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SEMIEMPIRICAL MO STUDIES ON THE PROTON TRANSFER EQUILIBRIA OF AMIDES[1]

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Abstract - Intramolecular proton transfer equilibria of acetamide and methyl carbamate have been studied by AM1 MO calculations, and the results are compared with those of the MNDO method. It was found that the two semi-empirical methods predict essentially the same proton transfer mechanism, but MNDO tends to overestimate the activation barriers. Participation of one solvate water in the proton transfer led to a considerable lowering of the activation barrier, by nearly the same amount, in both methods. One notable conflict between the two methods was that the methoxy-O-protonated form of methyl carbamate, in the gas phase, can be a local energy minimum with MNDO, whereas it leads to dissociation into two species instead of an optimized structure with AM1. It was concluded that the MNDO method can be useful for this type of process, especially when one is interested in the relative activation barriers only.

INTRODUCTION

The mechanism of acid hydrolysis of amides in moderate acidic media depends on which protonated form is involved in the rate-determining attack by water.[2] It is therefore of interest to understand protonation behaviors of amides and related compounds.[3] In a previous paper,[4] we reported the results of our MNDO MO studies on the intramolecular proton transfer equilibria of acetamide and methyl carbamate. We found that even one solvate water molecule lowers the energy barrier to proton transfer substantially, and the process proceeds in an intermolecular manner through the intermediacy of the water molecule via a triple-well type potential energy surface. We however noted that in various structures corresponding to the transition state(TS), proton bridges are formed between two heteroatoms, O and N. This may result in an unduly high energy barrier since the hydrogen bonding energies are not properly accounted for in the MNDO method.[5] We therefore have undertaken similar studies using the AM1 method[6] in which such a deficiency inherent to the MNDO method is rectified, and have compared the two methods to see if there is any mechanistic differences predicted between the two methods.

CALCULATIONS

All calculations were carried out using the AM1 program.[7] Geometries of the species at stationary points were fully optimized by the energy gradient method.[8] Transition states were characterized by confirming only one negative eigenvalue in the Hessian matrix.[9]

RESULTS AND DISCUSSION

Relative stabilities($\Delta\Delta H_f$) of protonated tautomers calculated by the two methods, MNDO and AM1 for acetamide and methyl carbamate are compared in Table 1. Reference to this Table reveals that : (i) The two methods agree in that the carbonyl-O-protonated tautomer is the more stable form

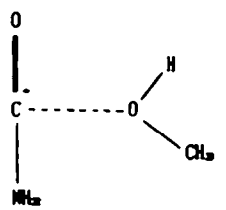
Table 1. Relative stabilities(kcal/mol) of protoned tautomers of acetamide, $(CH_3CONH_2)H^+(H_2O)_n$, and methyl carbamate, $(CH_3OCONH_2)H^+(H_2O)_n$, with n = 0 and 1.

Program	MNDO[a]					AM1				
Protonated tautomer / n	Acetamide		Methyl carbamate			Acetamide		Methyl carbamate		
	O-	N-	Carbonyl O-	N-	Methoxy O-	O-[b]	N-	Carbonyl O-	N-	Methoxy O-
0	0	17.19	0	18.95	36.12	0	10.91	0	13.21	-
1	0	16.45	0	19.13	36.27	0	9.89	0	10.33	-

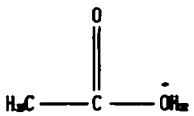
(a) Data from reference (4).
(b) Heat of formation, ΔH_f, for reference substrates are given in figures showing optimized geometries.

as found experimentally.[2] However, the energy differences between the two tautomers are smaller by 5 ~ 9 kcal/mol with AM1 compared to those with MNDO. The smaller energy differences suggest thermodynamically more facile tautomeric equilibration. This is consistent with the experimental[10] as well as theoretical[11] acid hydrolysis mechanism. The nucleophilic attack of the N-protonated form by water in the rate determining step follows a rapid pre-equilibrium between the more stable carbonyl-O-protonated and the N-protonated tautomers. (ii) The two methods predict that relative to the carbonyl-O-protonated form, the N-protonated tautomer of acetamide is thermodynamically more favored than that of methyl carbamate, indicating the relative abundance of the N-protonated form will be greater for acetamide under the same conditions.

