Theoretical Studies on the Acid Hydrolysis of Methyl Carbamate*

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Received 11 August 1986; accepted 3 December 1986

The mechanism of the A2 acid hydrolysis of methyl carbamate was investigated using MNDO method. The reaction was found to proceed in two steps: (1) the rate-determining nucleophilic attack of water on the carbonyl carbon of the N-protonated tautomer involving the tetrahedral TS; and (2) the fast subsequent proton abstraction by the leaving group, NH_3, to form products. The mechanism is similar to that involved in the A2 hydrolysis of acetamide. Effects of substituents, R^1, R^2, and R^3 in $R^1OCONR^2R^3$, on rates can be predicted by the changes in electron densities on alkoxy oxygen and N, in complete agreement with the experimental results. We concluded that there is no need for invoking two different mechanisms for amides and carbamates since a common mechanism can easily accommodate all the experimental results.

INTRODUCTION

In our previous articles in this series of work, we reported on the proton transfer equilibria involving protonated acetamide and methyl carbamate[1] and also on the A2 hydrolysis mechanism of acetamide[2] using the MNDO method.[3] Our conclusion as to the proton transfer equilibria was that the protonation behavior of methyl carbamate would be similar to that of acetamide; for both compounds the carbonyl O-protonated tautomer constitutes the predominant form, the minor form being the N-protonated one. The abundance of the methoxy O-protonated form of methyl carbamate can be neglected in the protonation equilibria since the tautomer was found to be unfavorable both thermodynamically and kinetically.[1] On the other hand, the rate-determining attack of water on the carbonyl carbon of protonated forms of acetamide was found to be a normal concerted nucleophilic displacement process with the tetrahedral transition state (TS). The bond interchange at the rate-determining step takes place concurrently with the proton interchange with an increase in the negative charge on N relative to the ground state;[2] the experimentally observed rate depression caused by N-methyl groups provided evidence in support of our mechanism.

One of our main interests in this series of theoretical work has been to explore the possibility of a common mechanism for amides and carbamates,[2] since different behaviors of N-substituents have led to different mechanisms being proposed for the two types of compounds.[4] In this work we investigated the mechanism of the A2 hydrolysis of methyl carbamate theoretically using the MNDO method. Although the methoxy O-protonated tautomer has been found to be negligible, we nevertheless examined the hydrolysis mechanism involving the rate-determining attack of water on this tautomer as well.

CALCULATIONS

MNDO program[3] was used throughout in this work. Geometries of all species at the stationary points were fully optimized with the energy gradient method,[5] and the TSs were characterized by confirming that there

*Part 45 in the series, *Determination of Reactivity by MO Theory.*

Journal of Computational Chemistry, Vol. 8, No. 6, 794–800 (1987)
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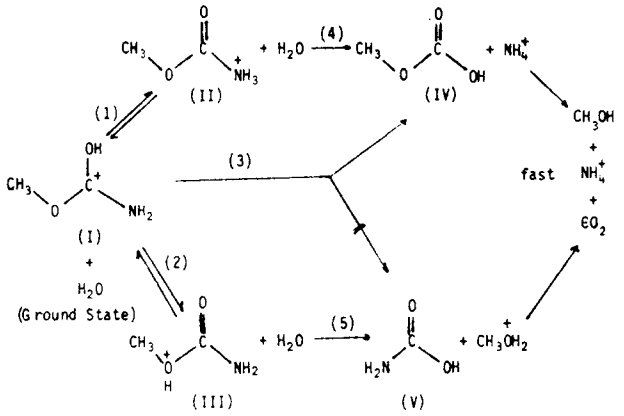
CCC 0192-8651/87/060794-07$04.00

is only one negative eigenvalue in the Hessian matrix.[6]

RESULTS AND DISCUSSION

It has been shown experimentally that the acid hydrolysis of carbamates proceeds by the $A_{AC}2$ mechanism[7] in which displacement at the protonated substrate by water takes place with acyl-oxygen bond fission.[7] Final products identified were ROH and NH_4^+ besides carbon dioxide from a protonated form of carbamate, $ROCONH_2$.[7] In this work, we limit our theoretical investigations to this type of the A2[7] hydrolysis of methyl carbamate.

