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THEORETICAL STUDIES ON THE ACID HYDROLYSIS OF ACETAMIDE†

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Abstract - The mechanism of the A2 hydrolysis of acetamide has been investigated theoretically using MNDO method. Fully optimized geometries of all species at the stationary points corresponding to energy minima and energy maxima along the reaction coordinate are determined for the two reaction paths: the rate-determining nucleophilic attack of water on the carbonyl carbon (i) of the O-protonated tautomer and (ii) of the N-protonated form. Results show that the latter provides a lower energy path by 7.5 Kcal/mol compared to the former. Tetrahedral species' found were not at the energy minima but at or near the saddle points. Optimized structures and formal charges on heavy atoms showed that the bond interchange with the concurrent proton interchange takes place at the rate-determining step. The negative charge on N atom was found to increase in the rate-determining step relative to that of the ground state, the O-protonated acetamide, and hence substitution of electron withdrowing group on N is predicted to depress the activation energy in agreement with the experimental results.

The hydrolysis of amides in aqueous acid solution has been investigated extensively[1] and is widely held to involve rate-determining nucleophilic attack of water on the carbonyl carbon of the amide which has been protonated in a pre-equilibrium step.[1] Since amides, carbamates and ureas are all protonated predominantly on the carbonyl oxygen atom(O-protonated tautomer),[2] a common mechanism of acid hydrolysis may be expected involving attack of water on the O-protonated form.[1d]

On the other hand, the attack of a nucleophile at a carbonyl carbon has received considerable attention from experimental as well as theoretical chemists because of its important role in many organic and biochemical reactions.[3] The process is believed to proceed through a tetrahedral intermediate. However at the present, there are two different views as to the role of the intermediate in the process: gas phase studies of the intrinsic reactivity of the carbonyl compound[4] indicated that the tetrahedral structure is located not at the energy minimum but at the saddle point, whereas solution phase studies[5] suggested that the tetrahedral species is an intermediate corresponding to a local minimum on the potential energy surface. Results of theoretical studies on the process[6] are also indecisive; reports are divided and fail to agree upon one or the other view.

In this work, we examine the hydrolysis mechanism of the protonated acetamide theoretically using MNDO method[7] with a view to casting light on the following questions: (i) Which protonated tautomer, the predominant O-protonated or the minor N-protonated, is involved in the rate-determining attack by water? (ii) What is the nature of the tetrahedral complex, the intermediate(IC) or the transition state(TS)? And finally, (iii) is there a common mechanism for the acid hydrolysis of amides, carbamates and ureas?

Conclusions regarding the third question must of course await our results of similar theoretical studies on the acid hydrolysis of carbamates and ureas.

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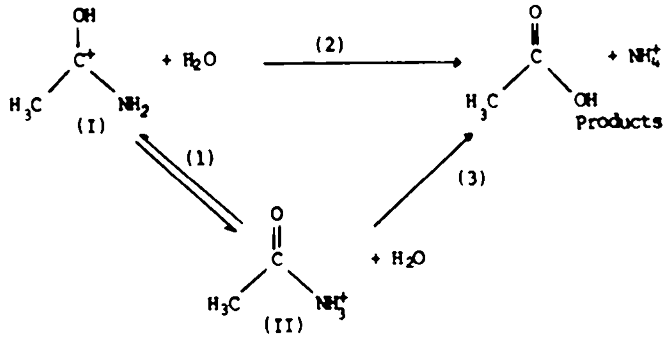
† Determination of Reactivity by MO Theory(Part 44)

RESULTS AND DISCUSSION

In this work we limit our investigations to the A2 reaction mechanism[1d,8] of the acid hydrolysis of acetamide, involving rate-determining nucleophilic attack of water on the carbonyl carbon of the amide which has been protonated in a pre-equilibrium step. In our previous work, we have shown that the predominant tautomer of acetamide in concentrated acid solution is the O-protonated form(I) and the N-protonated form(II) is the minor tautomer which is higher by 17 Kcal/mol in energy than (I).



Scheme 1

We therefore explore two models for the TS, each invloving nucleophilic attack of water on a different tautomer of the protonated acetamide. We should however keep in mind that the ground state consists of (I) and H_2O, from which the tautomer (II) and H_2O is formed by activation(process (1) in Scheme 1); our MNDO results[9] show that the activation barrier for (1) is 29 Kcal/mol with one solvate water acting as the intermediacy for the proton transfer from (I) to (II).

