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Computational study on the aminolysis mechanism of 4,4-dimethyl-2-vinyl-2-oxazolin-5-one with methylamine

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ABSTRACT

The mechanism of 4,4-dimethyl-2-vinyl-2-oxazolin-5-one (DMVO) with methylamine were studied at the B3LYP/6-311++G(d, p) level in the gas phase and solution. Two possible mechanisms of the concerted process and the addition/elimination stepwise pathway involving the general base catalysis by methylamine and the general acid catalysis by acetic acid were taken into account. In the gas phase, the first stages of the stepwise mechanism for all pathways are shown to be the rate-limiting processes with higher energy barriers than those for the second step. The results also predict that the concerted mechanisms of noncatalyzed and based-catalyzed aminolysis are more favorable than the stepwise mechanisms. Concerning the acid catalyzed aminolysis involving carboxylic group of the acetic group, the reaction prefers the neutral stepwise pathway to the concerted mechanism. In addition, the most favorable pathway appears to be the acid catalyzed stepwise process that includes formation of eight-membered rings in the transition state structure. The solvent effect by a polarized continuum model (PCM) does not significantly change the conclusion.

1. Introduction

As the model for the formation of peptide bonds, the aminolysis of esters and anhydrides has attracted considerable interest both theoretically [1–14] and experimentally [15–31] in recent decades. Up to now, three possible reaction mechanisms have been presented in the literatures: (a) the concerted mechanism where the formation of the two new bonds, the cleavage of old bonds and the transfer of the proton proceed simultaneously; (b) the stepwise pathway involving the zwitterionic intermediates; (c) the stepwise (addition/elimination) mechanism through neutral intermediates. By employing *ab initio* methods, Zipse et al. [19] explored the mechanism of aminolysis for methyl acetate with methylamine. Their calculations pointed out that the reaction rate mostly depends on the leaving group and the stepwise pathway is preferable to the concerted mechanism. Ilieva and his co-workers [23], adopting the QCISD/6-31G(d, p) and B3LYP/6-31G(d) methods, investigated the aminolysis of methyl formate with ammonia. The results showed that the most favorable pathway appears to be the stepwise process of general base catalyzed reaction and the solvent of acetonitrile reduces all energy barriers of the reaction greatly.

Some researchers tried to explore the stepwise mechanism through zwitterionic intermediates in theory [15,18,21,22]. For the aminolysis of formic acid with ammonia, Chalmet and his co-authors [21] did not find transition states associated with zwitterionic intermediates, and they noted that four explicit water molecules are needed to stabilize the zwitterionic complexes. Subsequently, Ilieva et al. [23] carried out the MP2/6-31G(d, p) method to study the aminolysis reaction of methylamine and failed to identify zwitterionic transition state and intermediates. Singleton and Merrigan [32] also made efforts to obtain the formation of the zwitterion between methyl amine and amine in water medium. Nevertheless, they did not detect the global minima for these structures. Lately, Sung et al. [33] explored the structure and stability of the zwitterionic intermediates in the reaction of phenyl acetate with ammonia. They predicted that at least five explicit water molecules are needed to stabilize the zwitterionic complexes.

It is well known that the differences in the ester structures [34–38], amine nature [39–41] and reaction medium [34,42] can lead to change of the mechanism and the rate determining step. Zipse et al. [19] predicted that the concerted mechanism of methyl acetate shows a similar energetic picture in comparison with the stepwise mechanism. Jin et al. [26] revealed that the concerted pathway for the aminolysis of phenyl formate is more favorable than the neutral stepwise process in the gas phase and solutions. The reaction of 2-benzoxazolinone with methylamine [23]

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preferred the concerted pathway to the stepwise mechanism in the gas phase and the solvent effects from the water, ethanol and acetonitrile do not change the conclusion based on gas-phase significantly. According to another work [25], the most favorable pathway for the aminolysis of methyl benzoate is through a base-catalyzed neutral stepwise mechanism. Subsequently, by using B3LYP/6-311+G(d, p) method, Xia et al. [28] reported the aminolysis and ammonia-assisted aminolysis of substituted methylformates $XC(O)OCH_3$, X = NH_2, H and CF_3 in the gas phase and acetonitrile solution. In the direct aminolysis reaction of HC(O)OCH_3, the free energies of the concerted and stepwise pathways are about 30–50 kcal/mol. Their results support the concerted pathway for the direct aminolysis. The most favorable pathway is through the general base catalyzed neutral stepwise mechanism in which the second ammonia plays the role of catalysis by facilitating the proton transfer processes. Simultaneously, through B3LYP/6-31G(d, p) method, Yi and co-workers [29] thoroughly examined the mechanism of aminolysis of p-substituted phenyl acetates ($CH_3C(O)OC_6H_4X$, X = H, NH_2, and NO_2) with ammonia in the gas phase. Their results support the concerted process for all three aminolysis reactions and the reaction is more favorable for X = NO_2 than for X = H and NH_2 in the gas phase and in acetonitrile. In the case of reaction of ethyl thioacetate and ethyl acetate [22], the stepwise process through neutral intermediates involving water-catalyzed proton transfer is the most advantageous of all possible pathways at the MP2/6-31+G(d) and MP2/6-31G(d, p) levels of theory. The energy barriers of the reaction in the gas are a bit high, about 40 kcal/mol. When the catalytic role of the waters are considered, the activation energies decrease significantly. Therefore, depending on the nature of the reactants and medium, the reaction can occur either through concerted or stepwise mechanisms.

