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Ab Initio Study of Substitution Effect and Catalytic Effect of Intramolecular Hydrogen Transfer of N-Substituted Formamides

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Intramolecular hydrogen transfer of N-substituted formamides has been examined by ab initio theoretical calculation. The potential surfaces, the global isomeric structures, and the transition geometries of intramolecular hydrogen transfer were determined at the MP2/6-31+G** level of calculation. The energy was further analyzed by a single point calculation, MP2/6-311++G**//MP2/6-31+G**, and the use of G2 theory. There are E and Z conformations in each substituted derivative. The calculated energy barrier for the intramolecular hydrogen transfer (carbon−hydrogen to the carbonyl oxygen) of formamide is 76.14 kcal/mol. The Z form of N-substituted formamides (regardless of the type of substituents, CH_3, OH, and OCH_3) all have lower barriers; nevertheless, the E form counterparts show significant substitution effect. The methyl group decreases the barrier by 1.35 kcal/mol, while the hydroxy and methoxy groups increase the barriers by 2.40 and 1.69 kcal/mol, respectively. The catalytic effect achieved by the added H_2O or NH_3 molecule to the formamides is substantial. Energy barriers decrease around 26.5∼30.1 kcal/mol in most of the complexes and the transfer mechanism of each complex is concerted.

Introduction

A lot of theoretical and experimental studies[1−20] have been performed on the formamide molecule. It is frequently used as a model to understand the properties of peptide-bond containing material, such as the proton transfer in protein[19] and the hydrolysis of the peptide bond in biological systems.[20] Considered as the smallest peptide linkage prototype (HNC═O) the formamide molecule contains two basic centers which can accept a proton separately.

The structure of formamide, planar or nonplanar, is still a debated issue. Evans[12] considered it as nonplanar from a low-resolution infrared absorption spectrum, while Kurland et al.[13] thought it to be planar from a microwave spectrum of four isotopic species. Costain et al.[15] and Evans[14] all further confirmed the nonplanar structure by performing a microwave spectrum analysis of 10 isotopic species and high-resolution infrared absorption spectrum, respectively. Radom et al.[18] also gave a nonplanar result by carrying out a theoretical calculation. The inversion barrier of NH_2 was very low and this near flat energy surface led to a structure close to planar. Kwiatkowski et al.[21] performed a theoretical study on the relative stability of nucleic acid base tautomers of uracil and guanine. Formamide was used as a model to mimic the HNCO peptide-linkage in these amino acids. Tortajada et al.[3] performed a high-level ab initio calculation to investigate the potential energy surfaces corresponding to the protonation of formamide and to formamide's association to different metal monocations, Li^+, Na^+, Mg^+, and Al^+. The structures, relative stabilities, and gas-phase reactivities of its tautomers, formamidic acid (HN═CHOH) and aminohydroxy carbene (H_2NCOH), were also investigated. The energy barrier for the formamide−formamidic acid isomerization was estimated by Wang et al.[2] to be 48.9 kcal/mol, and reduced to 22.6 kcal/mol when it was catalyzed with a single H_2O molecule. An estimation for the isomerization barrier for formamide−aminohydroxy carbene has been reported to be 77 kcal/mol[22] and more accurately as 72.5 kcal/mol by the G2 method.[1] Bitterevora et al.[23] calculated the hydrogen transfer energy barrier of HCO → COH to be 66.8 kcal/mol by the SCF method. Comparison of these two data shows that the attachment of NH_2 group to the formyl radical (HCO) increases this transfer barrier (HCO → COH) by around 6 kcal/mol. The effect of substitution on the proton transfer energy barrier has been studied in our previous report.[24] Generally, an electron-releasing group such as CH_3 would decrease the barrier, while an electron withdrawing group would increase it. Additionally, the position and the geometry of the substitution in the molecule also affect the barrier. *N*-Methyl formamide (MF) has been studied widely.[25−49] It can be used as a drug combined with ultrasound to kill cultured HL-60 human promyelocytic leukemia cells.[36] The underlying mechanism is still unknown; however, it has been suggested that the formation is by virtue of longer lifetime and higher selectivity likely to be the radical species $^{\bullet}CH_2$-NHCHO and $^{\bullet}$NHCHO rather than the $^{\bullet}$OH radical in the sonic solution were responsible for sonodynamic cell killing. The radicals can be released by the combined effect of ultrasound, $CH_3NHCHO \rightarrow {}^{\bullet}CH_3 + {}^{\bullet}NHCHO$, and $CH_3NHCHO + {}^{\bullet}OH \rightarrow {}^{\bullet}CH_2NHCHO + H_2O$.

We have reported the tautomerism of hydroxamic acid (NHOHCHO ↔ NOHCHOH).[50] However, the isomerization barrier, NHOHCHO → NHOHCOH, has not been studied yet. We are interested in a systematic study, using high-level ab initio techniques to examine the potential energy surfaces of intramolecular hydrogen transfer in N-substituted formamide, including *N*-methyl (MF), *N*-hydroxy (OF) and *N*-methoxy (MO) formamides. This study would provide useful information

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to understand the substitution effect (including the electron-withdrawing and -releasing substituents) to the transfer barriers. Our definition of electron-releasing and -withdrawing substituents in the system is as follows. The methyl group causing the electron flow of the system heading toward the carbonyl direction via the nitrogen atom is called electron-releasing substituent, while the other two groups, OH and OCH_3, causing the electron-flow heading toward the opposite direction, are called electron-withdrawing substituents. The significance of the catalytic effect introduced in the presence of one H_2O or NH_3 molecule is also examined in this paper.