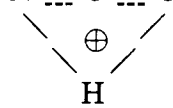


Two protonated forms, (II) and (III), are in equilibrium with the predominant carbonyl oxygen (O_1)-protonated tautomer (I) as shown in Scheme 1. Depending on which tautomer is attacked by water, we have three paths of the reaction, (3), (4), and (5), and same final products are formed irrespective of the reaction path through unstable intermediates, (IV) and (V). We will therefore explore three models for the TS, each involving nucleophilic attack of water on a different tautomer of the protonated methyl carbamate corresponding to the paths (3), (4) and (5) in Scheme 1.

(A) Hydrolysis of the Carbonyl O-Protonated Tautomer: Path (3)

Results of our MNDO calculations are presented as a potential energy profile in Figure 1. General pattern of the energy profile is quite similar to that of acetamide.[2] Here again we have a tetrahedral complex (TC) before the highest barrier (TS 1) is reached. At the rate-determining step (TS 1), concerted bond breaking (C-N bond) and bond formation (carbon-water oxygen, C-O_2, bond) take place maintaining near the tetrahedral geometry with concurrent proton interchange. Fully optimized geometries of all species at the stationary points are given in Figure 2. Final charges and bond lengths for some of the relevant species are summarized in Table I for the three paths of the reaction.

Reference to this table reveals that the length of C-N bond increases (being broken), while that of C-O_2 decreases (being formed) as the reaction proceeds along the reaction coordinate TC → TS 1 → IC 1 in path (3). Bond lengths of C-O_1 and carbon-methoxy oxygen (O_3) change little during the process. Furthermore, the negative charge on N is seen to decrease (becomes more positive), while that on O_2 increases (becomes less positive) indicating the proton interchange from O_2 to N. At the TS 1, the positive charge is delocalized over the N ⋯ C ⋯ O_2 frame. All of these



features are similar to those involved in the corresponding process of the acetamide hydrolysis.[2]

We have two intermediate complexes, IC 1 and IC 2, besides the reactant (RC) and product complexes (PC). Subsequent barriers, TS 2 and TS 3, correspond to relatively fast bond breaking processes of the C-N and O-H bonds, respectively.

The activation enthalpy for the path (3) was calculated to be 51.7 kcal/mol.

Here, in contrast with the corresponding reaction path in the acetamide hydrolysis,[2] the proton from O_2 can be transferred to either N or O_3 atom at the TS 1. However, we have disregarded the latter possibility, since it has been shown that the proton transfer to O_3 is not only much slower, but also leads to a more unstable high energy form compared with the transfer to N.[1]

(B) Hydrolysis of the N-Protonated Tautomer: Path (4)

In the path (4), water attacks the N-protonated tautomer (II) and forms NH_4^+ and (IV) as products. The MNDO potential energy profile obtained is a typical triple-well type as shown in Figure 3. Fully optimized geometries for all species at the stationary points are presented in Figure 4.

The overall process consists of two steps: (i) addition of water on the carbonyl carbon, con-