For the aminolysis of cyclic anhydride, Petrova et al. [27] explored different possible mechanisms of the aminolysis reaction of succinic anhydride including the general base catalysis by methylamine and the general acid catalysis by acetic acid. The results indicated that the most favorable pathway of the aminolysis is acid catalyzed stepwise mechanism that formed the eight-membered rings in the transition state structures and the aprotic solvent benzene lowers all energy barriers. Several possible mechanisms for the aminolysis of propylene carbonate [31] were reported in our previous work by applying computational techniques in the gas phase and in benzene and water mediums. The uncatalyzed, base-catalyzed and acid-catalyzed aminolysis reaction were also taken into account. Among the different mechanisms of this reaction, the stepwise pathway of the acid catalysis involving carboxylic acid of the acetic acid was predicted to be the most favorable. The solvent effect by a polarized continuum model (PCM) reduces the energy barriers slightly.

As a kind of significant five-membered heterocyclic compounds, oxazolin-5-ones are important intermediates in peptide synthesis and other quantities of organic synthesis [43–51] and are considered as activated internal esters of N-acylamino acids. Recently, Zeng et al. [52] examined N-protonated and O-protonated two types of reaction mechanism, and predicted the mechanism for the acid-promoted hydrolysis of 2,4,4-trimethyloxazolin-5-one (TMO) by applying a higher level of electronic structure theory. Their results manifest that the reaction supports the water-assisted pathways and the O-protonated pathway is more favorable than N-protonated one. In the case of aminolysis of 2-benzoxazolinone [24], the most preferable mechanism is the neutral concerted route in the gas phase and the solvent effects do not change the conclusion based on the gas-phase investigation.

To our best knowledge, few efforts have been devoted to a systemic investigation on the mechanism of the 4,4-dimethyl-2-vinyl-2-oxazolin-5-one (DMVO) with methylamine as well as the influences of the solution from a theoretical point of view. In the present work, the aim is to examine the ring opening of DMVO in the process of aminolysis by employing high levels of quantum chemical methods including the general base catalysis by methylamine and the general acid catalysis by acetic acid. Moreover, the influence of the solution effects including the water, ethanol and acetonitrile is assessed in this paper.

2. Computational details

All calculations were carried out with Gaussian 09 program package at the B3LYP level of theory. The geometric structures for all the reactant complex (RC), product complex (PC), intermediate (INT) along with transition state (TS) were fully optimized at the B3LYP/6-311++G(d, p) [53–56] level. The stationary points were verified by the harmonic frequency analysis as a minimum with all positive frequencies or as a transition state with one imaginary frequency at the same level. Meanwhile, all transition states associated with the correct reactant and product were checked by intrinsic reaction coordinate (IRC) computations [57]. Natural atomic charges and Wiberg bond orders for all optimized structures were calculated at the same level through Natural Bond Orbital Theory (NBO) [58].

As the reaction actually takes place in aqueous solution, the solvent effect for aminolysis should be considered. We chose water, ethanol and acetonitrile as the solvent to mimic the surroundings of aminolysis, and reoptimized the structures of all stationary points in solvent at B3LYP/6-311++G(d, p) level based on the polarizable continuum model (PCM) [59]. The change of the energy barriers at the corresponding optimized structures were also taken into account in the reaction. The standard dielectric constants for water, ethanol and acetonitrile implemented in the Gaussian programs were employed.

3. Results and discussion

3.1. Uncatalyzed aminolysis

According to the results discussed above, the most likely pathways for the aminolysis of DMVO are the concerted and neutral stepwise mechanisms, as described in Scheme 1. The mechanisms of the two processes are different in attack manner. We use the term "uncatalyzed" for the processes which do not contain additional molecules of catalyst in the overall reaction.

For the concerted pathway of the direct aminolysis, the reaction consists of only one step in which all bond-forming and bond-breaking proceed simultaneously (Scheme 1). The concerted mechanism mainly corresponds to the nucleophilic methylamine molecule attack of the electrophilic carbonyl carbon atom from DMVO, the simultaneous rupture of the ester C—O single bond, and a proton transfer from the methylamine to the oxygen atom of the ester C—O single bond. Thus, the transition state for the concerted mechanism (named 1A-TS) is composed of the formation of the C1—N5 bond, the cleaving of C1—O2 bond, and a proton transfer from the N5 to O2 atom. The optimized structures and important bond lengths for the transition state at the B3LYP/6-311++G(d, p) level are illustrated in Fig. 1. From the figure, we can see that with the interaction of C1 and N5 atom of methylamine, O2 atom and H4 atom of methylamine, a four-membered ring transition state is formed (1A-TS). At the 1A-TS, the C1—O2 bond is obviously elongated to 2.320 Å and the C1—N5 bond is 1.604 Å at the B3LYP/6-311++G(d, p), suggesting that the amide bond is almost formed in the transition state. At the same time, the H4 is transferred to O2 atom and shared by N5 and O2 atoms, although it is closer to N5 (N5—H4, 1.038 Å) than to the O2 (O2—H4, 1.849 Å). The imaginary frequency in the transition state