Method of Calculation

The ab initio molecule orbital calculations were carried out by using the Gaussian 94 program package.[55] Geometric optimization of all the proposed structures and tautomers were evaluated at MP2/6-31+G** level. The harmonic vibrational frequencies of the different stationary points on the potential energy surface have been calculated at this level in order to identify the local minima and the transition states. The obtained final geometries were further calculated at the MP2/6-311++G**//MP2/6-31+G** level to have as reliable energetics as possible. Zero-point energy (ZPE) was also considered. The transfer of hydrogen from the carbon atom of formamide to the carbonyl oxygen was performed first. Local minima and the transition point were then determined. The same scheme was applied to the N-substituted formamide derivatives and the calculated energetic data were compared. The catalytic effect to the hydrogen transfer barrier of N-substituted formamides was evaluated by adding one H_2O or NH_3 molecule to the N-substituted system. The stationary points can also be located and the energetics compared.

Results and Discussion

To simplify the nomenclature of the studied molecules a one- or two-character notation is applied to each molecule as shown in Figure 1. The process of transfering a hydrogen from a nitrogen atom to the carbonyl oxygen of formamide is denoted as path F_N, while the similar process from the carbon atom is denoted as path F_C. MF represents *N*-methyl formamide, OF for *N*-hydroxy formamide (formohydroxamic acid), MO for *N*-methoxy formamide, W for the H_2O molecule, and A for the NH_3 molecule. The subscript Z represents a Z-form conformer and subscript E for E-form conformer. The "#" represents the transition state of the hydrogen transfer and that of "*" represents the final structure that the hydrogen being shifted to the oxygen atom, shown in Figure 2 to Figure 5.

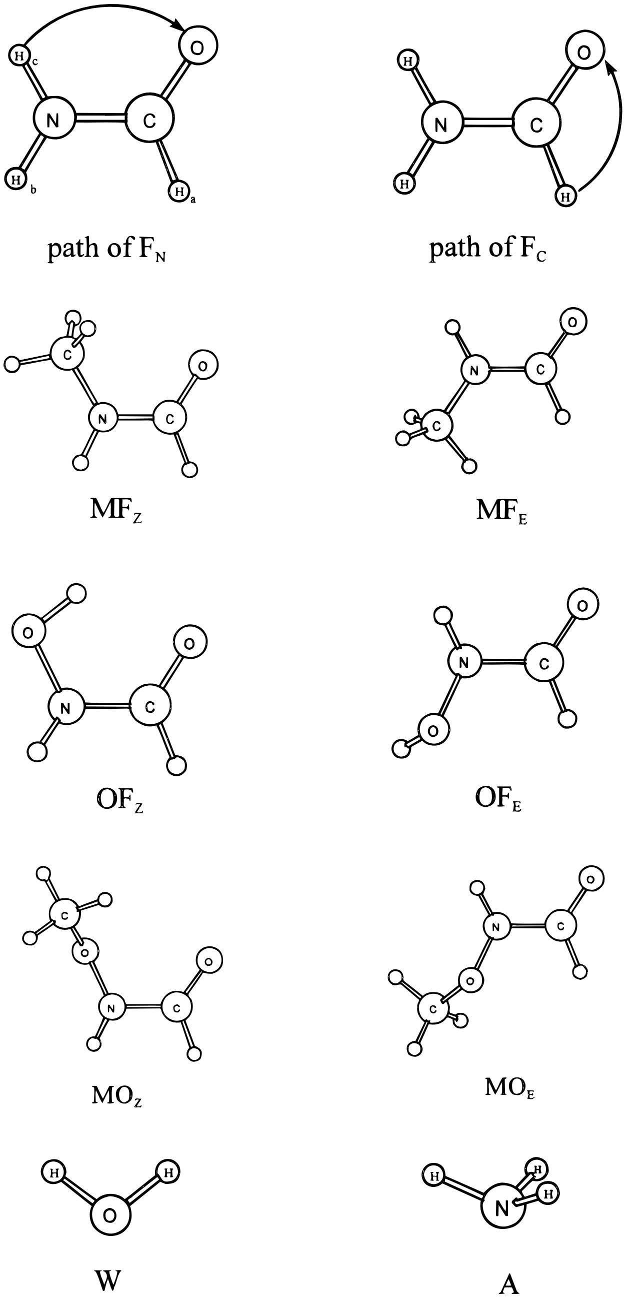

Figure 1. A one- or two-character notation is applied to each isomer to simplify the nomenclature.

Geometries. At first we performed path F_N calculation at several different levels for the formamide molecule and compared the calculated results with the literature data in order to choose which level would yield satisfactory agreement. The bond lengths and bond angles of formamide obtained from geometric optimization at HF/6-31G*, MP2/6-31G*, and MP2/6-31+G** levels are listed in columns 2, 3, and 4 of Table 1. Some other calculations and experimental data from the literature are listed in columns 5, 6, 7, and 8, as a comparison. The optimized geometric structures were shown in the upper part of Figure 2. The calculated structural data (MP2/6-31+G**) of other two stationary points ($F_N^{\#}$ and F_N^{*}) as well as other referred calculations were also listed in the right-hand portion of Table 1. Among all the listed levels of calculation, the set of MP2/6-31+G** data best approaches the calculation done using G2 theory.[3] Intramolecular hydrogen transfer via path F_C for formamide and other N-substituted formamides were then carried out at this level. The calculated relative energies for the tautomers of formamide following paths F_N and F_C are listed in Table 2. Path F_C needs to overcome a much higher barrier to form another unstable tautomer F_C*. Hydrogen transfer schemes from carbon atom to carbonyl oxygen in N-substituted formamide derivatives are shown in Figures 2 and 3. These three schemes (each has Z and E forms) have some similar structural alteration when they reach the transition states. Bond length R(H−C) increases gradually from 1.10 to 1.23 Å, and the bond angle ∠HCO decreases from 124.7° to 56.5°. The R(C−N) bond length decreases but R(C−O) increases. Dihedral angles, D(CNCO) of MF, D(ONCO) of OF and MO, and D(HNCO) of all three compounds approach 0° or 180°; that is, the bonding structure of nitrogen shifts from nonplanar to planar. Some dissimilar structural changes also occur. The methyl group in Z-form *N*-methyl formamide (MF_Z) rotates during the transfer. Originally the dihedral angle $D(H_aCNC)$ was 50.0°, and shifted

