE	w/o BSSE	w/BSSE
				FA-FA Dimers				
1	−15.95	−12.56	−13.62	−13.18	−13.12	−12.82	−15.80	−14.68
2	−10.87	−8.01	−9.03	−8.75	−8.55	−8.31	−10.81	−9.01
3	−8.63	−6.04	−6.46	−6.15	−6.09	−5.89	−8.63	−6.22
4	−7.72	−5.69	−6.42	−6.15	−6.04	−5.87	−7.66	−5.77
5	−5.63	−3.35	−4.28	−4.09	−3.96	−3.79	−5.97	−4.61
				TFA-TFA Dimers				
6	−10.39	−9.77	−10.12	−9.96	−10.01	−9.77		
7	−7.64	−7.16	−7.52	−7.42	−7.41	−7.13		
8	−6.25	−5.08	−5.46	−5.24	−5.26	−5.04		
9	−5.76	−4.99	−5.36	−5.26	−5.26	−5.09		
10	−4.36	−4.07	−4.41	−4.37	−4.33	−4.95		
				TFA-FA Dimers				
11	−13.56	−11.54	−12.17	−11.84	−11.86	−12.11		
12	−9.21	−7.39	−8.06	−7.91	−7.86	−8.09		
13	−10.26	−8.64	−9.07	−8.75	−8.65	−8.38		
14	−6.44	−4.07	−5.34	−5.05	−5.12	−4.92		
15	−9.11	−7.71	−7.11	−6.84	−6.70	−6.92		
16	−5.04	−3.22	−4.58	−4.29	−4.52	−4.34		
17	−8.99	−7.91	−7.40	−7.30	−6.95	−7.20		
18	−5.55	−4.18	−4.59	−4.47	−4.37	−4.15		

[a] Ref 2.

TABLE 4: The Average Hydrogen Bond Strengths for Formamide and Thioformamide Calculated on the Basis of the Dimers 1−18

	6-311G(d,p)		6-31+G(d,p)		6-311++G(2d,2p)	
	w/o BSSE	w/BSSE	w/o BSSE	w/BSSE	w/o BSSE	w/BSSE
OCN−H- - -O=C	−8.1 ± 0.5	−6.0 ± 0.3	−6.6 ± 0.2	−6.3 ± 0.3	−6.2 ± 0.3	−6.1 ± 0.3
SCN−H- - -S=C	−5.7 ± 0.3	−5.0 ± 0.1	−5.3 ± 0.2	−5.2 ± 0.2	−5.2 ± 0.2	−5.0 ± 0.1
OCN−H- - -S=C	−5.1 ± 0.9	−3.8 ± 0.5	−4.9 ± 0.3	−4.7 ± 0.4	−4.9 ± 0.3	−4.8 ± 0.3
SCN−H- - -O=C	−8.4 ± 0.9	−7.9 ± 0.4	−7.2 ± 0.3	−7.1 ± 0.4	−6.9 ± 0.3	−7.3 ± 0.4
OC−H- - -O=C	−2.8 ± 0.4	−1.9 ± 0.3	−2.4 ± 0.2	−2.4 ± 0.3	−2.2 ± 0.3	−2.2 ± 0.3
SC−H- - -S=C	−2.0 ± 0.5	−2.2 ± 0.1	−2.2 ± 0.2	−2.2 ± 0.1	−2.2 ± 0.1	−2.2 ± 0.2
OC−H- - -S=C	−1.6 ± 0.9	−0.7 ± 0.4	−1.7 ± 0.4	−1.5 ± 0.4	−1.6 ± 0.3	−1.0 ± 0.3
SC−H- - -O=C	−4.0 ± 0.9	−3.5 ± 0.5	−2.9 ± 0.4	−3.0 ± 0.4	−2.8 ± 0.3	−3.1 ± 0.3

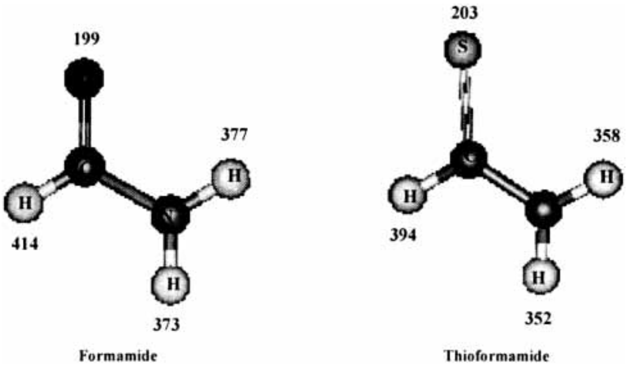

Figure 6. Proton affinities calculated at the B3LYP/6-31G(d) level for all sites of FA and TFA.

showing that thioamide has a stronger hydrogen-bond donating ability but a weaker accepting ability than amide.