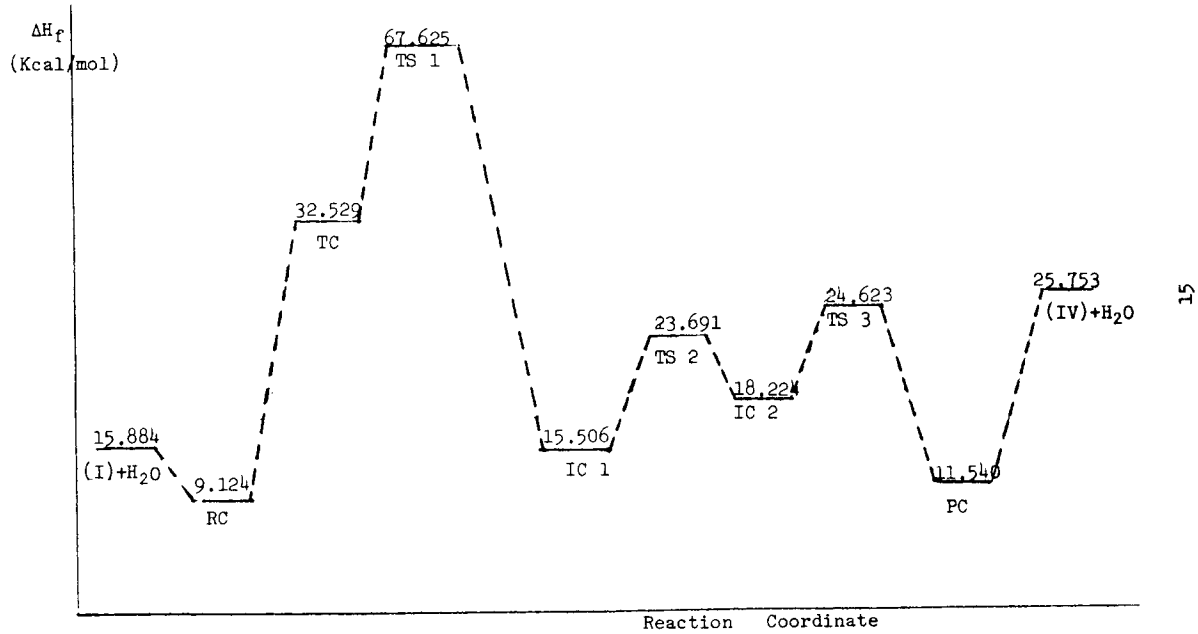


Figure 1. Potential energy profile for the hydrolysis of the carbonyl O-protonated tautomer.

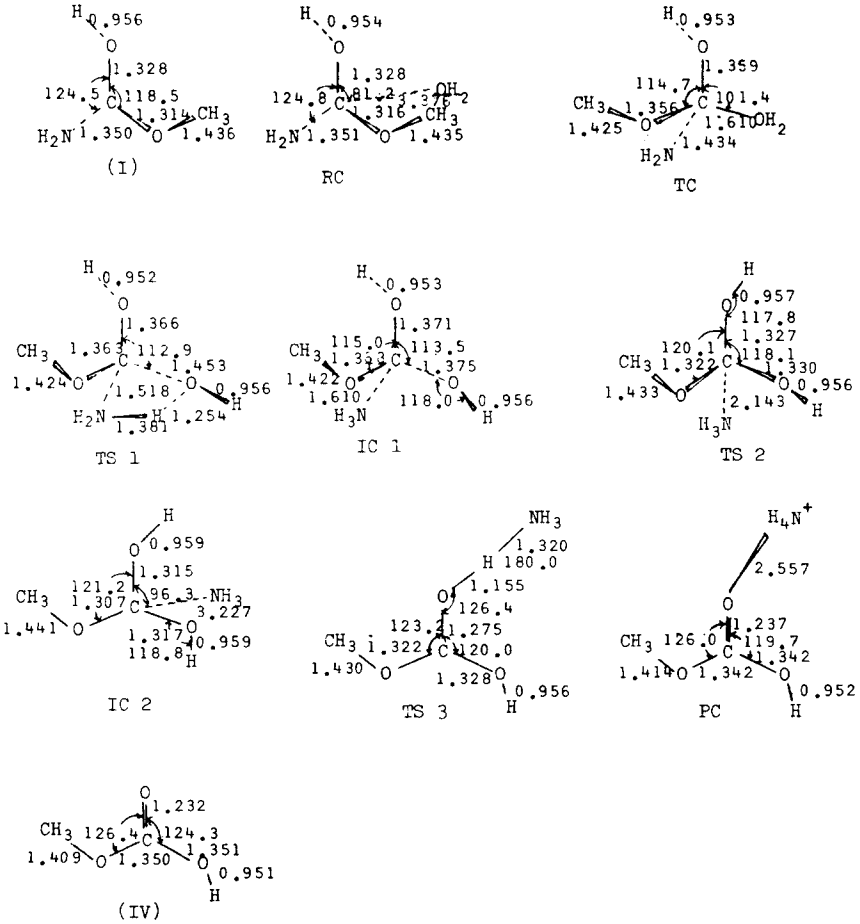


Figure 2. Geometries of all species at the stationary points on the potential energy profile for the hydrolysis of the carbonyl O-protonated tautomer (bond lengths and angles are in Å and degree).