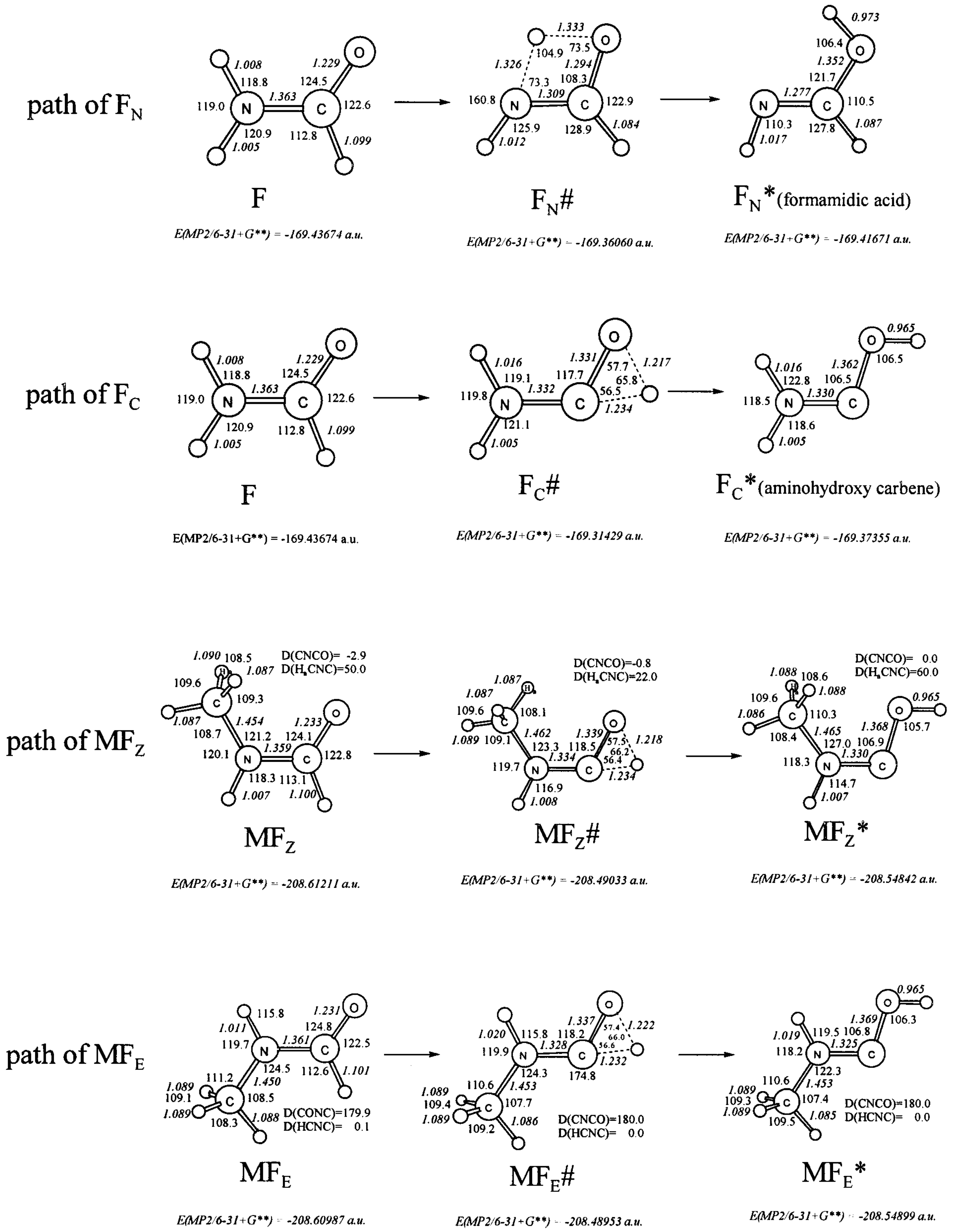

Figure 2. The geometric diagram of hydrogen transfer of formamide in two different paths (F$_N$ and F$_C$). "#" represents transition structure and "*" the final product of the transfer. The calculated transfer schemes of Z and E forms of *N*-methyl formamide are also presented.

to 22.0° in the transition state (MF$_Z$$^\#$), then went back to 60° when the transfer completed (MF$_Z$*). A weak H-bonding forms between methyl-hydrogen and the oxygen atom in the transition structure. Therefore the dihedral angle shifts to a smaller angle to keep the H, C, N, C, and O atoms being closer on the same plane as much as possible. As the transfer completes the O−H bond forms and the weak H-bonding disappears, so that the dihedral angle returns to 60°. The other E form conformation, MF$_E$, does not rotate the methyl group during the transfer. The dihedral angle does not change in the transition state, since the methyl group is far away (on the other side) from the carbonyl oxygen; and hence no interaction occurs in between. Formohydroxamic acid also has two geometric isomers, OF$_Z$ and OF$_E$. Their hydrogen transfer schemes and energetics are shown in

