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AM1 STUDIES ON THE ACID HYDROLYSIS OF ACETAMIDE[1]

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The A2 hydrolysis of acetamide was investigated using the AM1 method and the results were compared with those of MNDO. The two methods agree in the general mechanism but differ in detail; MNDO assigns an unduly high energy for a complex with long bonds in contrast to AM1 and *ab initio* (at the 3–21G and 6–31G levels) methods, which predict a stable structure for such a complex. Inclusion of solvate water molecules has the effect of lowering activation barriers in general. An increase in the number of solvating molecules up to four results in narrowing of the activation energy gap between the two rate-determining steps of the A2 hydrolysis of the *N*- and *O*-protonated acetamide, but no reversal of the relative order of the barrier height occurs; the A2 hydrolysis proceeding through the less stable *N*-protonated tautometer is therefore likely to remain as a major reaction path in solution-phase reactions, in agreement with experimental results.

INTRODUCTION

The A2 hydrolysis of acetamide in aqueous acid solution has been extensively studied, and is believed to proceed by a rate-determining attack of water on the carbonyl carbon which has been protonated in a pre-equilibrium step.[2] Our theoretical studies on the mechanism using the MNDO method[3] indicated that the rate-determining nucleophilic attack of water occurs at the carbonyl carbon of the *N*-protonated form and tetrahedral species[4] found on the reaction coordinate are not intermediates but resemble more transition states (TS).[5] The problem of whether the tetrahedral species is a TS or an intermediate in the nucleophilic substitution at a carbonyl carbon has long been controversial. In this respect, results of recent studies on the nucleophilic displacement reactions of acyl compounds in the gas phase together with MO theoretical analysis have been helpful in unravelling mechanisms occurring in solution. It has been shown that the tetrahedral species is likely to become a tetrahedral TS when weak nucleophiles and good leaving groups (LG) are involved, whereas tetrahedral intermediates can be expected when strong nucleophiles and poor LG are involved.[5,6] On the other hand, the involvement of even one solvate molecule is known to cause a profound change in the gas-phase reaction mechanism.

In this work, we investigated the A2 hydrolysis of acetamide theoretically using the AM1 method,[7] in which the hydrogen bonding energies are properly accounted for, in contrast to the MNDO method. In particular, we studied in some detail the solvent effect on the A2 hydrolysis mechanism of acetamide.

CALCULATIONS

All calculations were carried out with the AM1 method.[8] Geometries of equilibrium species were fully optimized by the energy gradient method. Transition states were located by the reaction coordinate method,[9] refined by the gradient norm minimization[10] and characterized by confirming only one negative eigenvalue in the Hessian matrix.[11] In the solvent effect studies, up to two solvating water molecules were attached to the water nucleophile successively in a stepwise manner in the entire reaction process calculations and were compared with the unsolvated gas-phase reaction paths. Two additional solvating water molecules were attached again successively to the ground state, the *O*-protonated tautomer and the TS corresponding to the rate-determining step in order to elucidate solvent effects on the barrier heights. The solvated TSs in these cases were re-optimized for the supermolecules consisting of protonated acetamide and solvating water molecules and characterized again by confirming only one negative eigenvalue in the Hessian matrix. However, no structural changes in the TSs were noted by the solvating water molecules attached to the bare TSs.

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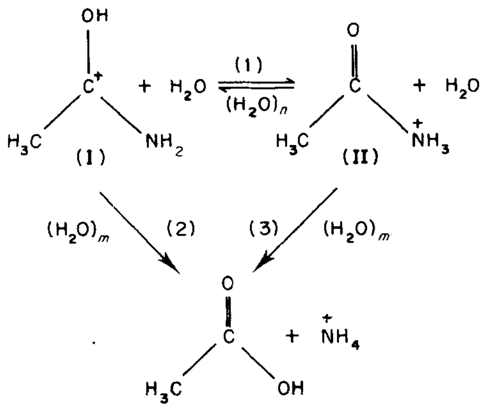
RESULTS AND DISCUSSION

Attention was focused on the A2 hydrolysis mechanism[12] of protonated acetamide in acid solution; in particular we examined the effect of the solvent on the reaction processes in order to shed some light on the preferred reaction path involved in the solution-phase acid hydrolysis.[2] The conceivable reaction paths are shown in Scheme 1.