Table I. Formal charges (in electronic charge unit) and bond lengths (in Å) of some relevant species in the three paths of the A2 hydrolysis of methyl carbamate.

	G.S.	Path (3)			Path (4)			Path (5)		
	(I) + H_2O	TC	TS1	IC1	RC	TS1	IC	RC	TS1	IC
N[a]	−0.2963	−0.3415	−0.2808	−0.0544	−0.0044	−0.2360	−0.3051	−0.2641	−0.2896	−0.2745
O_2	−0.3256	−0.2182	−0.2696	−0.3241	−0.3821	−0.1810	−0.1159	−0.3729	−0.2529	−0.1344
O_3	−0.2438	−0.3432	−0.3580	−0.3751	−0.2956	−0.3126	−0.2801	−0.2149	−0.3051	−0.4002
C—O_1	1.3279	1.3590	1.3657	1.3709	1.2100	1.2145	1.2055	1.2029	1.2113	1.2033
C—N	1.3496	1.4337	1.5177	1.6099	1.5236	2.0136	3.5740	1.3827	1.4104	1.3831
C—O_2	∞	1.6104	1.4532	1.3750	3.6134	1.5143	1.4620	3.4299	1.6564	1.4845
C—O_3	1.3142	1.3557	1.3630	1.3682	1.3268	1.3343	1.3190	1.4899	1.7081	3.8508
Δq_N[b]			+0.0155			+0.0603			+0.0067	
Δq_{O_3}			−0.1142			−0.0688			−0.0613	

[a] O_1, O_2, and O_3 refer to the carbonyl oxygen, water oxygen, and methoxy oxygen, respectively.
[b] $\Delta q_X = q_X(\text{TS 1}) - q_X(\text{I})$.

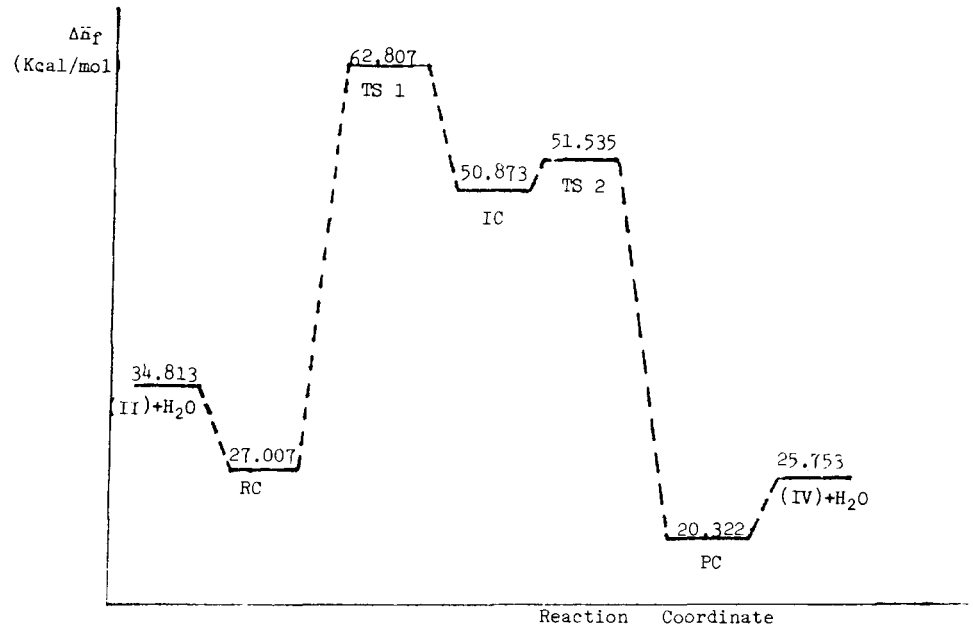


Figure 3. Potential energy profile for the hydrolysis of the N-protonated tautomer.

certed with bond breaking of the leaving group; and (ii) abstraction of the proton by the leaving group, NH_3. The first step is a normal concerted nucleophilic displacement process at the carbonyl carbon as Yamabe, et al. has shown.[8] The two encounter complexes, RC and IC, are π-complexes formed by the attacking (H_2O) and leaving (NH_3) fragments approximately in the perpendicular direction to the molecular plane. These correspond to the two π-complexes, RC and PC, which form the two wells in the double-well potential energy profile reported by Yamabe et al. on the gas-phase nucleophilic displacement of halides on acetyl chloride.[8] In complete agreement with their *ab initio* results,[8] as well as with the experimental results of Brauman et al.,[9] we obtained a tetrahedral TS(TS 1) in between the two π-complexed-wells of RC and IC. The reason why we obtained a triple-well instead of a double-well type is that the second step of the proton abstraction by the leaving group follows subsequently.