The OC−H- - -S=C hydrogen bond strength is calculated using the data of **13** and **18**. The mean hydrogen bonding strength is −1.5 ± 0.4 kcal/mol at the B3LYP/6-31+G(d,p) level, which is comparable to the strength of an OC−H- - -O=C hydrogen bond, −2.4 ± 0.3 kcal/mol. In contrast, the hydrogen bonding strength of a SC−H- - -O=C interaction, calculated from the data of **12** and **18**, is high as −3.0 ± 0.4 kcal/mol at the B3LYP/6-31+G(d,p) level. The results clearly demonstrate that the thioformyl hydrogen atom of TFA is a good hydrogen bond donor relative to that of FA.[20] This is also true for the SC−H- - -S=C and OC−H- - -S=C hydrogen bonding interactions (see Table 4).

3.3. Relationship between Proton Affinities and the Hydrogen Bond Strengths. Hydrogen bonding ability relates to the basicity of the acceptor and the acidity of the donor. The acceptor basicity could be predicted by the proton affinity (PA).[19,21] We calculated the PA value of the carbonyl oxygen (O-site) in FA and the thiocarbonyl sulfur (S-site) in TFA at the B3LYP/6-31G(d) level. Figure 6 displays the calculated PA value of O-site in FA and of S-site in TFA. The PA value of FA and TFA is 199 and 203 kcal/mol, respectively. This indicates that the formation of the protonated TFA is more favorable than that of protonated FA.[17,22] Recently, Ghanty and Ghosh explained this preferable protonation at the sulfur atom of TFA through the calculated Fukui reactivity indices.[22] Although the S-site of TFA has a stronger basicity than the O-site of FA, we noticed, TFA could form the weaker hydrogen bonds than FA. Thus, the strengths of N−H- - -S=C (or C−H- - -S=C) and N−H- - -O=C (or C−H- - -O=C) hydrogen bonding interaction is not directly correlated with the PA values of FA and TFA.

The acidity of the hydrogen bond donors has been estimated by calculating the PA value of the deprotonated conjugate anions for FA and for TFA.[3a] The six anions of the deprotonated FA and TFA were examined as displayed in Figure 6. For the two N−H groups, the PA values of the FA anions are 377 and 373 kcal/mol while those of the TFA anions are 358 and 352 kcal/mol, at the B3LYP/6-31G(d) level. For the C−H group, the

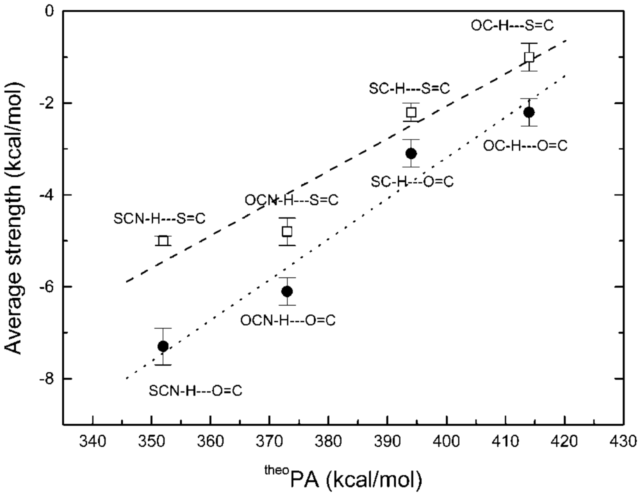

Figure 7. A plot of the PA values of TFA and FA anions versus the average strengths of hydrogen bonds at the B3LYP/6-311++G(2d,2p) level.

respective PA value of the FA and TFA anions is 414 and 394 kcal/mol. Here the PA values of FA and TFA anions versus the hydrogen bond strengths of the N−H- - -O(S)═C and C−H- - -O(S)═C have been plotted as shown in Figure 7, showing a remarkable linear correlation. In particular, the N(C)−H- - -O═C hydrogen bond shows a good linearity. Vargas et al. also noticed the relation between the hydrogen bond strengths and the experimental (or theoretical) proton affinities.[3a] Thus, we suggest that the PA values of the deprotonated TFA and FA anions would be a benchmark for their abilities as hydrogen bond donors.