Let us first examine the mechanism for attack of water on the normally dominant tautomer (I), the process (2) in Scheme 1. Results of our calculations are summarized in the potential energy profile, Fig 1. It is widely held that the process (2) leads to a tetrahedral intermediate.[5,6] Indeed we found

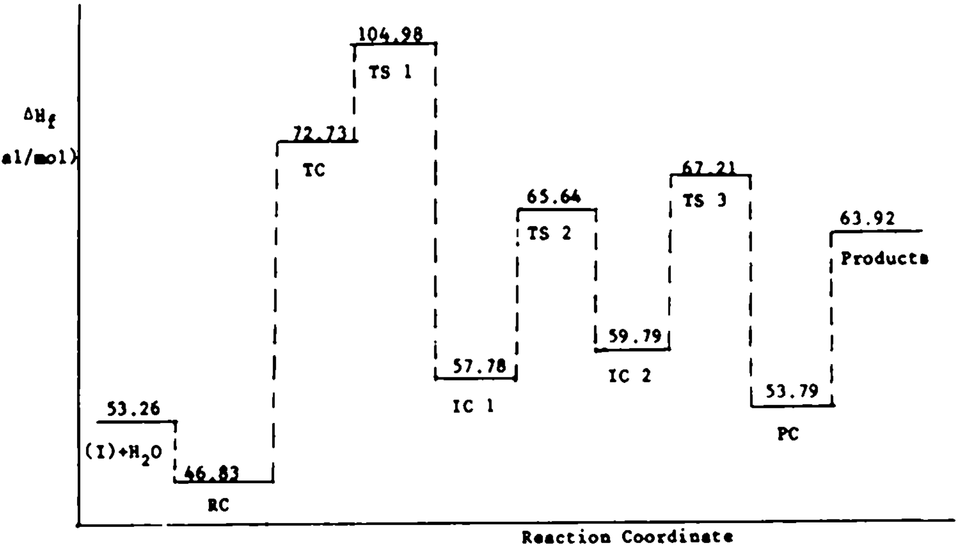


Figure 1. Potential energy profile for the hydrolysis of the O-protonated tautomer.

a tetrahedral complex(TC) as a stationary point on the energy profile; it however corresponds to neither an energy minimum nor a saddle point but it is located in between the reactant complex(RC), an energy minimum, and the TS, a saddle point. There are two more intermediate complexes, IC 1 and IC 2, besides the reactant(RC) and product complexes(PC). Fully optimized structures of all species at the stationary points are collected in Fig 2. At the highest barrier(TS 1) corresponding to the