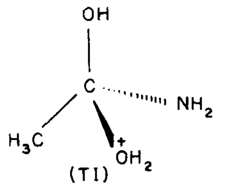
where n and m are solvate number ($n = 0$–2 and $m = 0$–4).

Scheme 1

The intramolecular proton transfer (path 1) between the two protonated tautomers, I and II, is a rapid process compared with the subsequent A2 hydrolysis processes (paths 2 and 3), as has been described.[13] These results are in agreement with those obtained by MNDO,[14] except that a lower energy difference of $\Delta\Delta H_f = \Delta H_f(\mathbf{II}) - \Delta H_f(\mathbf{I}) = 10{\cdot}9$ kcal mol^{-1} is obtained in contrast to the corresponding value of 17 kcal mol^{-1} given by MNDO. The lower energy gap between the two forms obtained by AM1 provides additional support for the mechanism involving the nucleophilic attack of water on the less stable form (**II**), since the equilibrium amounts of the two tautomer will be similar.

Gas-phase A2 hydrolysis of the *O*-protonated tautomer (I)

This process corresponds to path 2 with $n = 0$ in Scheme 1. The potential energy profile and structures of equilibrium species involved in this process are presented in Figures 1 and 2. The potential energy profile in Figure 1 is similar to that obtained by MNDO,[5] but it lacks the oxonium ion-type transient intermediate (TI) suggested by McClelland *et al.*[15] and found to exist by MNDO between the reactant complex (RC) and the TS1 corresponding to the rate-determining step. In order to confirm the existence of TI, we attempted *ab initio* optimization at the 3–21G and 6–31G levels,[16] but it was unsuccessful; the failure to obtain an optimized structure for the TI by both AM1 and *ab initio* calculations tacitly suggests that AM1 is superior to MNDO in reproducing the *ab initio* results. One reason why AM1 fails to give TI could be the more positive charge delocalization over the entire molecule **I** compared with MNDO, as shown in Table 1; the positive charge localization on the oxygen atom in TI can be energetically



(TI)

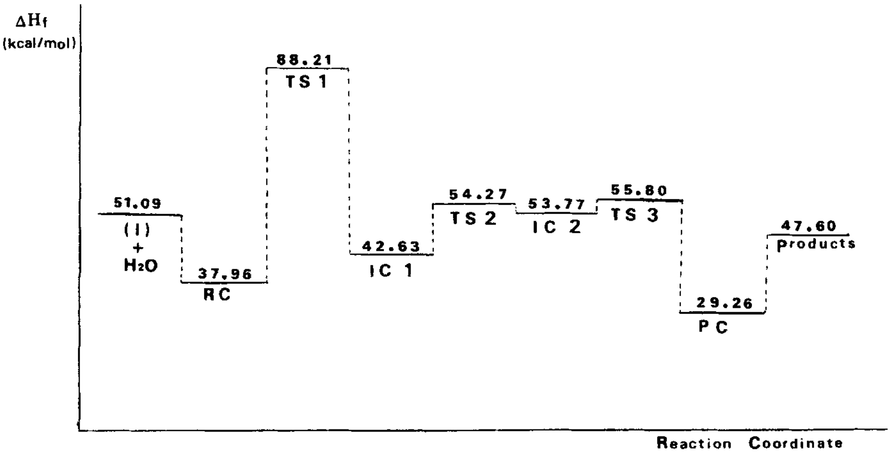


Figure 1. Potential energy profile for the gas-phase A2 hydrolysis of protonated tautomer (I)