4. Conclusion

We obtained the hydrogen bonding strengths of TFA and FA as a hydrogen bond donor or acceptor using the DFT method with the 6-311G(d,p), 6-31+G(d,p), and 6-311++G-(2d,2p) basis sets. On the basis of the 18 minimum energy structures for FA-FA, TFA-FA, and TFA-FA dimers, the hydrogen bonding abilities of FA and TFA were disclosed. As a hydrogen bond acceptor, TFA is weaker than FA; however, TFA is a strong hydrogen bond donor as compared to FA.[11] The SCN−H- - -O═C hydrogen bond is more favorable than the OCN−H- - -O═C hydrogen bond by about 2 kcal/mol. The SC−H- - -O═C hydrogen bond is stronger than the OC−H- - -O═C hydrogen bond by about 1 kcal/mol.

The proton affinities of FA and TFA were calculated at the B3LYP/6-31G(d) level. The relation between the PA value and the hydrogen bond strength was investigated. The stronger basicity of TFA at S site than that of FA at O-site cannot explain the weaker strength of N−H- - -S═C (or C−H- - -S═C) than that of N−H- - -O═C (or C−H- - -O═C) hydrogen bond. We found that the PA values of the deprotonated TFA and FA anions have a linear correlation with the ability as hydrogen bond donors. These data could be useful to understand the stability of the designed peptide secondary structure, containing the thioamide functional group.[23]

Acknowledgment. This work was supported by grants from the Korea Research Foundation (2001-037-DA0016, 2001-015-DPO217).

Supporting Information Available: Table S1 contains the B3LYP/6-311++G(2d, 2p)-optimized geometries for **1**−**18**. This information is available free of charge via the Internet at http://pubs.acs.org.

References and Notes

(1) (a) Marigliano, A. C. G.; Varetti, E. L. *J. Phys. Chem. A* **2002**, *106*, 1100. (b) Desfrancois, C.; Perquet, V.; Carles, S.; Schermann, J. P.; Andamowicz, L. *Chem. Phys.* **1998**, *239*, 475. (c) Gung, B. W.; Zhu, Z. *Tetrahedron Lett.* **1996**, *37*, 2189. (d) Gardner, R. R.; Gellman, S. H. *J. Am. Chem. Soc.* **1995**, *117*, 10411. (e) Eberhardt, E. S.; Raines, R. T. *J. Am. Chem. Soc.* **1994**, *116*, 2149. (f) Gellman, S. H.; Dado, G. P.; Liang, G.-B.; Adams, B. R. *J. Am. Chem. Soc.* **1991**, *113*, 1164. (g) Sneddon, S. F.; Tobias, D. J.; Brooks, C. L., III. *J. Mol. Biol.* **1989**, *209*, 817.

(2) (a) Vargas, R.; Garza, J.; Friesner, R. A.; Stern, H.; Hay, B. P.; Dixon, D. A. *J. Phys. Chem. A* **2001**, *105*, 4963. (b) Buck, M.; Karplus, M. *J. Phys. Chem. B* **2001**, *105*, 11000. (c) Kobko, N.; Paraskevas, L.; Rio, E. D.; Dannenberg, J. J. *J. Am. Chem. Soc.* **2001**, *123*, 4348. (d) Kang, Y. K. *J. Phys. Chem. B* **2000**, *104*, 8321. (e) Gresh, N.; Guo, H.; Salahub, D. R.; Roques, B. P.; Kafafi, S. A. *J. Am. Chem. Soc.* **1999**, *121*, 7885. (f) Ben-Tal, N.; Sitkoff, D.; Topol, I. A.; Yang, A.-S.; Burt, S. K.; Honig, B. *J. Phys. Chem. B* **1997**, *101*, 450. (g) Suhai, S. *J. Phys. Chem.* **1996**, *100*, 3950. (h) Adalsteinsson, H.; Maulitz, A. H.; Bruice, T. C. *J. Am. Chem. Soc.* **1996**, *118*, 7689. (i) Hobza, P.; Šponer, J. *J. Mol. Struct. (THEOCHEM)* **1996**, *388*, 115. (j) Yoon, C.-J.; Choi, Y.-K.; Choi, Y.-S.; Gothe, S. A. *Bull. Korean Chem. Soc.* **1996**, *17*, 209. (k) Florián, J.; Leszczynski, J.; Johnson, B. G. *J. Mol. Struct.* **1995**, *349*, 421. (l) Florian, J.; Johnson, B. G. *J. Phys. Chem.* **1995**, *99*, 5899. (m) Hong, G.; Karplus, M. *J. Phys. Chem.* **1992**, *96*, 7273. (n) Tobias, D. J.; Sneddon, S. F.; Brooks, C. L., III. *J. Mol. Biol.* **1992**, *227*, 1244. (o) Novoa, J. J.; Whangbo, M. H. *J. Am. Chem. Soc.* **1991**, *113*, 9017. (p) Wojcik, M. J.; Hirakawa, A. Y.; Tsuboi, M.; Kato, S.; Morokuma, K. *Chem. Phys. Lett.* **1988**, *143*, 450. (q) Sapse, A. M.; Fugler, L. M.; Cowburn, D. *Int. J. Quantum Chem.* **1986**, *29*, 1241. (r) Peters, D.; Peters, J. *J. Mol. Struct.* **1980**, *68*, 255. (s) Yamabe, S.; Kitaura, K.; Nishimoto, K. *Theor. Chim. Acta* **1978**, *47*, 11 (t) Johansson, A.; Kollman, P.; Rothenberg, S.; McKelvey, J. *J. Am. Chem. Soc.* **1974**, *96*, 3794. (u) Dreyfus, M.; Maigret, B.; Pullman, A. *Theor. Chim. Acta* **1970**, *17*, 109.