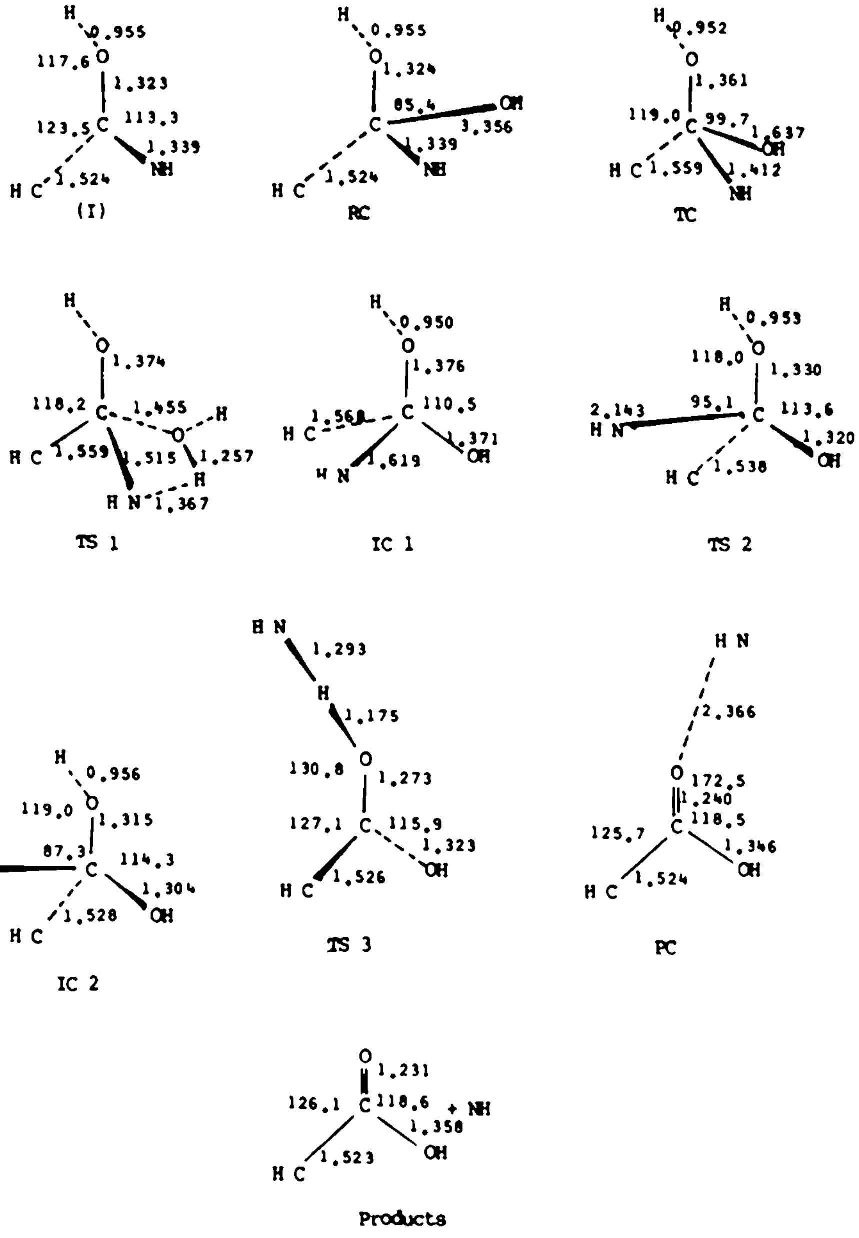


Figure 2. Geometries of all species at the stationary points on the potential energy profile for the hydrolysis of the O-protonated tautomer(bond lengths and angles are in Å and degree).

rate-determining step, concerted bond breaking(C-N bond) and bond formation(C-OH_2 bond) take place maintaining near tetrahedral geometry with concurrent proton interchange between N and water oxygen (O_2).

Table 1. Formal charges(FC, in electronic charge unit) and bond lengths(BL, in Å) for relevant species on reaction paths (2) and (3)

		Ground State(I)	Path (2) TC	Path (2) TS 1	Path (2) IC 1	Path (3) RC	Path (3) TS 1	Path (3) IC
FC	N	−0.2190	−0.3742	−0.2610	−0.0635	−0.0669	−0.2353	−0.3002
	O_2	−0.3256	−0.2050	−0.2376	−0.2955	−0.3793	−0.2664	−0.1611
BL*	C-O_1	1.3237	1.3608	1.3739	1.3760	1.2021	1.1999	1.1967
	C-N	1.3394	1.4105	1.5150	1.6190	1.5583	1.9600	3.5754
	C-O_2	∞	1.6365	1.4548	1.3716	3.6776	1.6360	1.5016

*Bond length for the bond involving carbonyl carbon(C); O_1 and O_2 are the carbonyl and water oxygen, respectively.

In table 1 we have summarized relevant atomic charges and bond lengths for the species around the TS 1 on the reaction paths (2) and (3). We note in this table that length of the C - N bond increases (being broken) whereas that of the C - O_2 bond decreases(being formed) as the reaction proceeds along the reaction coordinate, TC → TS 1 → IC1. Bond length of the C = O bond changes little or is kept almost constant during the process. Moreover the negative charge on N decreases(becomes more positive) while that on water oxygen(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 $\underset{\oplus \, H}{N \cdots C \cdots O_2}$ frame.

The activation barrier calculated for the process (2) was 51.7 Kcal/mol. In the other two TSs, simple bond breaking is involved, the C - N and O - H bonds in the TS 2 and TS 3, respectively.

Next we consider the rate-determining attack of water on the N-protonated tautomer(II), the process (3) in Scheme 1. The potential energy profile, a triple-well type, in Fig 3 is relatively simple compared with that for the process (2) above. Fully optimized geometries for all species at the