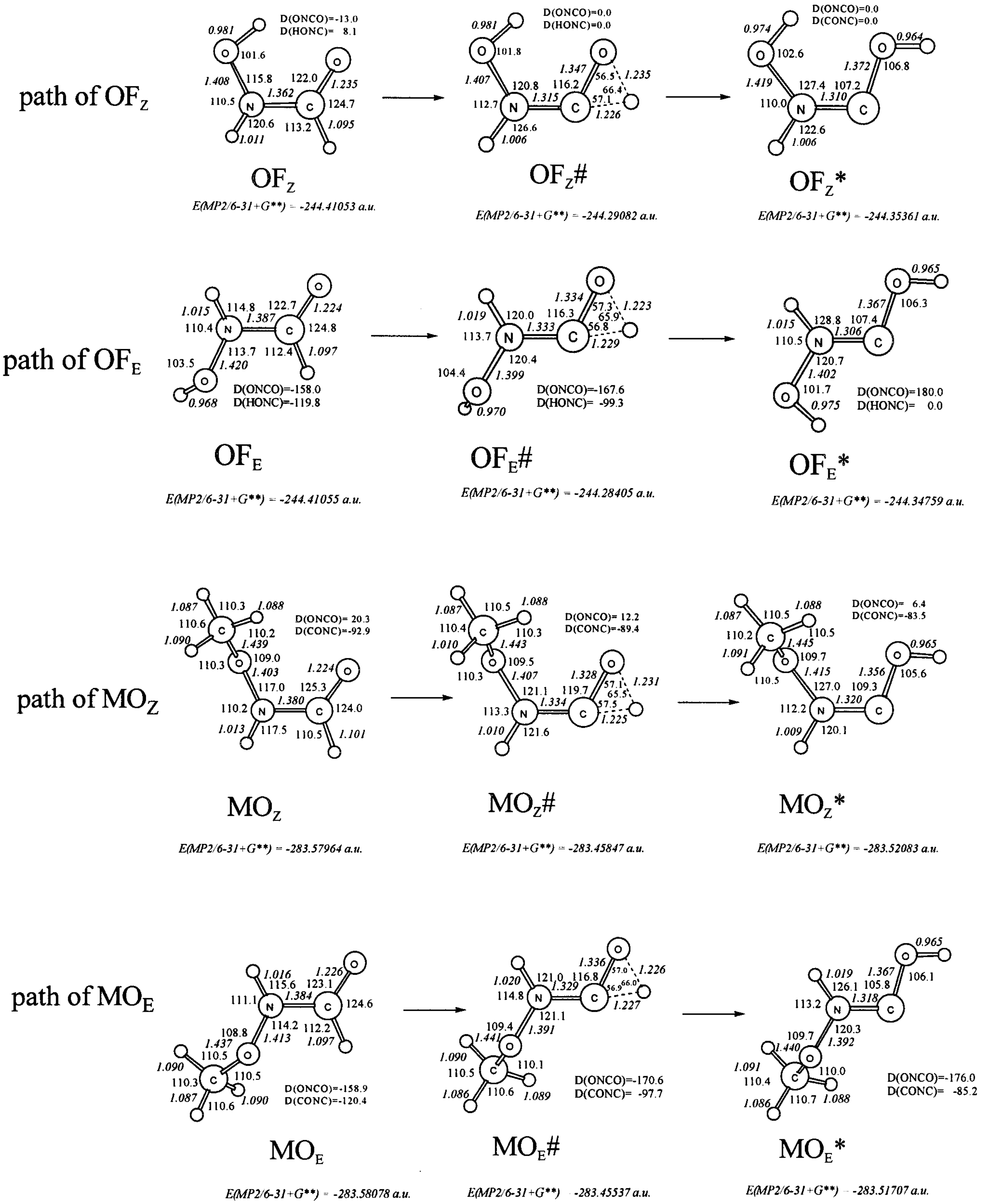

Figure 3. The calculated schematic diagram of hydrogen transfer of *N*-hydroxyl and *N*-methoxy formamides in Z and E forms.

Figure 3. In the stable structure of OF$_Z$ the hydroxyl hydrogen deviates from the molecular plane with the dihedral angle *D*(HONC) being 8.1° and *D*(ONCO) 13.0°. As the transfer proceeds the hydroxyl hydrogen rotates and reaches to the molecular plane, *D*(HONC) = *D*(ONCO) = 0° when the transition state is encountered. In OF$_E$ the hydroxyl hydrogen deviates greatly from the molecular plane, *D*(HONC) = −119.8°, *D*(ONCO) = −158.0°. The hydroxyl group rotates along the C−N bond to *D*(HONC) = −99.3°, and *D*(ONCO) = −167.6° in the transition structure, and settles down on the molecular plane (*D*(HONC) = 0°, and *D*(ONCO) = 180°), when the hydrogen transfer completes (OF$_E$*). The Z conformation, OF$_Z$, has H-bonding between hydroxyl hydrogen and carbonyl oxygen, which keeps the hydroxyl hydrogen near the molecular plane at all times. The E conformation does not have the same situation. As the hydrogen transfers to the carbonyl oxygen, a