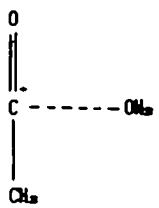
In a striking contrast to these general agreements, a serious conflict was noted between the two semiempirical methods. The MNDO method predicts a stationary equilibrium point corresponding to the methoxy-O-protonated tautomer for methyl carbamate with an optimized structure which is less stable by 36 kcal/mol relative to the carbonyl-O-protonated form, whereas no such optimized structure was obtained with AM1. Instead an attempt of optimization leads to complex (A), in which partial bond cleavage has taken place. In order to elaborate on this matter further, we have carried out geometry optimization of a related structure (B), with three methods, i.e., MNDO, AM1 and ab initio 3-21G basis set. The results showed that an optimized structure for (B) was obtainable only with MNDO ; the other two, AM1 and 3-21G, gave instead complex (c), which is analogous to (A).[12] It appears therefore that the existence of the methoxy-O-protonated form is unlikely in the gas phase, in view of the fact that the AM1 results were more realistic in predicting facile proton transfer equilibria, in Table 1. We disregarded the methoxy-O-protonated form in our discussion of the proton transfer mechanism accordingly.



(A)



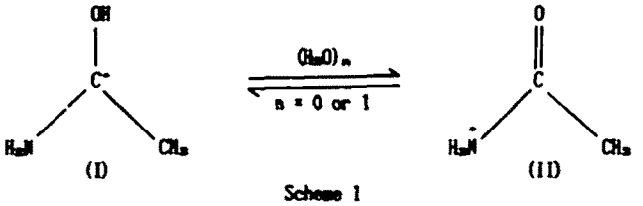
(B)



(C)

Proton Transfer Mechanism

(I) Protonated Acetamide :



Scheme 1

The gas phase proton shift (n = 0) consists of two steps :

(i) Out of plane rotation of O—H⁺ around the C—O bond from the direction pointing the CH_3 group toward the NH_2 group.

(ii) 1.3-proton shift[13] from the carbonyl-O to N.

The potential energy profile representing the two steps is given in Figure 1, and geometries of the species at the stationary points are collected in Figure 2. In this gas phase process, the TS structure corresponding to the rate determining step is a four-membered ring involved in the typical 1,3-proton shift. The TS structure is very similar to that obtained by MNDO, but the

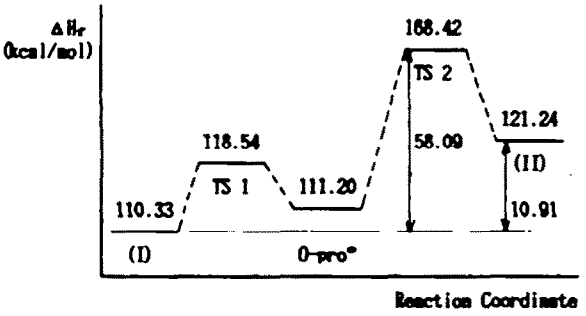


Figure 1. Potential energy profile for the proton transfer, (I) → (II).

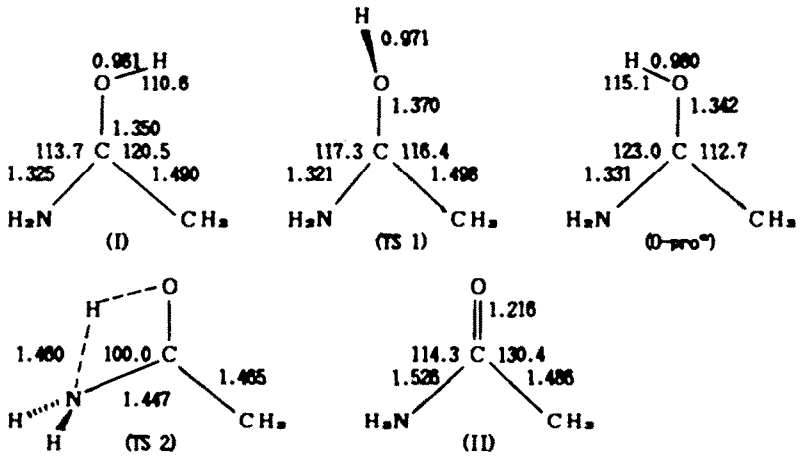


Figure 2. Geometries of species at stationary points on the potential energy profile for the proton transfer, (I) → (II) (bond lengths and angles are in Å and degrees).

activation barrier is lower by 12.8 kcal/mol compared to that by MNDO. The two methods, thus, give quite similar potential energy profiles with a similar TS structure, but a higher energy barrier is obtained with MNDO. Nevertheless the gas phase activation barrier of 58.1 kcal/mol obtained by AM1 is still too high to be practicable.