Here also in the path (4), the proton interchange takes place concurrently with the bond interchange at the rate-determining step. Structural changes along the reaction coordinate (Fig. 4) RC → TS 1 → IC reveal that C-N and C-O_2 bonds interchange at the TS 1 in the same way as described for the hydrolyis of N-protonated acetamide[2] and halide exchanges at the carbonyl center.[8] The concerted bond formation and bond breaking can be traced in the bond length changes

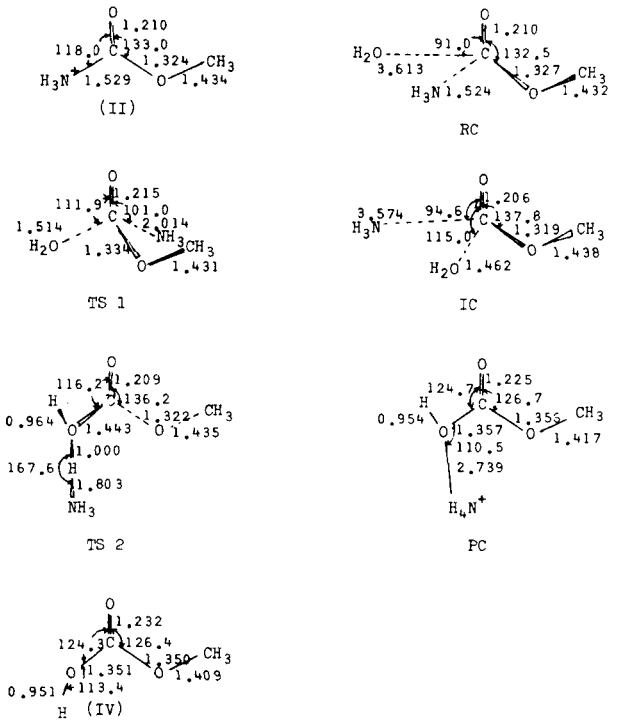


Figure 4. Geometries of all species at the stationary points on the potential energy profile for the hydrolysis of the N-protonated tautomer (bond lengths and angles are in Å and degree).

shown for the process in Table I. The concurrent proton interchange is evidenced by the increase and decrease in the negative charges on N and O_2 atoms, respectively. In this path, the proton shifts from N to O_2 and at the TS 1 the positive charge is delocalized over the relatively loose N ⋯ C ⋯ O_2 frame.

The entire process is similar to the corresponding one for acetamide.[3] The activation enthalpy relative to the ground state ((I) + H_2O) was computed to be 46.9 kcal/mol, which is lower by ca. 5 kcal/mol than that for the path (3). On the other hand, it is higher by ca. 2 kcal/mol than that for the corresponding path in the A2 hydrolysis of acetamide,[2] which is in accord with the experimental results of slower rates for carbamates.[4,10]

(C) Hydrolysis of the Methoxy O-Protonated Tautomer: Path (5)

In this path, water attacks the carbonyl carbon of the methoxy O-(O_3) protonated tautomer (III). The MNDO potential energy profile shown in Figure 5 is, again, a typical triple-well type. Fully optimized geometries for the species at the stationary points are collected in Figure 6.