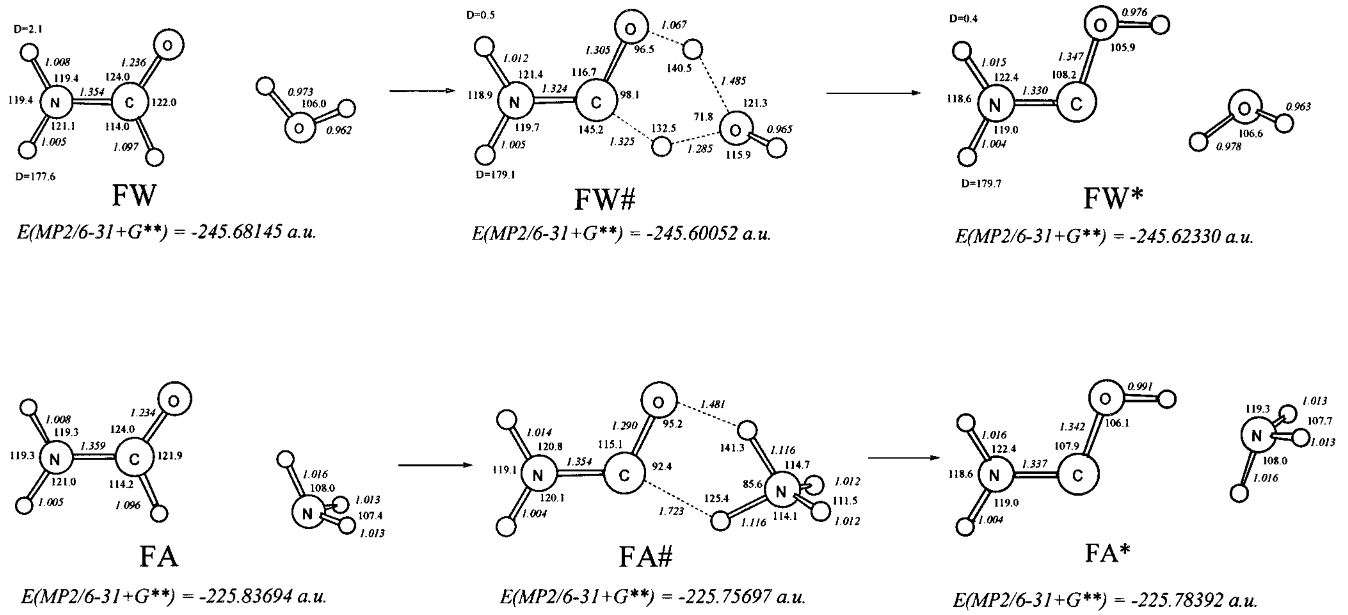

Figure 4. The calculated schematic diagram of hydrogen transfer of H_2O- and NH_3-assisted formamides.

TABLE 1: Bond Lengths (*R* in Å) and Bond Angles (*A* in deg) of the Three Stationary Points of Path F_N of Formamide Calculated at Several Different Levels. Other Calculated Data from References and Experimental Data are also Presented for a Comparison

								F_N*			F_N#		
	RHF/ 6-31G*	MP2/ 6-31G*	MP/ 6-31+G**	ref.[a]	ref.[b]	exp.[c]	exp.[d]	calcd. MP2/ 6-31+G**	ref.[a]	ref.[b]	calcd. MP2/ 6-31+G**	ref.[a]	ref.[b]
R(CO)	1.193	1.225	1.229	1.1885	1.225	1.193	1.219	1.294	1.2592	1.290	1.352	1.3296	1.352
R(CN)	1.348	1.364	1.363	1.3537	1.364	1.376	1.352	1.309	1.2882	1.307	1.277	1.2477	1.275
R(CH)[a]	1.091	1.105	1.099	1.1011	1.105	1.102	1.098	1.084	1.0871	1.089	1.087	1.0885	1.092
R(NH)[b]	0.993	1.009	1.005	0.9970	1.009	1.002	1.002	1.012	1.0002	1.016	1.017	1.0072	1.021
R(NH)[c]	0.996	1.011	1.008	1.0000	1.011	1.014	1.002	1.326	1.3091	1.344	2.303	2.2956	
R(OH)[c]	2.521	2.543	2.550	2.5105				1.333	1.3037	1.348	0.973	0.9511	0.960
A(OCN)	124.9	124.7	124.5	124.99	124.7	123.8	124.7	108.3	108.12	108.9	121.7	122.55	
A(OCH)[a]	122.3	122.9	122.6	122.46	122.9	123.0	122.5	122.9	123.50	122.5	110.5	110.66	
A(NCH)[a]	112.7	112.4	112.8	112.54		113.2	112.7	128.9	128.38		127.8	126.78	128.3
A(CNH)[b]	121.8	121.2	120.9	120.20	121.2	120.0		125.9	125.86	122.5	110.3	110.87	110.4
A(CNH)[c]	119.3	118.2	118.8	117.95	118.2	117.1	118.5	73.3	73.25	73.6	54.5	53.80	
A(H_bNH)[b,c]	119.0	118.6	119.0	117.99		118.9	121.6	160.8	160.89		164.7	164.67	
A(H_cOC)[c]	52.6	52.6	52.5	52.73				73.5	74.38		106.4	107.75	105.4

[a] See ref 2 Wang et al. *J. Phys. Chem.* **1991**, *95*, 10419. [b] See ref 3 Tortajada et al. *J. Phys. Chem.* **1995**, *99*, 13890. [c] See ref 15 Costain et al. *J. Phys. Chem.* **1960**, *32*, 158. [d] See ref 16 Hirota et al. *J. Mol. Spectrosc.* **1974**, *49*, 251.

TABLE 2: Calculated Relative Energies (kcal/mol) of Stationary Points of Formamide for Hydrogen Transfer Following Path F_N and Path F_C

energy difference	MP2/ 6-31+G**	MP2/6-311++G**// MP2/6-31+G**	G2	G2 (MP2) ref.[a]	CISD (FULL) ref.[b]
$E(F_N^* - F)$	12.6(12.9)[c]	11.5(11.8)	11.5	11.4	11.4(12.1)
$E(F_N^\# - F)$	47.8(44.8)	47.3(44.3)	44.5	45.9	51.9(48.9)
$E(F_C^* - F)$	39.7(39.9)	38.9(39.2)	37.4	37.4	
$E(F_C^\# - F)$	76.8(73.2)	76.1(72.5)	72.5	72.0	

[a] See ref 3. Tortajada et al. *J. Phys. Chem.* **1995**, *99*, 13890. [b] See ref 2. Wang et al. *J. Phys. Chem.* **1991**, *95*, 10419. [c] ZPE correction data are listed in parentheses.