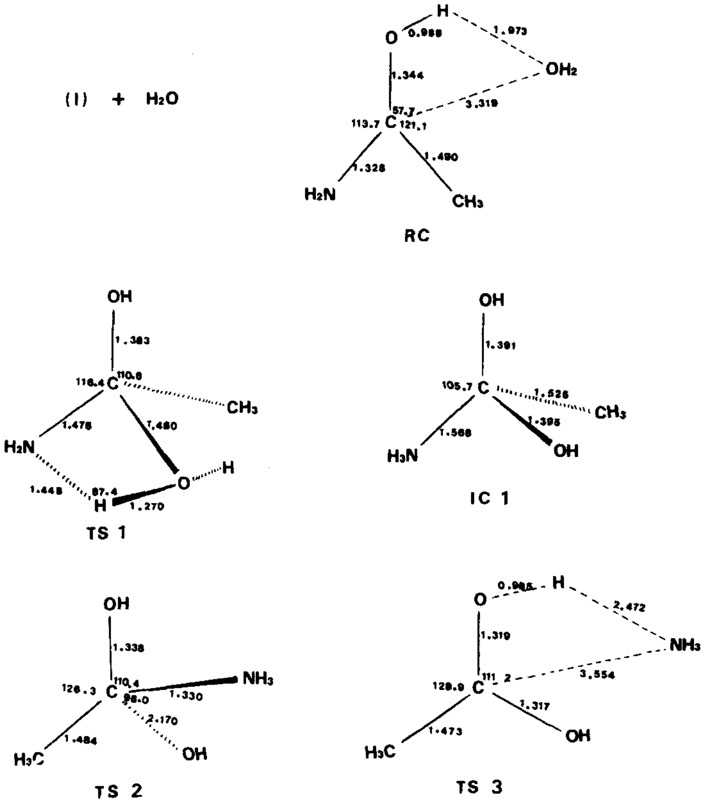


Figure 2. Geometries of some species at stationary points on the potential energy profile for the gas-phase A2 hydrolysis of protonated tautomer (I)

unfavourable by AM1 so that the structure corresponding to TI may become destabilizing. The existence of such transient intermediate seems very debatable, however, since the TI found by MNDO was not a stationary point species and it may have very short lifetime in the solution-phase experiment, with little possibility of actual experimental identification in real situations.

Since TI was not found by AM1 calculation, TS 1 is formed by the nucleophilic attack of a water molecule on the carbonyl carbon with the simultaneous 1,3-shift of a water proton toward the nitrogen atom, which is similar to the structure of TS 1 by MNDO.[5] The other reaction processes are essentially the same as those by MNDO; TS 1 is followed, in succession, by a tetrahedral intermediate (IC 1), TS 2 in which C—N bond cleavage takes place and IC 2 which is a *gem*-diol type similar to RC with NH_3 and OH_2 interchanged.

Table 1. Comparison of charge distribution in tautomer **I** by MNDO and AM1

Method	Carbonyl-C	—OH	—NH_2	—CH_3
AM1	+0·315[a]	+0·104	+0·358	+0·224
MNDO[b]	+0·319	+0·090	+0·298	+0·222

[a] Electronic charge unit.
[b] Ref. 5.

Gas-phase A2 hydrolysis of *N*-protonated tautomer (II)

This process corresponds to path 3 with $m = 0$ in Scheme 1. The less stable tautomer, **II**, formed by a proton transfer from the stable form, **I**, proceeds to hydrolyse as shown by the potential energy profile in Figure 3 with stationary point species in Figure 4. Inspection of Figure 3 reveals that the rate-determining step in this process corresponds to TS 2, which is lower by ca 14 kcal mol^{-1} than the activation barrier, TS 1, in the A2 hydrolysis of the tautomer **I**. This process starting from the less stable form, **II**, provides the lowest path in the gas-phase A2 hydrolysis of acetamide, which is in agreement with but varies in mechanistic details from that of MNDO; the rate-determining step was the formation of intermediate A via the concerted S_N2-type TS (TS 1) in the nucleophilic attack of a water molecule

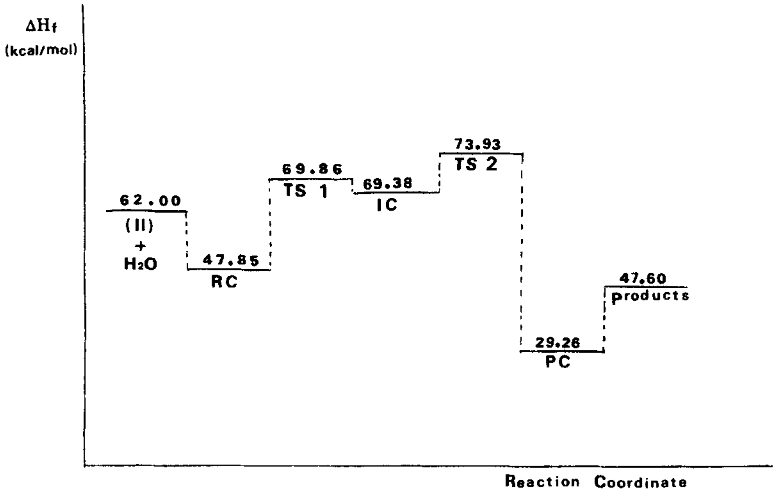


Figure 3. Potential energy profile for the gas-phase A2 hydrolysis of protonated tautomer (II)