General shape of the potential energy profile, as well as the structural features of all the complexes, intermediate and TSs, are similar to the path (4) above, except that in this path, (5), the leaving group is CH_3OH instead of NH_3. Thus, the overall process is in two steps, the first step being the rate-

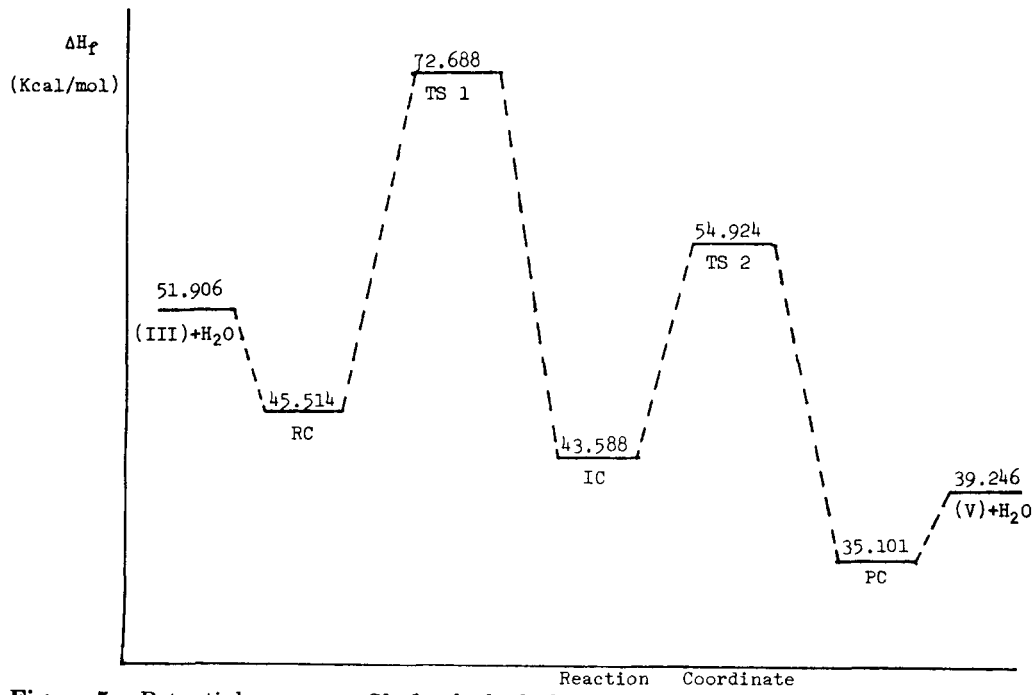


Figure 5. Potential energy profile for the hydrolysis of the methoxy O-protonated tautomer.

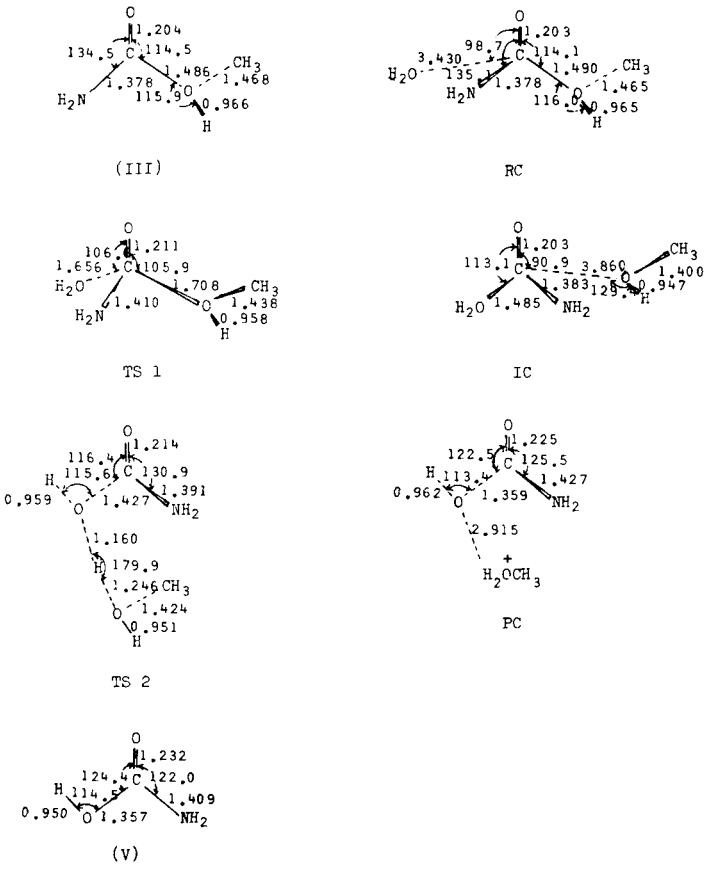


Figure 6. Geometries of all species at the stationary points on the potential energy profile for the hydrolysis of the methoxy O-protonated tautomer (bond lengths and angles are in Å and degree).

determining bond interchange of C-O_2 and C-O_3 bonds with the concurrent proton interchange from O_3 to O_2 (Table I). At the TS 1, the positive charge is delocalized over the $O_2 \cdots C \cdots O_3$ frame. In the second step, the leaving group, CH_3OH, abstracts the proton a fast process (TS 2) to form products.