carbene is formed which behaves as a strong carbon base to attract the hydroxyl hydrogen and compels the final product OF_E* to have the OH group rotate toward carbon atom.[1]

The structures, energetics, and hydrogen transfer schemes of two *N*-methoxy formamide geometric isomers, MO_Z and MO_E, are also shown in Figure 3. The methoxy group deviates greatly from the molecular plane (dihedral angle *D*(CONC) = −92.9° in MO_Z and −120.4° in MO_E). Both of these two calculated structures agree very well with the experimental data done by Styger et al.[52] When the hydrogen transfer proceeds the dihedral angle *D*(CONC) in each isomer (MO_Z and MO_E) shifts from −92.9° → −89.4° → −83.5°, and −120.4° → −97.9° → −85.2°, respectively. Each methoxy group rotates along the C=O axis toward the molecular plane only in some certain amount. It is not like the case of formohydroxamic acid (OF) in which the substituted OH group is finally on the molecular plane.

Energetics. Single point calculations in the extended basis set, including diffuse functions, MP2/6-311++G**//MP2/6-31+G** were performed to calculate the energies of the local points and transition conformations on the potential energy

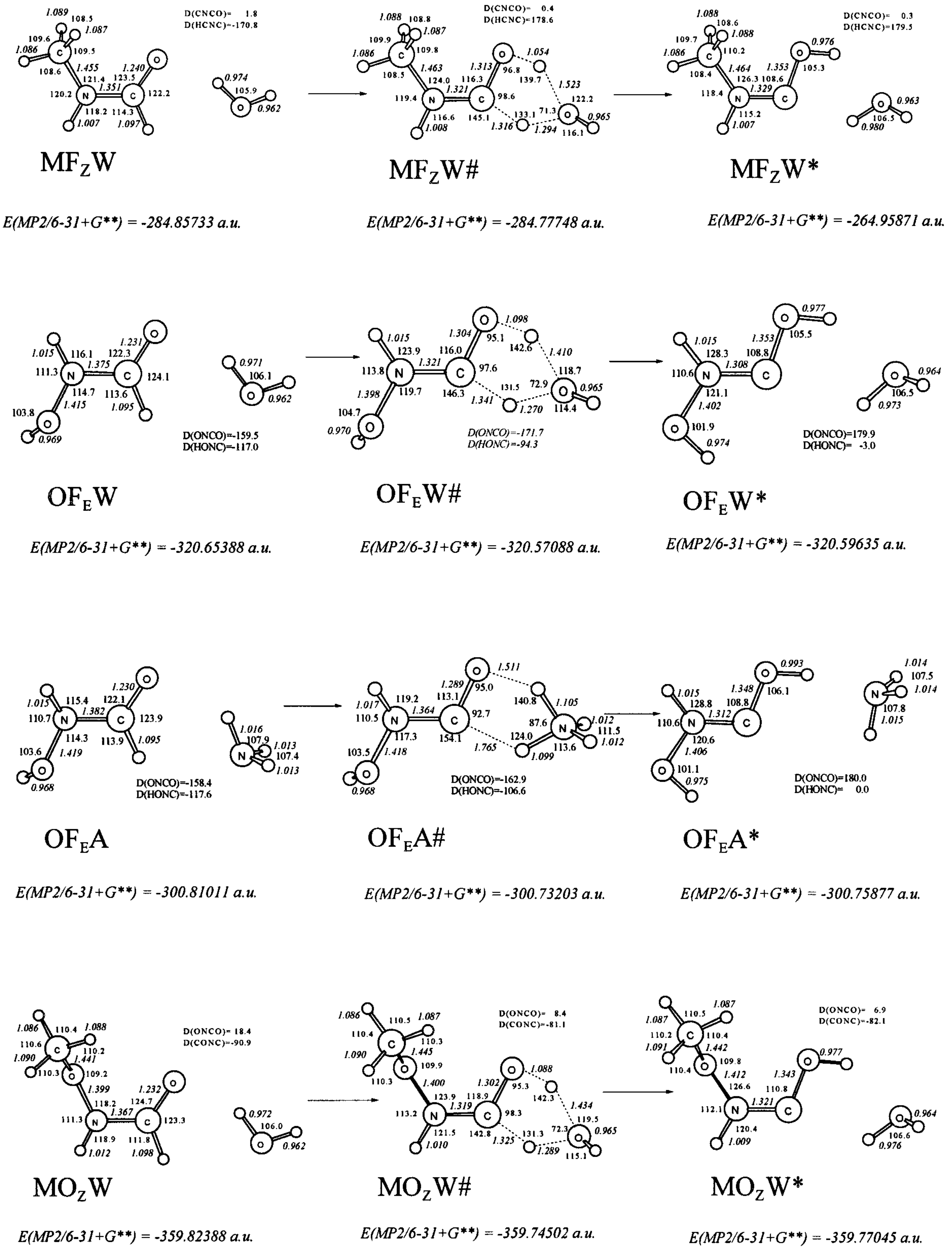

Figure 5. Some of the calculated geometric diagrams of hydrogen transfer of H_2O and NH_3-assisted N-substituted formamides in Z and E forms.

hypersurfaces. These calculated energy data are shown in Table 3. The calculated energy barriers for the forward (E_f) and the backward (E_r) reactions, and the reaction energies (ΔE) of the hydrogen transfer of formamide and its derivatives are listed in Table 4. The last two columns (ΔE_f, ΔE_r) represent the differences of the energy barriers in forward as well as backward reactions between the substituted and the unsubstituted formamides when the hydrogen transfer reactions are carried out. From previous experiences[6,24] the electron-releasing substituent would decrease the energy barrier of the hydrogen transfer, while the energy barrier of the electron-withdrawing substituent would increase. As expressed in the fifth column of Table 4 the ΔE_fs of the Z conformations, MF$_Z$, OF$_Z$, and MO$_Z$ are −0.36, −1.23, and −0.46 kcal/mol, respectively. They are all negative disregarding the electron-releasing or -withdrawing character of the substituents. However, the E conformations, MF$_E$, OF$_E$, and MO$_E$, the ΔE_f's are −1.35, 2.40, and 1.69 kcal/mol, respectively. They appear to follow the electron-releasing or