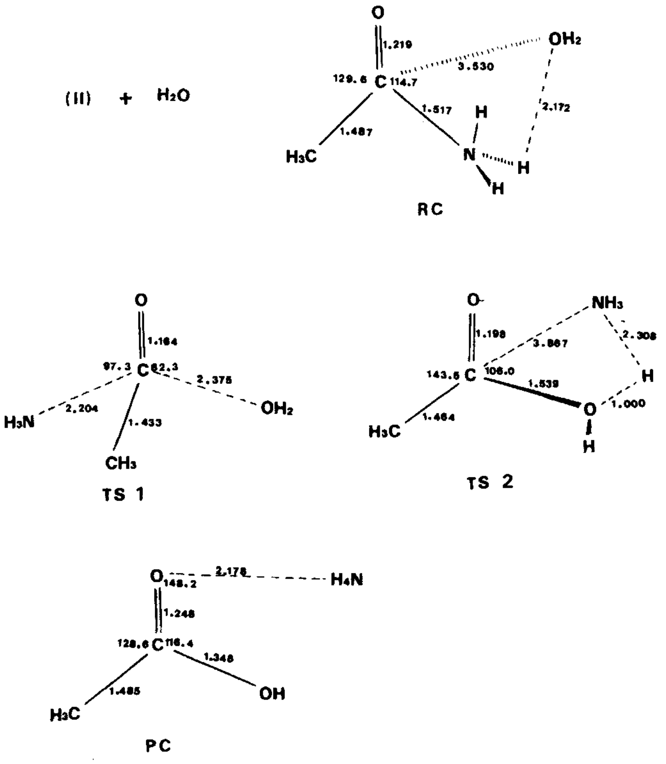
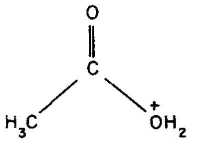
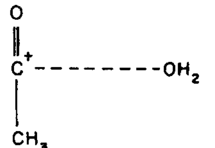


Figure 4. Geometries of some species at stationary points on the potential energy profile for the gas-phase A2 hydrolysis of protonated tautomer (II)

on the carbonyl carbon of the tautomer **II** by MNDO, whereas it was the formation of the product complex PC via TS 2 by AM1. This difference in the rate determining step between the two methods originates from the fact that AM1 does not give a stationary point species (A), but instead predicts a long-range complex (B). The discrepancy between the two methods regarding the existence of (A) stems from the difference in the stability of an acylium ion. Table 2 shows relevant atomic charges for the optimized structures of acylium ion by AM1 and MNDO. We note that AM1 predicts a more evenly delocalized positive charge, indicating more effective resonance as shown in Scheme 2. This is a similar situation to the problem of whether TI should exist as an optimizable structure or not in the A2 hydrolysis of the tautomer **I**. In the oxonium ion-type species (A), the positive charge delocalization through the resonance effect in Scheme 2 is not possible and most of the charge is expected to become localized on $—OH_2^+$. This charge localization should result in energy destabilization so that structure (A) cannot exist as an optimized structure by AM1. Another reason for this difference in the two methods in the well known weakness of MNDO that a long-bond species, such as (B), has an unduly high energy, so that MNDO prefers a localized structure (A) instead of a long-bond species (B).