When one solvate water molecule participates in the proton transfer (n = 1), the barrier becomes substantially lowered. In this process, the overall reaction consists of three steps as can be seen in the potential energy profile presented in Figure 3 :

(i) Out of plane rotation of O−H* toward the NH_2 group, similar to the gas phase process.

(ii) Deprotonation from the carbonyl-O-protonated tautomer, (I), by the solvate water molecule.

(iii) Re-protonation to form the N-protonated tautomer, (II), in the rate determining step.

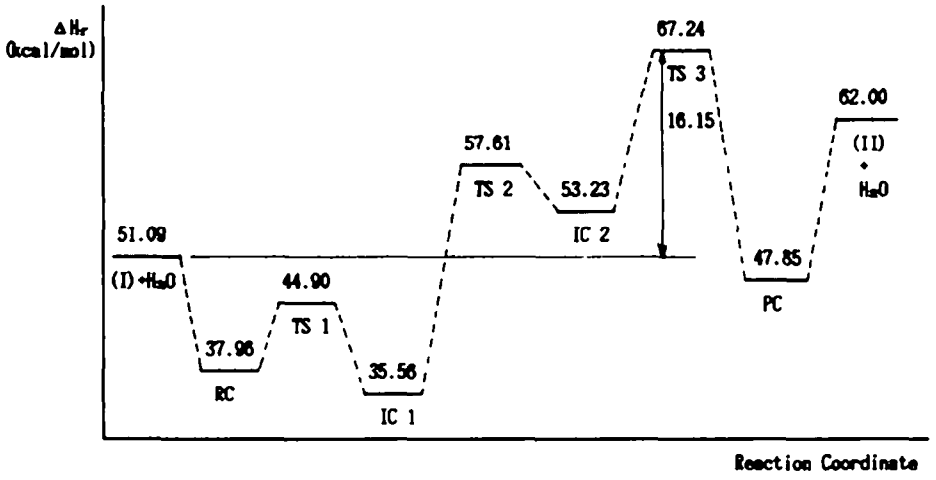
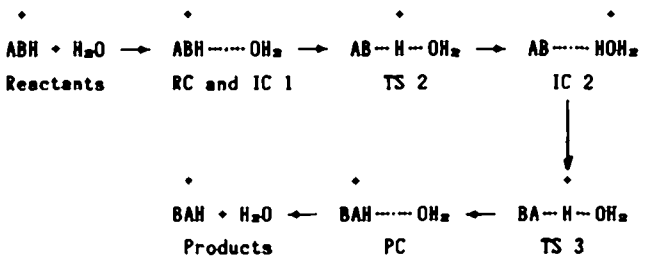


Figure 3. Potential energy profile for the proton transfer, (I) + H_2O → (II) + H_2O.

In addition to reactant(RC) and product complexes(PC), there are two intermediate complexes(IC) formed in between the three TSs. Optimized structures of all complexes and TSs are collected in Figure 4. All of the complexes, (RC, IC and PC), and TS 1 are seen to consist of a pair of proton donor(protonated species) and acceptor fragments, whereas in the TSs 2 and 3 the proton forms a bridge between the two fragments. These features are in good agreement with the MNDO results of proton transfer studies reported recently. The overall proton transfer in a substrate with two basic centers(heteroatoms) A and B involving one solvate water can be represented in a simple form of Scheme 2. The structure of IC 1 differs from that of RC only in the direction of O−H*, and there is a small rotational barrier, TS 1, in between (step (i) above).