TABLE 3: Calculated Energies (au) of the Stationary Points on the Hydrogen Transfer Potential Energy Surface of Formamide (F), *N*-Methyl Formamide (MF), *N*-Hydroxyl Formamide (OF), *N*-Methoxy Formamide (MO), and Their H_2O (W)-, NH_3 (A)-Assisted Complexes[a]

E(MP2/6-311++G**// MP2/6-31+G**)	N	$N^\#$	N*
F	−169.50532	−169.38399	−169.44330
MF_Z	−208.69205	−208.57128	−208.62931
OF_Z	−244.51677	−244.39740	−244.46022
MO_Z	−283.69582	−283.57522	−283.63748
MF_E	−208.68969	−208.57050	−208.63017
OF_E	−244.51682	−244.39166	−244.45534
MO_E	−283.69616	−283.57213	−283.63419
FW	−245.79080	−245.71073	−245.73434
MF_ZW	−284.97808	−284.89885	−284.92093
OF_ZW	−320.80170	−320.72432	−320.75172
MO_ZW	−359.98089	−359.90264	−359.92848
MF_EW	−284.97584	−284.89775	−284.92111
OF_EW	−320.80115	−320.71929	−320.74541
MO_EW	−359.98079	−359.90027	−359.92557
FA	−225.92827	−225.84897	−225.87656
MF_ZA	−265.11514	−265.03472	−265.06233
OF_ZA	−300.94013	−300.86888	−300.89553
MO_ZA	−340.11880	−340.04357	−340.07157
MF_EA	−265.11297	−265.03384	−265.06278
OF_EA	−300.93923	−300.86142	−300.88925
MO_EA	−340.11871	−340.04101	−340.06826

[a] Each formamide derivative has Z and E forms. N represents the local minimum on the potential surface of each species. $N^\#$ represents the transition point on the potential surface of each species. N* represents the stationary point of the final structure of transfer on the potential surface of each species.

-withdrawing substitution effect and follow the previous prediction. Since the OH group is more electron-withdrawing in nature it raises the barrier more than the OCH_3 group. While in the Z conformation of the electron-withdrawing substituent, OF_Z or MO_Z, an extra weak H-bonding between the carbonyl oxygen and the hydrogen of the substituent forms, which stabilizes the transition state and reduces the barrier. Clearly, the OF_Z has stronger H-bonding interaction than the MO_Z and reduces the barrier further. The Z conformation of *N*-methyl formamide (MF_Z) shows a higher energy barrier (about 1 kcal/mol) than the energy barrier of MF_E. Probably, methyl group rotation accompanying hydrogen transfer in the Z conformation escalates the difficulty of the transfer.

Addition of H_2O and NH_3. A water or ammonia molecule is added to the formamide and its derivatives to study the catalytic effect to the hydrogen transfer. Some of the optimized geometric structures and transfer schemes of these complexes at the MP2/6-31+G** level are shown in Figures 4 and 5. Hydrogen bonding forms between the added molecule (H_2O or NH_3) and the formamides. The hydrogen transfer is assisted by the H_2O or NH_3 molecule via the concerted process. At this point, a hydrogen in H_2O or NH_3 is abstracted and moved to the carbonyl oxygen; simultaneously the C−H bond breaks and the hydrogen moves toward the H_2O or NH_3. The transition structures assisted by the H_2O molecule (FW#, MFW#, MOW#) have the two hydrogen atoms located in the middle between the two units. The ones assisted by the NH_3 molecule (FA#, MFA#, OFA#, and MOA#) have two hydrogen atoms near the

TABLE 4: Calculated Energy Barriers and Reaction Energies (kcal/mol) of the Hydrogen Transfer Reaction of Formamide (F), *N*-Methyl Formamide (MF), *N*-Hydroxyl Formamide (OF), and *N*-Methoxy Formamide (MO)[a]

E(MP2/6-311++G**// MP2/6-31+G**)	E_f[b]	E_r[c]	ΔE[d]	ΔE_f[e]	ΔE_r[f]
F	76.14(72.47)[g]	37.22(33.29)	38.92(39.18)	0.00(0.00)	0.00(0.00)
MF_Z	75.78(72.79)	36.41(32.65)	39.37(39.64)	−0.36(0.32)	−0.81(−0.64)
OF_Z	74.91(70.70)	39.42(35.47)	35.49(35.22)	−1.23(−1.77)	2.20(2.18)
MO_Z	75.68(71.87)	39.07(35.27)	36.61(36.60)	−0.46(−0.60)	1.85(1.98)
MF_E	74.79(71.02)	37.44(33.70)	37.35(37.32)	−1.35(−1.45)	0.22(0.41)
OF_E	78.54(74.38)	39.96(36.40)	38.58(37.98)	2.40(1.91)	2.74(3.11)
MO_E	77.83(73.77)	38.94(35.14)	38.89(38.63)	1.69(1.30)	1.72(1.85)

[a] Each formamide derivative has Z and E forms. [b] E_f represents the energy barrier of hydrogen transfer in the forward reaction. [c] E_r represents the energy barrier of hydrogen transfer in the backward reaction. [d] ΔE represents the reaction energy of the hydrogen transfer. [e] ΔE_f represents the energy barrier difference of each formamide derivative with respect to formamide in the forward hydrogen transfer reaction. [f] ΔE_r represents the energy barrier difference of each formamide derivative with respect to formamide in the backward hydrogen transfer reaction. [g] ZPE correction data are listed in parentheses.