The activation enthalpy for this path relative to the ground state was 56.8 kcal/mol, which is the highest among the three paths, (3), (4), and (5).

An overview of the activation barriers for the processes (1) ~ (5) is presented in Figure 7; the barrier heights for the attack of water on the three protonated forms, i.e., path (3), (4), and (5) are in the order, (4) < (3) < (5) and there is ca. 10 kcal/mol difference between the lowest, (4), and the highest, (5).

We conclude that the A2 acid hydrolysis of methyl carbamate proceeds mainly by the rate-determining attack of water on the N-protonated tautomer, with possibly some competitive reaction via the direct attack of water on the carbonyl O-protonated, ground state, form.

The activation barriers obtained in this work are in general overestimated[11] due to the well-known weakness of the MNDO method.[11] However, the results of present studies clearly demonstrate that a common mechanism operates in the A2 acid hydrolysis of amides and carbamates involving the rate-determining attack of water on the carbonyl carbon of the N-protonated form with the tetrahedral transition state.

Reference to Table I reveals that the electron density on N atom decreases while that on methoxy-O(O_3) increases at the rate-determining step (TS 1) relative to the ground state (I) irrespective of the reaction path involved

The order of reactivity of the protonated carbamates toward A2 reaction found experimentally[12] $EtOCONMe_2$ > $EtOCONHMe$ > $EtOCONH_2$ > $EtOCONHCH_2COOH$, $EtOCONHCH_2CF_3$. This observed accelerative effects of N-methyl groups and the rate depression caused by the electron-withdrawing N-CH_2CF_3 and N-CH_2COOH groups[12] are in accord with our MNDO results of the electron density de-

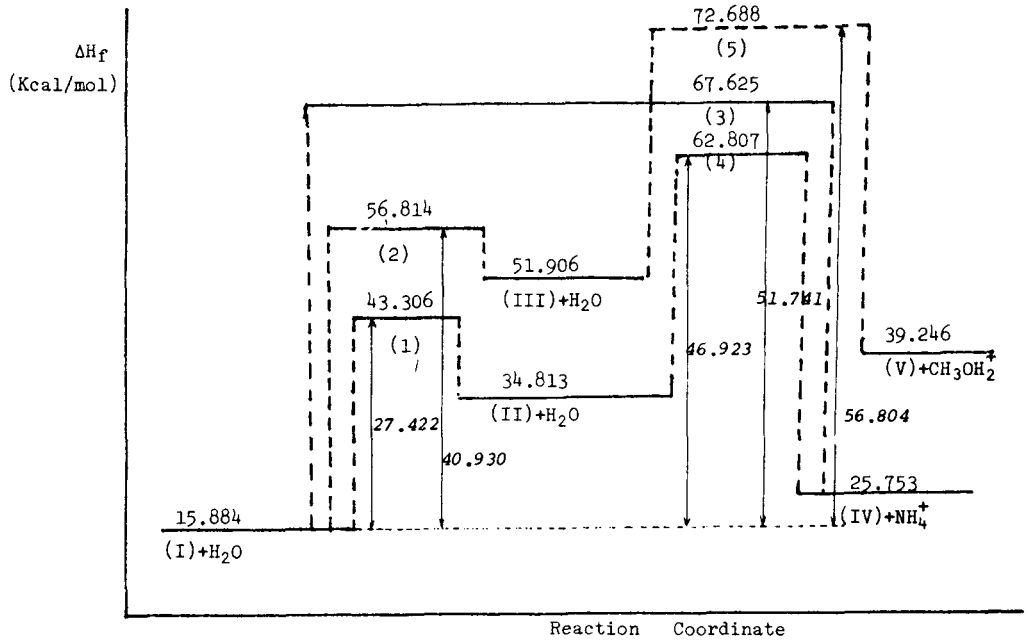


Figure 7. An overview of activation barriers involved in the A2 hydrolysis of methyl carbamate. (1) and (2) are the TSs for the proton transfer to the N- and methoxy-O-protonated forms of methyl carbamate, respectively. (3), (4), and (5) are the TSs for the attack of water on the carbonyl O-, N- and methoxy-O-protonated methyl carbamates.