Scheme 2

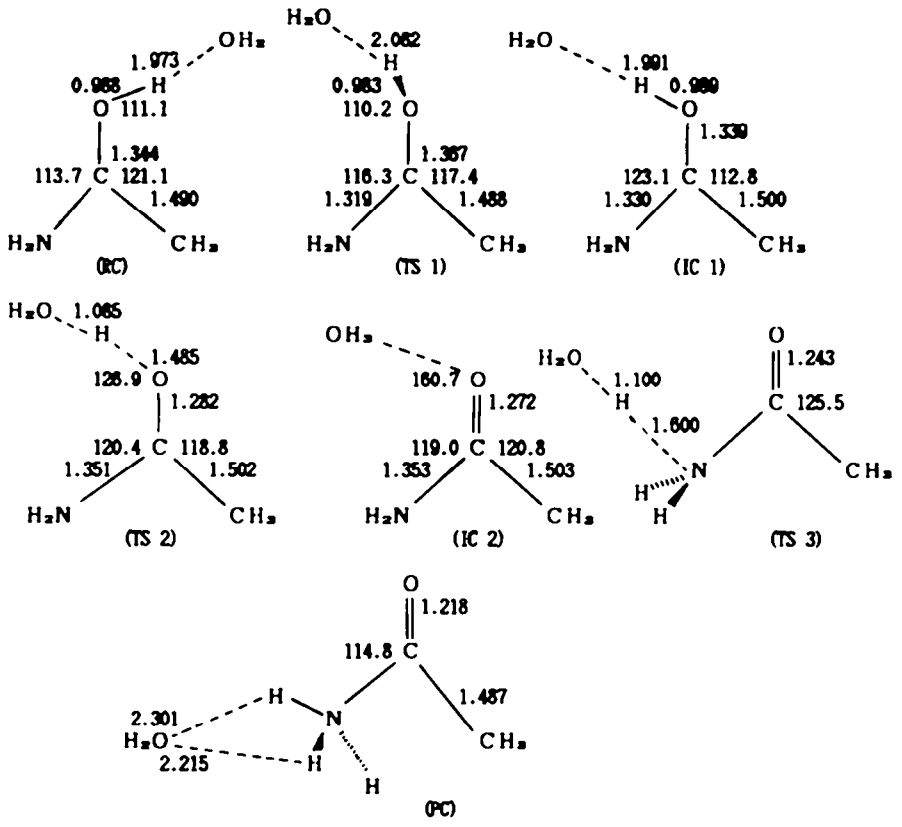
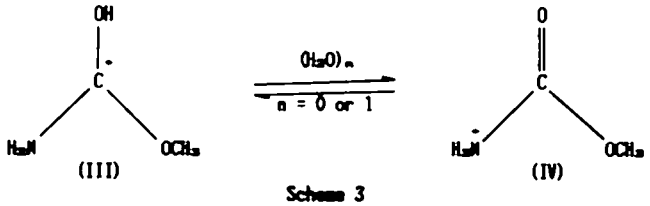


Figure 4. Geometries of species at stationary points on the potential energy profile for the proton transfer, (I) + H_2O ⟶ (II) + H_2O (bond lengths and angles are in Å and degree).

The activation barrier in this case is 16.2 kcal/mol as shown in Figure 3, which is lower by 41.9 kcal/mol than that for the gas phase process. Quite similar barrier height lowering, by 41.7 kcal/mol, was realized with MNDO with the participation of one water molecule in the proton transfer, although the barrier height was higher by 13.0 kcal/mol compared with that obtained with AM1. Comparison of AM1 structures with those of the corresponding species obtained by MNDO indicates that the distance between the substrate proton and water molecule is reduced, in general, from ~2.5 Å (MNDO) to 2.0 ~ 2.2 Å (AM1) ; an extra stabilizing interaction resulting in the distance decrease should originate in the hydrogen bonding that is accounted for in AM1, since the charge-dipole interaction is common to both methods. However, other structural features of the corresponding complexes and TSs on the potential energy profile are quite similar in both methods. Moreover the essential mechanistic details were also found to agree in the two methods.