(3) (a) Vargas, R.; Garza, J.; Dixon, D. A.; Hay, B. P. *J. Am. Chem. Soc.* **2000**, *122*, 4750, and references therein. (b) Sandrone, G.; Dixon, D. A.; Hay, B. P. *J. Phys. Chem. A* **1999**, *103*, 3554. (c) Desfrancois, C.; Periquet, V.; Carles, S.; Schermann, J. P.; Adamowics, L. *Chem. Phys.* **1998**, *239*, 475. (d) Neuheuser, T.; Hess, B. A.; Reutel, C.; Weber, E. *J. Phys. Chem.* **1994**, *98*, 6459.

(4) (a) Senes, A.; Ubarretxena-Belandia, I.; Engelman, D. M. *Proc. Natl. Acad. Sci. U.S.A.* **2001**, *98*, 9056. (b) Charkrabarti, P.; Chakrabarti, S. *J. Mol. Biol.* **1998**, *284*, 867. (c) Bella, J.; Berman, H. M. *J. Mol. Biol.* **1996**, *264*, 734. (d) Derewenda, Z. S.; Lee, L.; Derewenda, U. *J. Mol. Biol.* **1995**, *252*, 248. (e) Derewenda, Z. S.; Derewenda, U.; Kobos, P. M. *J. Mol. Biol.* **1994**, *241*, 83.

(5) (a) Nakagawa, Y.; Irie, K.; Ohigashi, H.; Hayashi, H.; Wender, P. A. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 2087. (b) Zacharie, B.; Lagraouti, M.; Dimarco, M.; Penney, C. L.; Gagnon, L. *J. Med. Chem.* **1999**, *42*, 2046 (c) Varma, R. S.; Kumar, D. *Org. Lett.* **1999**, *1*, 697. (d) Brain, C. T.; Hallett, A.; Ko, S. Y. *J. Org. Chem.* **1997**, *62*, 3808. (e) Clausen, K.; Spatola, A. F.; Lemieux, C.; Schiller, P. W.; Lawesson, S.-O. *Biochem. Biophys. Res. Commun.* **1984**, *120*, 305.

(6) Artis, D. R.; Lipton, M. A. *J. Am. Chem. Soc.* **1998**, *120*, 12200, and references therein.

(7) (a) Tran, T. T.; Burgess, A. W.; Treutlein, H.; Perich, J. *J. Peptide Res.* **2001**, *58*, 67. (b) Pedireddi, V. R.; Chatterjee, S.; Ranganathan, A.; Rao, C. N. R. *J. Am. Chem. Soc.* **1997**, *119*, 10867.

(8) Tran, T. T.; Treutlein, H.; Burgess, A. W. *J. Comput. Chem.* **2001**, *22*, 1026.

(9) Laurence, C.; Berthelot, M.; Le Questel, Y. J.; El Ghomari, M. L. *J. Chem. Soc., Perkin Trans.* **1995**, *2*, 2075.

(10) (a) Kim, N.-K.; Lee, H.-J.; Choi, K.-H.; Yu, J.-A.; Yoon, C.-J.; Park, J.; Choi, Y.-S. *J. Phys. Chem. A* **2000**, *104*, 5572. (b) Kim, K.-Y.; Lee, H.-J.; Karpfen, A.; Park, J.; Yoon, C.-J.; Choi, Y.-S. *Phys. Chem. Chem. Phys.* **2001**, *3*, 1973.

(11) Alemán, C. *J. Phys. Chem. A* **2001**, *105*, 6717.

