Intramolecular Amide Hydrolysis in N-Methylmaleamic Acid Revisited

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Abstract: The intramolecular amide hydrolysis of N-methylmaleamic acid have been revisited by use of density functional theory and inclusion of solvent effects. The results indicate that concerted reaction mechanism is favored over stepwise reaction mechanism. This is in agreement with the previous theoretical study. Sovlent effects have significant influence on the reaction barrier.

Keywords: Density functional theory, N-methylmaleamic acid, reaction mechanism.

As models for hydrolytic enzymes, intramolecular systems containing carboxy group have been extensively investigated for many decades and continue to be a subject of great interests[1,2]. The recent theoretical study[2] on N-methylmaleamic acid (at HF/4-31G level and in the gas phase) indicated that concerted mechanism is favored over stepwise mechanism on amide hydrolysis. In this paper, we revisited the reaction mechanism by use of density functional theory (DFT) since DFT is more accurate in predicting the energy. Solvent effects are considered because they play crucial role in biological processes.

All geometry optimizations were performed at B3LYP/6-31G (d,p) level using the GAUSSIAN 98 programs[3]. The B3LYP function is a combination of Becke's three-parameter hybrid exchange function[4], and Lee-Yang-Parr correlation function[5]. Single point energy calculation is given at B3LYP/6-311G(2df,p). Zero point energy correction and entropy contribution at 298.15 K are included in both the gas phase and the solution. Solvent effects were investigated using Onsager model [6] with dielectric constant of 78.39. Single point energy calculation in the solution is done by use of conductor-like polarized continuum solvent model (CPCM)[7].

The reaction mechanisms are schematically shown in **Scheme 1**. Route A is the concerted mechanism, that is, the proton transfer from oxygen to nitrogen and C-N bond cleavage occurs simultaneously. Route B is stepwise mechanism with two steps. The first step is the nuclophilic attack of carboxyl oxygen on aminocarbonyl carbon, accompanied by the proton transfer to carbonyl oxygen. This gives an intermediate

shown as **2** in **Scheme 1**. The second step is the lengthening of C-N bond and the proton transfer from oxygen to nitrogen. This forms the transition state **TS2** in **Scheme 1**. Our calculated results are shown in **Figure 1**.

Scheme 1
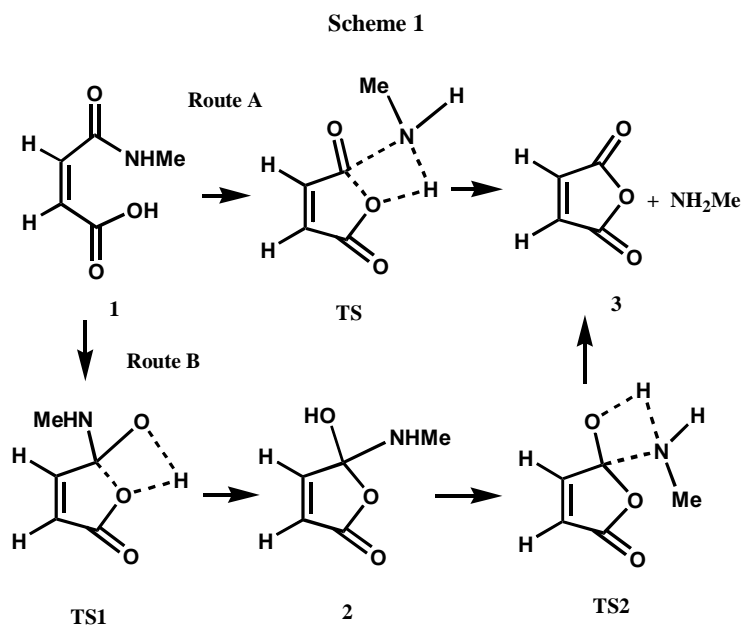
It can be seen that for route A (left diagram) in the gas phase, the energy barrier **TS** lies 36.5 kcal mol^{-1} higher than reactant **1**, the separated system 3 has a relative energy 3.2 kcal mol^{-1} compared with reactant **1**. In the solution, however, the energy barrier drops significantly, which is 14.8 kcal mol^{-1} lower than that in the gas phase. The separated system is slightly higher (by 0.7 kcal mol^{-1}) than that in the gas phase.

For route B (right diagram) in the gas phase, it costs 32.0 kcal mol^{-1} (TS1) in order to form **2**. The intermediate **2** is 18.9 kcal mol^{-1} higher than **1**. From **2** (**Scheme 1**), the proton transfer from oxygen to nitrogen (TS2) lies 49.6 kcal mol^{-1} higher than **1**. The higher energy barrier from **TS2** is certainly not profitable for the reaction, although **TS1** in route B is slightly lower **TS** in route A. In the solution, it can be seen that **TS1** drops significantly (by 12.7 kcal mol^{-1}) compared with that in the gas phase, while the second transition state drops slightly (by 2.4 kcal mol^{-1}).

Figure 1 Energy profiles of the reaction mechanism.
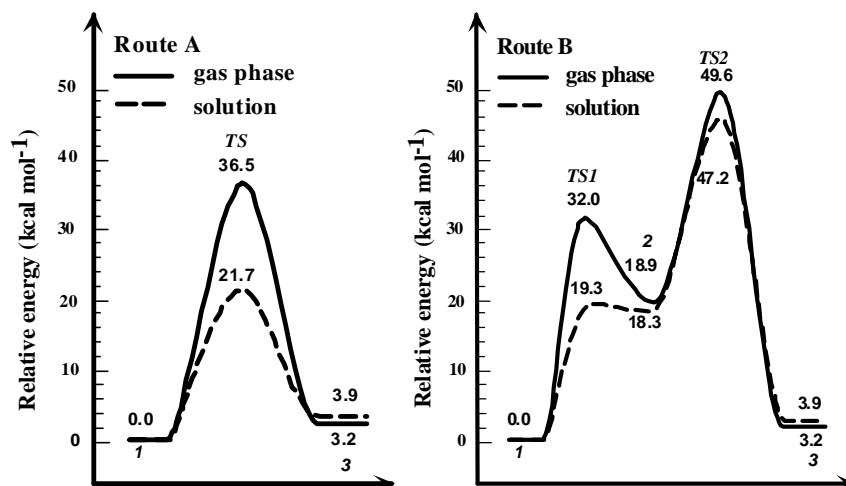
Therefore, concerted reaction mechanism (route A) is energetically more favorable over stepwise reaction mechanism (route B). This is in agreement with previous theoretical study[2]. Although for proton transfer from oxygen to amidic nitrogen (**TS2**), solvent only slightly lowers the reaction barrier, it has significant effects in lowering the reaction barrier for the processes with C-O bond formation (**TS** and **TS1**). This indicates that solvent effects play an important role in biological processes of the amide hydrolysis.

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