(II) Protonated Methyl Carbamate :



Scheme 3

The proton transfer process of protonated methyl carbamate in Scheme 3 is very similar to that of protonated acetamide in Scheme 1. The potential energy profile for the gas phase (n = 0) proton transfer in methyl carbamate is shown in Figure 5, and the optimized structures of the species at the stationary points are collected in Figure 6. Reference to Figure 5 shows that rotation of CH_3 in the methoxy group gives the TS 1, the proton rotation toward the NH_2 group, as was found in the acetamide case, yields the TS 2, and lastly the 1,3-proton shift from the carbonyl-O to N is the rate determining step with the TS 3. The overall process is again in good agreement with that found with MNDO ; here also the activation barrier is lower by 11.3 kcal/mol with AM1 compared to the corresponding barrier height by MNDO. The gas phase barrier to the proton shift seems still too high (~ 58 kcal/mol) to be practicable.

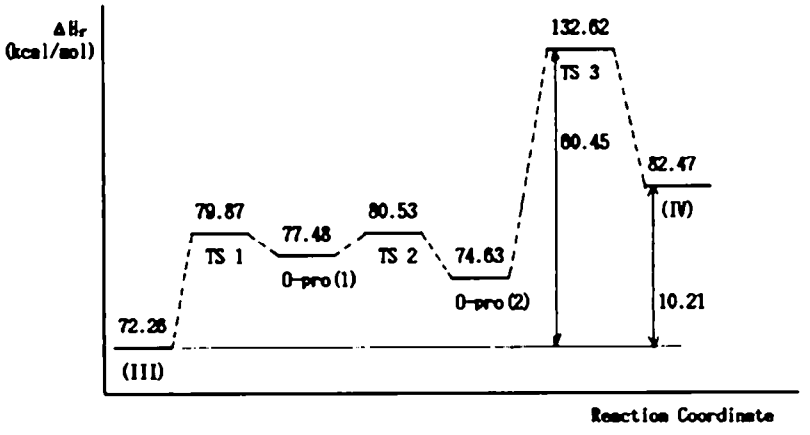


Figure 5. Potential energy profile for the proton transfer, (III) → (IV).

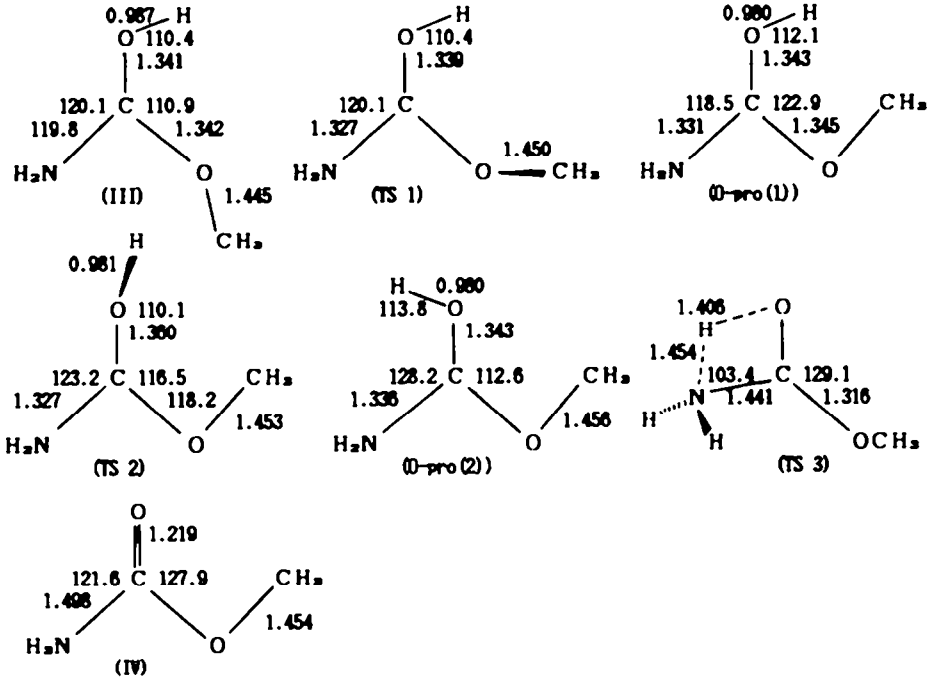


Figure 6. Geometries of species at stationary points on the potential energy profile for the proton transfer, (III) → (IV) (bond lengths and angles are in Å and degree).