TABLE 5: Calculated Energy Barriers and Reaction Energies (kcal/mol) of the Hydrogen Transfer Reaction of H_2O (W)- or NH_3 (A)-Assisted Complexes in Z and E Forms

E(MP2/6-311++G**// MP2/6-31+G**)	E_f[a]	E_r[b]	ΔE[c]	ΔE_f[d]	ΔE_r[e]
FW	50.24(48.14)[f]	14.82(11.83)	35.43(36.31)	0.00(0.00)	0.00(0.00)
MF_ZW	49.72(47.47)	13.86(10.83)	35.86(36.64)	−0.52(−0.67)	−0.96(−1.00)
OF_ZW	48.56(45.52)	17.19(13.75)	31.36(31.77)	−1.68(−2.62)	2.37(1.92)
MO_ZW	49.10(46.43)	16.21(13.04)	32.89(33.39)	−1.14(−1.71)	1.39(1.21)
MF_EW	49.00(46.66)	14.66(11.85)	34.34(34.80)	−1.24(−1.48)	−0.16(0.02)
OF_EW	51.37(48.42)	16.39(13.53)	34.98(34.89)	1.13(0.28)	1.57(1.70)
MO_EW	50.53(47.79)	15.88(12.77)	34.65(35.02)	0.29(−0.35)	1.06(0.94)
FA	49.76(48.18)	17.31(14.96)	32.45(33.22)	−0.48(0.04)	2.49(3.13)
MF_ZA	50.46(48.56)	17.33(14.71)	33.14(33.85)	0.22(0.42)	2.51(2.88)
OF_ZA	44.71(43.49)	16.72(15.20)	27.99(28.29)	−5.53(−4.65)	1.90(3.37)
MO_ZA	47.21(45.63)	17.57(17.57)	29.64(30.05)	−3.03(−2.51)	2.75(3.74)
MF_EA	49.65(47.60)	18.16(15.74)	31.49(31.86)	−0.59(−0.54)	3.34(3.91)
OF_EA	48.83(47.31)	17.46(16.09)	31.36(31.21)	−1.41(−0.83)	2.64(4.26)
MO_EA	48.76(47.19)	17.10(15.29)	31.66(31.90)	−1.48(−0.95)	2.28(3.46)

[a] E_f represents the energy barrier of the hydrogen transfer in forward reaction. [b] E_r represents the energy barrier of the hydrogen transfer in backward reaction. [c] ΔE represents the reaction energy of the hydrogen transfer. [d] ΔE_f represents the energy barrier difference of each H_2O- or NH_3-assisted formamide derivative complex with respect to H_2O-assisted formamide complex in the forward hydrogen transfer reaction. [e] ΔE_r represents energy barrier difference of each H_2O or NH_3-assisted formamide derivative complex with respect to H_2O-assisted formamide complex in the backward reaction. [f] ZPE correction data are listed in parentheses.

NH_3 unit to form a distorted NH_4-like portion which might contribute some stability to the transition complexes. In fact, the calculated energy barriers in most of the NH_3-assisted complexes are about 1−4 kcal/mol smaller than the corresponded H_2O-assisted counterparts, except in the *N*-methyl formamide case (MF_ZW vs MF_ZA, MF_EW vs MF_EA) shown in Table 5. The forward energy barriers (E_f) are around 44.71−51.37 kcal/mol, which are about 26−30 kcal/mol less than those of the compounds that are not H_2O- or NH_3-assisted. The catalytic effect is believed to come from the release of tension in the transition structures. It was a three member ring cyclic structure without the added H_2O or NH_3 molecule, but became a five member ring with the added catalysts. The hydrogen transfer turns out to be much easier in a circular (indirect but concerted) process and the catalytic effect of NH_3 molecule is more effective than H_2O.

Summary

The structures of N-substituted formamides are optimized at the MP2/6-31+G** level. The single point calculations for energetics are performed at the MP2/6-311++G**//MP2/6-31+G** level. There are E and Z forms in each substitution. The energy barrier of hydrogen transfer varies in these two forms. The E form is being higher than the Z form except in the case of *N*-methyl formamide (MF) in which the E form is about 1 kcal/mol smaller. The H_2O or NH_3-assisted *N*-methyl formamide complex (MFW or MFA) also gives a similar result; that is, the E form has a lower energy barrier (about 1 kcal/mol) than the Z form. The steric effect of *N*-methyl formamide may be more enhanced in the Z form, while the electron releasing character of the methyl group may be more significant in the E form.

The transfer barriers of H_2O-assisted *N*-methyl formamides (MF_ZW and MF_EW) and the E form of *N*-hydroxy and -methoxy formamides (OF_EW and MO_EW) follow the predicted electron-releasing or -withdrawing substitution effect when compared with the nonsubstituted counterpart (FA). They are shown in column 5 of Table 5 (the ΔE_f of MF_ZW and MF_EW are negative and that of OF_EW and MO_EW are positive). However, the Z-form counterparts (OF_ZW and MO_ZW) do not show the predicted electron-withdrawing substitution effect (ΔE_f's are negative). On the other hand, the NH_3-assisted complexes, MF_ZA and MF_EA, do not show the predicted electron-releasing substitution effect when compared to FA (ΔE_f's are positive). Furthermore, both E and Z forms of OFA and MOA do not follow the predicted electron-withdrawing substituent effect (ΔE_f's are all negative); and OF_ZA deviates the most ($\Delta E_f = -5.53$ kcal/mol). A strong H-bonding interaction is involved in this transition structure. In conclusion, structural orientation has a more significant effect on the barrier size than does the type of substituent concerned. The formation of H-bonding in the complex structure is also an important factor in lowering the energy barrier of hydrogen transfer.

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