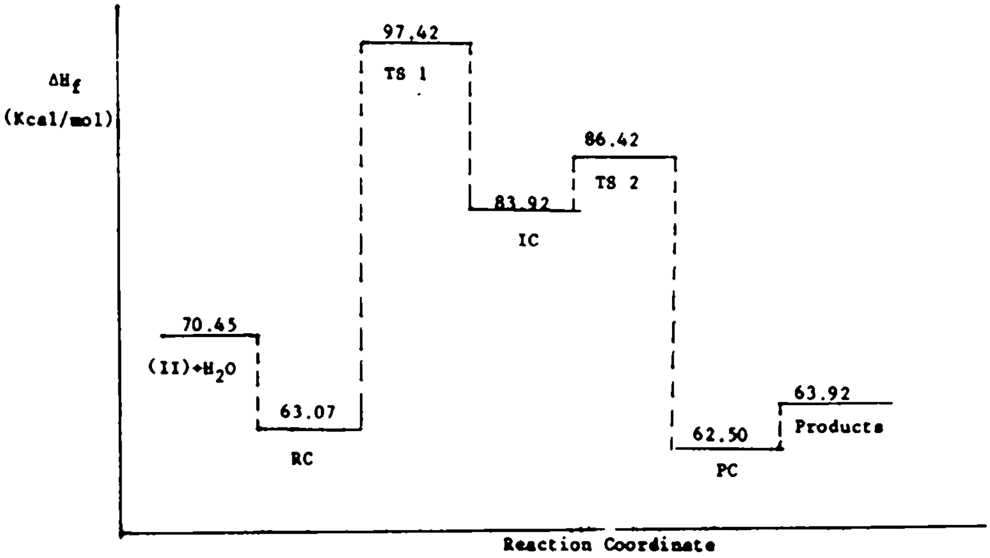
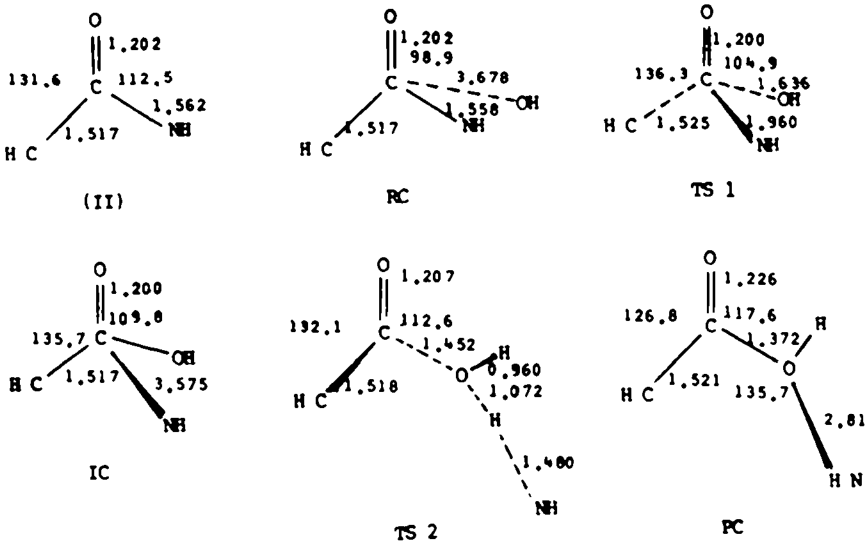


Figure 3. Potential energy profile for the hydrolysis of the N-protonated tautomer.

stationary points are given in Fig 4. Three wells correspond to RC, PC and IC; the two encounter



(II) RC TS 1

IC TS 2 PC

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).

complexes, RC and IC, are formed with the attacking(H_2O) and leaving(NH_3) fragments located approximately in the perpendicular direction to the substrate plane, respectively. These correspond to the two π-complexes of RC and PC, which form the two wells, in the ab initio results of Yamabe et al.[6e] on the gas-phase nucleophilic displacement on acetyl chloride. In agreement with the results of these theoretical studies as well as with the experimental results of Brauman et al.[4], we obtained the tetrahedral TS(TS 1) in between the two π-complex-wells. The only reason why we obtained a triple-well potential energy profile instead of a double-well type is that the process of proton abstraction by the leaving group NH_3 to form NH_4^+ follows subsequently along the reaction coordinate as shown by the TS 2 and PC in Fig 3.

The whole process can be considered to consist of two steps: (i) addition of water molecule on the protonated substrate with concerted breaking away of the leaving group, NH_3, and (ii) abstraction of the proton from the substrate by the leaving group to form NH_4^+. The first step is a normal concerted nucleophilic displacement process at the carbonyl carbon atoms, as Yamabe et al., have shown.[6e] In this step the bond interchange takes place; the π-complexed nucleophile, H_2O, in RC forces down the leaving group, NH_3, and forms the tetrahedral TS, which subsequently proceeds to the IC where the leaving group is further forced down to form the π-complex. The formation of $C - O_2$ bond and the breaking of C - N bond are reflected in the decrease and increase in the bond lengths, respectively, in Table 1. The concurrent proton interchange with the bond interchange also takes place in the path (3) as can be seen in Table 1; the negative charge on N increases(becomes less positive) while that on O_2 decreases(becomes more positive) as the reaction proceeds along RC → TS 1 → IC. Here the proton shifts from N to O_2 and at the TS 1 the positive charge is effectively delocalized over the $N\overset{\dots}{-}C\overset{\dots}{-}O$ frame. The bond lengths involved in the activation process for the path (3) appear, however, greater than those for the path (2), indicating that the positive charge is delocalized over larger area of the looser TS in the path (3).