When one solvate water molecule participates in the proton transfer (n = 1), the process proceeds via an intermolecular path, and the barrier height is depressed to 11.9 kcal/mol, which is lower by 48.5 kcal/mol than in the gas phase process. The potential energy profile and the optimized structures are presented in Figure 7 and 8. Here again the AM1 method gives substantially a lower (by 15.5 kcal/mol) activation barrier than the MNDO method. However the relative lowering (48.5 kcal/mol) with respect to the gas phase barrier is comparable to the corresponding value

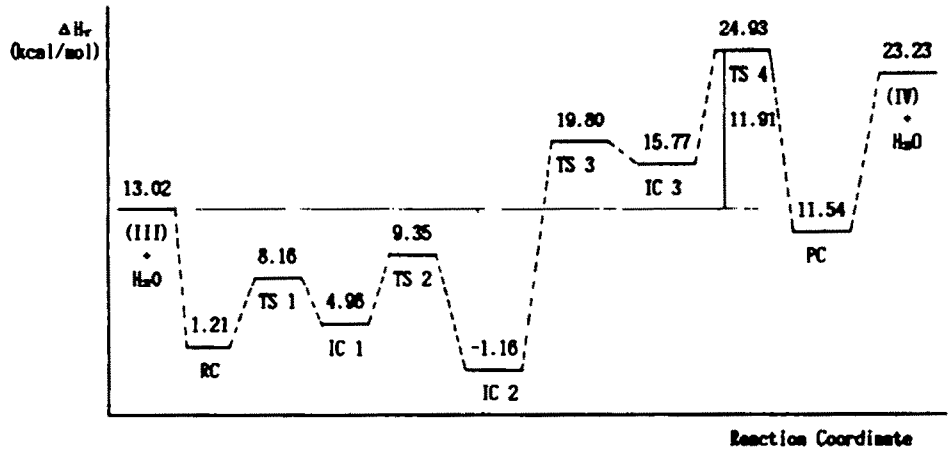


Figure 7. Potential energy profile for the proton transfer, (III) + H_2O → (IV) + H_2O.

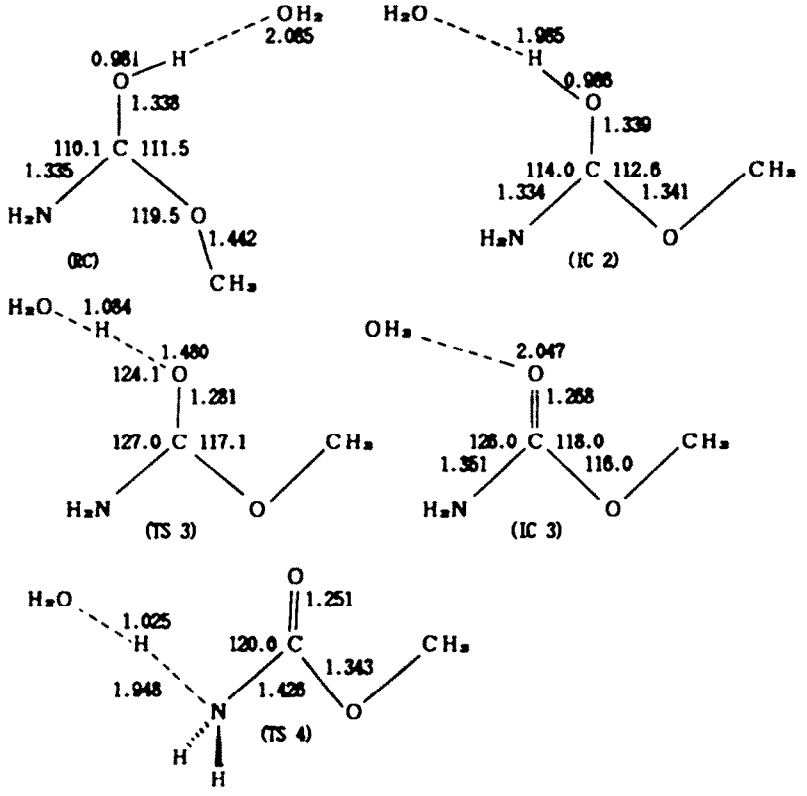


Figure 8. Geometries of some species at the stationary points on the potential energy profile for the proton transfer, (III) + H_2O → (IV) + H_2O (bond lengths and angles are in Å and degree).

obtained with the MNDO method (48.4 kcal/mol). The overall process of proton transfer in methyl carbamate is essentially the same as that in acetamide, and can be similarly represented as in Scheme 2.