(A)



(B)

Table 2. Comparison of charge distribution on acylium ion by MNDO and AM1

Method	—O	Carbonyl-C	$—CH_3$
AM1	+0·130[a]	+0·446	+0·424
MNDO	+0·138	+0·458	+0·405

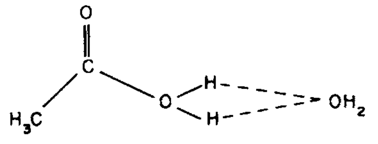
[a] Electronic charge unit.

$$H_3C—C\equiv\overset{+}{O} \leftrightarrow H_3C—\overset{+}{H}=O \leftrightarrow \overset{+}{H}\cdot H_2C=C=O$$

Scheme 2

Solvent effects

In order to simulate solution-phase reaction, solvating water molecules were added successively to the reaction system and the effect of solvent on the mechanism was studied. We found no changes in the reaction paths from those of the gas-phase reaction for the tautomer **I** with a general lowering of the barrier heights, but there was a considerable mechanistic change from the gas-phase process in addition to the lowering of the barrier heights for the reaction involving tautomer **II**. When one solvating water molecule is attached to the water nucleophile, species (C) is formed instead of species (A),



(C)

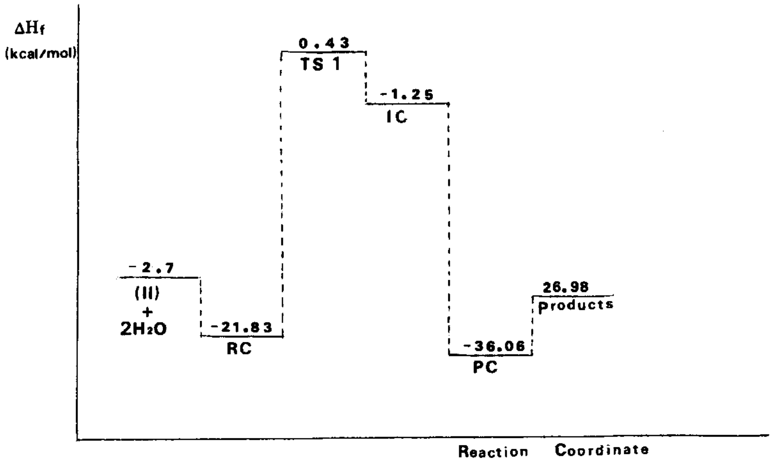


Figure 5. Potential energy profile for the solvated A2 hydrolysis of protonated tautomer (II)

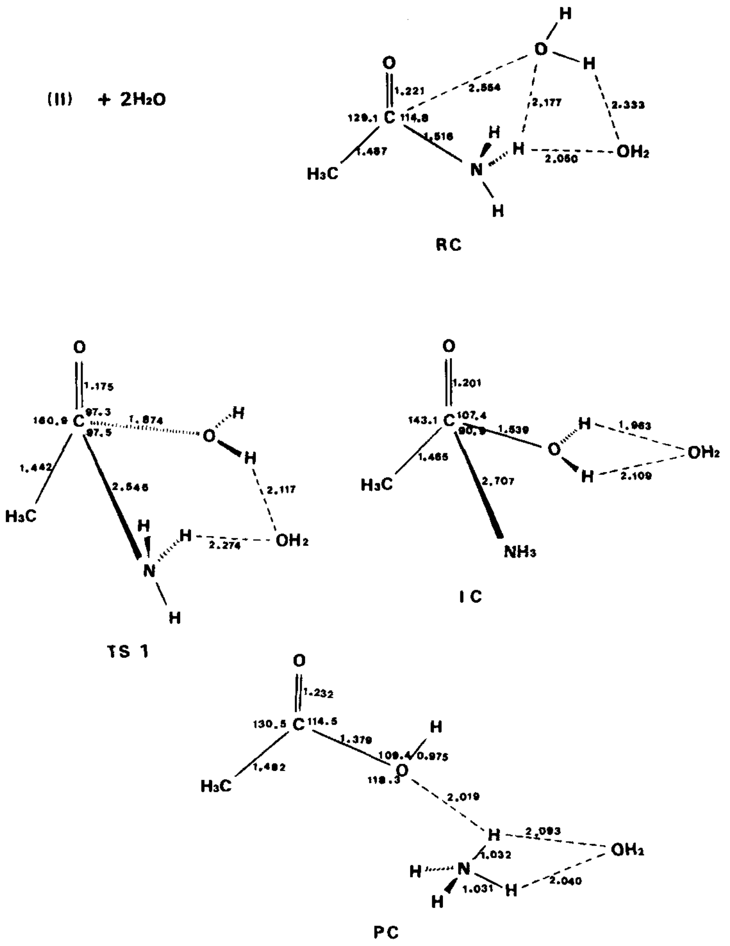


Figure 6. Geometries of species at stationary points on the potential energy profile for the solvated A2 hydrolysis of protonated tautomer (II)