crease (positive charge increase) on N for carbamate. This is in contrast with the electron density increase on N atom in the rate-determining step of the A2 acid hydrolysis of acetamide found in the previous work,[2] which was also in full accord with the rate depression effects of N-methyl groups observed experimentally.[13]

A corollary of the negative charge increase on O_3 atom in the rate-determining step will be the acceleration (depression) of the rate by the electron withdrawing (donating) group R in carbamates, $ROCONH_2$. This prediction is borne out in the experimental reactivity order of the protonated carbamates towards the A2 reaction[12] of $EtOCONMe_2 < PhOCONMe_2$ and $EtOCONH_2 < MeOCONH_2$, which are consistent with the order of electron withdrawing ability in terms of the Taft's polar substituent constant, σ^*,[14]

R →	Et <	Me <	Ph
σ^* →	−0.10	0.00	+0.60

Thus we are able to accommodate all the experimental observations with a common mechanism of the rate-determining attack of water on the N-protonated forms for amides and carbamates, and there is no need for invoking two different mechanisms.

The authors thank the Korea Science and Engineering Foundation and the Korea Center for Theoretical Physics and Chemistry for support of this work.

References

1. I. Lee, C. K. Kim, and H. S. Seo, *Bull. Korean Chem. Soc.*, **7**, 395 (1986).
2. I. Lee, C. K. Kim, and H. S. Seo, *Tetrahedron*, **42**, 6627 (1986).
3. (a) M. J. S. Dewar and W. Thiel, *J. Am. Chem. Soc.*, **99**, 4899 (1977); (b) M. J. S. Dewar and H. S. Rzepa, *J. Am. Chem. Soc.*, **100**, 784 (1978); (c) M. J. S. Dewar, *J. Mol. Struct.*, **100**, 41 (1983); (d) The MOPAC package, QCPE No. 464.
4. R. B. Moodie and R. Towill, *J. Chem. Soc.* Perkin II, **184** (1972).
5. (a) A. Komornicki, K. Ishida, and K. Morokuma, *Chem. Phys. Lett.*, **45**, 595 (1977); (b) J. W. McIver, Jr. and A. Komornicki, *J. Am. Chem. Soc.*, **94**, 2625 (1972).
6. I. G. Csizmadia, *Theory and Practice of MO calculations on Organic Molecules*, Elsevier, Amsterdam, the Netherlands; 1976, p. 239.
7. (a) T. H. Lowry and K. S. Richardson, *Mechanism and Theory in Organic Chemistry*, 2nd ed., Harper and Row, New York, 1981, Chap. 8; (b) R. A. Y. Jones, *Physical and Mechanistic Organic Chemistry*, Cambridge University Press, London, England, 1979, Chap. 11.
8. S. Yamabe and T. Minato, *J. Org. Chem.*, **48**, 2972 (1983).
9. O. I. Asubiojo and J. I. Brauman, *J. Am. Chem. Soc.*, **101**, 3715 (1979).
10. V. C. Armstrong and R. B. Moodie, *J. Chem. Soc.* (B), 1099 (1968).
11. M. J. S. Dewar, E. G. Zoebish, E. F. Healy, and J. J. P. Stewart, *J. Am. Chem. Soc.*, **107**, 3902 (1985).
12. V. C. Armstrong and R. B. Moodie, *J. Chem. Soc.* (B), 934 (1969).
13. (a) C. A. Bunton, C. O'Connor, and T. A. Turney, *Chem. and Ind.*, 1835 (1968); (b) J. A. Duffy and J. A. Leisten, *J. Chem. Soc.*, 545 (1960).
14. J. Shorter, *Correlation Analysis of Organic Reactivity*, Wiley, New York, 1982, Chap. 4.