The activation barriers for the rate-limiting step relative to the protonated ground state, i.e., carbonyl-O-protonated form, are summarized in Table 2 for the two protonated substrates studied in this work.

Table 2. Activation barriers (kcal/mol) to proton transfers from the dominant carbonyl-O-protonated tautomers (Ground state) to N-protonated tautomers.

	MNDO		AM1	
n	Acetamide carbonyl-O- to N-	Methyl carbamate carbonyl-O- to N-	Acetamide carbonyl-O- to N-	Methyl carbamate carbonyl-O- to N-
0	70.87	71.78	58.09	60.45
1	29.14	27.43	16.15	11.91

The results of the present studies can be summarized as follows.

(i) The AM1 and MNDO methods agree in that the activation barriers of the gas phase intramolecular proton transfers both in acetamide and methyl carbamate are prohibitively high (~60 kcal/mol), but the participation of even one solvate water molecule lowers the barriers considerably and leads the processes to become practicable via intermolecular paths.

(ii) The two semiempirical methods predict essentially the same proton transfer mechanism, but MNDO appears to overestimate the activation barrier.

(iii) Lower activation barriers exhibited by the AM1 method compared to those by MNDO, by 16.2 and 11.9 kcal/mol for acetamide and methyl carbamate, respectively, seem to better accommodate the experimental facts of the rapid proton transfer pre-equilibria prior to the A2 hydrolysis of the two compounds.

(iv) The difference in barrier height between that for the gas phase and that for the process with one water molecule agrees remarkably well in the two methods for the two compounds ; the MNDO method is therefore useful even for the this type of processes involving hydrogen bonds when one is interested in the relative activation barriers only.

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REFERENCES

1. Part 53 of the series : Determination of Reactivity by MO theory.
2. (a) V. C. Armstrong, D. W. Farlow and R. B. Moodie, *J. Chem. Soc.* (B), 1099 (1968) ; (b) D. W. Farlow and R. B. Moodie, *ibid.*, 934 (1969).
3. V. C. Armstrong and R. B. Moodie, *J. Chem Soc.* (B), 275 (1968).
4. I. Lee, C. K. Kim and H. S. Seo, *Bull. Korean Chem. Soc.*, 7, 395 (1986).
5. (a) M. J. S. Dewar and W. J. Thiel, *J. Am. Chem. Soc.*, 99, 4899 (1977); (b) M. J. S. Dewar and W. J. Thiel, *ibid.*, 99, 4709 (1977).
6. M. J. S. Dewar, E. G. Zoebisch, E. F. Healy and J. J. P. Stewart, *J. Am. Chem. Soc.*, 107, 3902 (1985).
7. Available from Quantum Chemistry Program Exchange (QCPE), No. 506.
8. (a) A. Komornichi, K. Ishida and K. Morokuma, *Chem. Phys. Lett.*, 45, 595 (1977); (b) J. W. Mclver, Jr., and A. Komornichi, *J. Am. Chem. Soc.*, 94, 2025 (1972); (c) R. Fletcher and M. J. D. Powell, *Comput. J.*, 6, 163 (1963).
9. I. G. Csizmadia, *Theory and Practice of MO calculations on Organic Molecules*, Elsevier, Amsterdam, 1976, p. 239.

10. (a) R. B. Moodie and R. Tovill, *J. Chem. Soc., Perkin.* 2, 184 (1972); (b) B. C. Challis and S. P. Jones, *ibid.*, 153 (1975).
11. (a) I. Lee, C. K. Kim and H. S. Seo, *Tetrahedron*, 42, 6627 (1986); (b) I. Lee, C. K. Kim and B. C. Lee, *J. Comput. Chem.*, 8, 794 (1987).
12. I. Lee and C. K. Kim, Unpublished Results.
13. (a) F. M. Menger, J. Grossman and D. C. Liotta, *J. Org. Chem.*, 48, 905 (1983); (b) K. Yamashita, M. Kaminoyama, T. Yamabe and K. Fukui, *Theoret. Chim. Acta*, 60, 303 (1981); (c) I. Lee, J. K. Cho and B-S Lee, *J. Comput. Chem.*, 5, 217 (1984).