in contrast to the gas-phase reaction. The A2 hydrolysis, in this case, proceeds via the S_N2 path in which the solvated nucleophile attacks the carbonyl carbon of tautomer **II** and cleavage of the leaving group, NH_3, occurs simultaneously. These reaction schemes are in line with the solution phase mechanism suggested by Armstrong, *et al.*[2b] and Smith and Yates.[2e] The potential energy profile for path 3 with $m = 1$ (Scheme 1) is presented in Figure 5 and the optimized structures for the equilibrium species on the reaction coordinate are shown in Figure 6.

The processes following the rate-determining step (TS 1) are rapid, as can be seen in Figure 5. The abstraction of a proton from $—OH_2^+$ by the leaving group, NH_3, which is from the intermediate complex (IC) of type (C), constitutes a general acid–base equilibrium, which should be a diffusion-controlled process. The reactions involving more than two solvating water molecules ($m > 2$), proceed in a similar manner to that for $m = 1$ accompanied by a corresponding lowering of activation barriers. Now there arises the problem of whether the reaction path change occurs or not due to the lowering of barrier heights by the solvent effects. The heats of formation of the TSs corresponding to the rate-determining step for the solvated A2 hydrolysis processes of tautomers **I** and **II** are summarized in Table 3. The results show that as the number of solvating molecules is increased, the difference in the activation energy barriers for the two tautomers decreases but no reversal in the relative barrier heights is realized, maintaining the preference of path 2 to path 1. Of course, there may still be the possibility of a reversal of the relative barrier heights in the bulk solvent of the solution-phase reaction to alter the preferred path 2 to 1, but the use of four solvate molecules represent approximately the first solvation shell which can account

Table 3. Activation energy barriers (kcal mol^{-1}) of rate-determining steps (r.d.s.) for the gas-phase and solvated A2 hydrolysis processes

m	Tautomer **I**:[a] $\Delta H_f^{\ne}$ (**I**)[b]	Tautomer **II**: $\Delta H_f^{\ne}$ (**II**)[c]	$\Delta\Delta H_f^{\ne}$ [d]
0	37·12	22·84	14·28
1	26·66	14·04	12·62
2	24·29	13·78	10·51
3	25·45	15·49	9·96
4	27·48	16·99	10·49

[a] Reference ground state.

[b] $\Delta H_f^{\ne}$ (**I**) = ΔH_f (TS for r.d.s.) − ΔH_f (tautomer **I**).

[c] $\Delta H_f^{\ne}$ (**II**) = ΔH_f (TS for r.d.s.) − ΔH_f (tautomer **I**).

[d] $\Delta\Delta H_f^{\ne} = \Delta H_f^{\ne}$ (**I**) − $\Delta H_f^{\ne}$ (**II**).

for major effects of solution. It therefore appears that the preferred path in bulk solution is likely to remain as predicted, i.e. path 2, in Table 3.

CONCLUSIONS

AM1 is better suited for the study of the A2 hydrolysis mechanism of acetamide than MNDO, since the latter cannot properly reproduce a relatively stable complex with long bonds.[7]

The A2 hydrolysis of acetamide proceeds via the less stable tautomer **II**, which is formed in a pre-equilibrium and is subsequently attacked by water. This mechanism is in complete agreement with that obtained by MNDO.[5]

Inclusion of solvating molecules not only lowers the activation barriers but also alters detailed mechanistic features along the reaction coordinate of the gas-phase A2 hydrolysis involving tautomer **II**.

An increase in solvation up to four solvating molecules results in narrowing of the activation energy gap between the two rate-determining steps for tautomers **I** and **II** without causing reversal of the relative order of the barrier height; extrapolation of this trend to bulk solution is likely to be justified, providing agreement with the solution-phase results of Armstrong *et al.*[2b] and Smith and Yates.[2e]

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