(12) (a) Min, B. K.; Lee, H.-J.; Choi, Y. S.; Park, J.; Yoon, C.-J.; Yu, J.-A. *J. Mol. Struct.* **1998**, *471*, 283. (b) Shaw, R. A.; Kollát, E.; Hollósi, M.; Mantsch, H. H. *Spectrochim. Acta* **1995**, *51A*, 1399. (c) Hollósi, M.; Zewdu, M.; Kollát, E.; Majer, Z.; Kajtár, M.; Batta, G.; Kövér, K.; Sándor, P. *Int. J. Peptide Protein Res.* **1990**, *36*, 173. (d) Sherman, D. B.; Spatola, A. F. *J. Am. Chem. Soc.* **1990**, *112*, 433.

(13) (a) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648. (b) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B* **1988**, *37*, 785.

(14) (a) Petersson, G. A.; Bennett, A.; Tensfeldt, T. G.; Al-Laham, M. A.; Shirley, W. A.; Mantzaris, J. *J. Chem. Phys.* **1988**, *89*, 2193. (b) Petersson, G. A.; Al-Laham, M. A. *J. Chem. Phys.* **1991**, *94*, 6081. (c) Hehre, W. J.; Radom, L.; Schleyer, P. v. R.; Pople, J. A. *Ab initio Molecular Orbital Theory*; Wiley: New York, 1986.

(15) Frisch, M. J.; Trucks, G. W.; Schlegel, G. B.; Gill, P. M. W.; Johnson, B. G.; Robb, M. A.; Cheeseman, J. R.; Keith, T.; Petersson, G. A.; Montgomery, J. A.; Raghavachari, K.; Al-Lagam, M. A.; Zakrzewski, V. G.; Ortiz, J. V.; Foresman, J. B.; Cioslowski, J.; Stefanov, B. B.; Nanayakkara, A.; Challacome, M.; Peng, C. Y.; Ayala, P. Y.; Chen, W.; Wong, M. W.; Anders, J. L.; Replogle, E. S.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Binkley, J. S.; Defrees, D. J.; Baker, J.; Stewart, J. P.; Head-Gordon, M.; Gonzalez, C.; Pople, J. A. *Gaussian 94*; Gaussian Inc.: Pittsburgh, PA, 1995.

(16) Boys, S. F.; Bernardi, F. *Mol. Phys.* **1970**, *19*, 553.

(17) Ou, M. C.; Chu, S. Y. *J. Phys. Chem.* **1995**, *99*, 556.

(18) (a) Kim, W.; Lee, H.-J.; Choi, Y.-S.; Choi, J.-H.; Yoon, C.-J. *J. Chem. Soc., Faraday Trans.* **1998**, *94*, 2663. (b) Lauvergent, D.; Hiberty, P. C. *J. Am. Chem. Soc.* **1997**, *119*, 9478. (c) Glendening, E. D.; Hrabal, J. A., II. *J. Am. Chem. Soc.* **1997**, *119*, 12940. (d) Laidig, K. E.; Cameron, L. M. *J. Am. Chem. Soc.* **1996**, *118*, 1737. (e) Wiberg, K. B.; Rablen, P. R. *J. Am. Chem. Soc.* **1995**, *117*, 2201.

(19) (a) Tsuzuki, S.; Houjou, H.; Nagawa, Y.; Goto, M.; Hiratani, K. *J. Am. Chem. Soc.* **2001**, *123*, 4255. (b) Choi, K.-H.; Lee, H.-J.; Karpfen, A.; Yoon, C.-J.; Park, J.; Choi, Y.-S. *Chem. Phys. Lett.* **2001**, *345*, 338.

(20) Borrmann, H.; Persson, I.; Sandström, M.; Stålhandske, C. M. V. *J. Chem. Soc., Perkin Trans. 2* **2000**, 393.

(21) (a) Gu, Y.; Kar, T.; Scheiner, S. *J. Am. Chem. Soc.* **1999**, *121*, 9411. (b) Rablen, P. R.; Lockman, J. W.; Jorgensen, W. L. *J. Phys. Chem. A* **1998**, *102*, 3782. (c) Kim, K.; Friesner, R. A. *J. Am. Chem. Soc.* **1997**, *119*, 12952. (d) Rovira, M. C.; Novoa, J. J.; Whangbo, M.-H.; Williams, J. M. *Chem. Phys.* **1995**, *200*, 319.

(22) Ghanty, T. K.; Ghosh, S. K. *J. Phys. Chem. A* **2000**, *104*, 2975.

(23) Miwa, J. H.; Patel, A. K.; Vivatrat, N.; Popek, S. M.; Meyer, A. M. *Org. Lett.* **2001**, *3*, 3373−3375.