Since (II) is formed from (I) in a pre-equilibrium process (1), the activation barriers should be relative to the ground state i.e., (I) + H_2O in Scheme 1; the barrier height obtained was 45.2 Kcal/mol, which is lower by 7.5 Kcal/mol compared to that in the process (2) as illustrated in an overview of activation barriers involved in Fig 5.

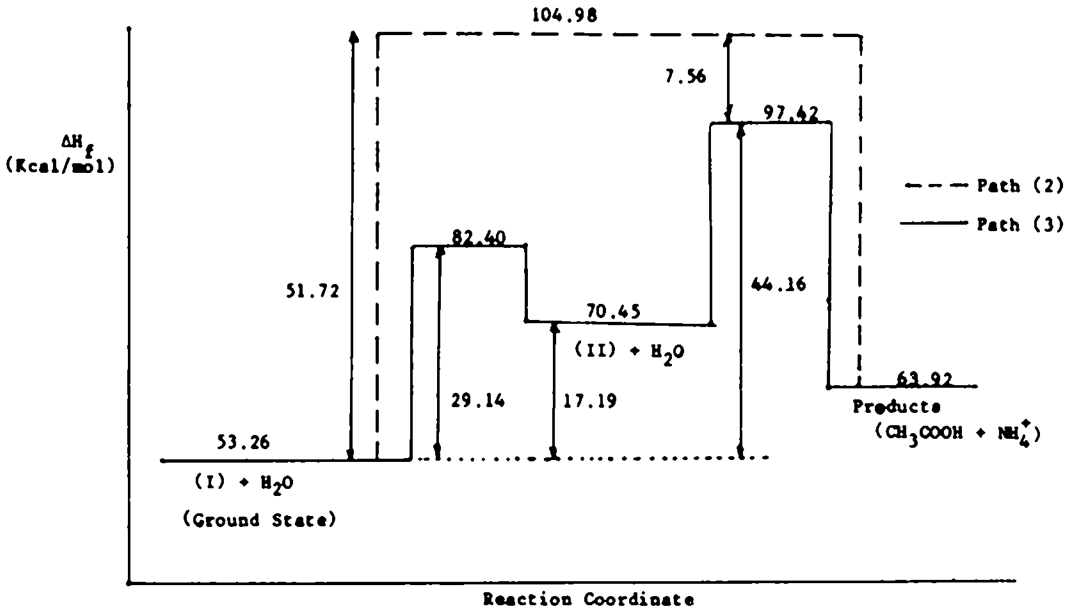


Figure 5. An overview of activation barriers involved in the A2 hydrolysis of acetamide.

We therefore conclude that the acid hydrolysis of acetamide proceeds via the minor N-protonated tautomer, which is formed in a pre-equilibrium and subsequently is attacked by water. However we can not completely rule out the route (2) as a possible competitive reaction path, since the difference in activation energy of 7.5 Kcal/mol is relatively small.

Absolute values of activation enthalpies obtained in this work seem certainly too high,[10] but this stems of course from a well-known weakness of the MNDO method.[11] However we are little concerned with the absolute values as we set out to pursue mechanistic aspects. Furthermore this is a gas-phase study for which no experimental comparison is available.

Finally the negative charge on N increases(Table 1) at the TS 1 by $\Delta q_N = q_N(TS\ 1) - q_N(I) = -0.0420$ and -0.0163, respectively, for the path (2) and (3) proceeding from the ground state, the O-protonated form(I). We would therefore expect that electron donating substituents on N, e.g. $-CH_3$ group, will destabilize the TS 1 and will elevate the activation barrier retarding the rate of acid hydrolysis. This type of behavior has been, indeed, evidenced in the experimental results of the effect of N-substituents on the amide hydrolysis rate.[5b,12]

CALCULATIONS

MNDO program[7] was used throughout in this work. All structures corresponding to stationary points were fully optimized with the energy gradient,[13] and the TSs were characterized by confirming only one negative eigenvalue in the Hessian matrix.[14]

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