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Theoretical Study on the Isomerization Mechanism of Enol Ester from 2-Acyl-1, 3-cyclohexanediones

Yan Hua WANG[1,3], Jian Wei ZOU[1]*, Bing ZHANG[2], Min ZENG[1], Gui Xiang HU[1], Ke Wen ZHENG[2], Qing Sen YU[1,2]

[1] Key Laboratory for Molecular Design and Nutrition Engineering of Ningbo City, Ningbo Institute of Technology, Zhejiang University, Ningbo 315100,
[2] Department of chemistry, Zhejiang University, Hangzhou 310027
[3]College of Biology and Environment Protection, Zhejiang Shuren University, Hangzhou 310015

Abstract: The present paper employed density function theory to investigate two reaction pathways for isomerization of enol ester proposed by Yang(path a) and the present authors(path a), respectively. The base catalytic effects of solvent triethylamine on these two reactions were also evaluated. It is demonstrated that path B is more preferable than path a due to low barrier height for the rate-determining step.

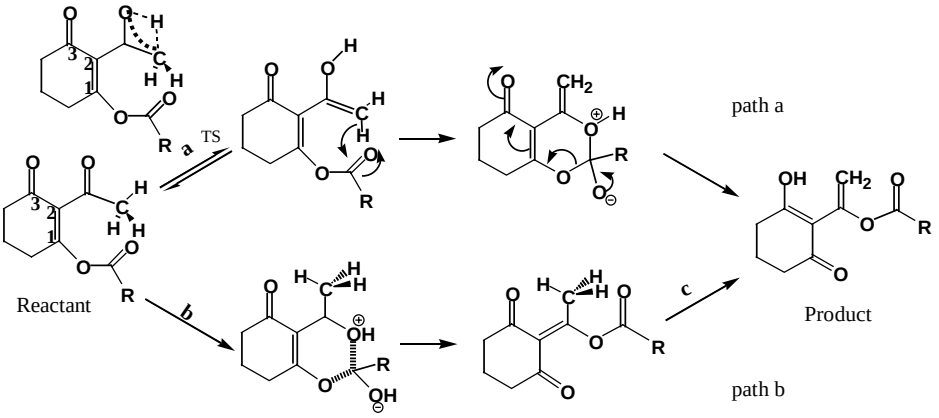
Keywords: Density function theory, reaction mechanism, solvent effect, 1, 3-H shift, proton transify, 1, 5-H shift.

The compounds containing β-tricarbonyl group have been used extensively in traditional and modern medicine for their various biological activities[1]. In past few years, organic chemists have paid close attention to their synthesis[2]. Our group have investigated the tautomeric behavior of benzoylcyclohexane 1, 3-diones and performed 3D-QSAR studies on their inhibition activities[3,4] on 4-hydroxyphenylpyruvate dioxygenase(HPPD) enzyme. Most recently, Yang[5] *et al*. discovered an unprecedented isomerization of enol esters derived from 2-acyl-1, 3-cyclohexanediones at ambient temperature when they synthesized a new type of potent HPPD inhibitors. The X-ray crystallographic analysis of the structure of isomerization product is unequivocal and the reaction mechanism was proposed as depicted as path a in **Scheme 1**. The reaction was thought to begin with a 1, 3-H shift, which is the intrinsic keto-enol tautomerization of 2-acyl group, then the ester carbonyl group is attacked by the oxygen atom of the enol to form the product.

To best of our knowledge[6,7], the reaction barrier for 1, 3-H shift in model compound CH_3-CH=O is generally up to 250 kJ·mol^{-1}. Although substituent groups and solvent effects may significantly reduce the barrier height as theoretical calculations demonstrated, the barrier is hardly found to be lower than 120 kJ·mol^{-1}. Thus, it seems impossible for 1, 3-H shift of the title compound to occur. Here we suggested an alternative isomerization mechanism, depicted as path b in **Scheme 1**, in which the pro-

* E-mail: jwzou@css.zju.edu.cn

Scheme 1 Reaction mechanism for path a and path b



a:1, 3-H shift, b:1, 5-acyl shift, c:1, 5-H shift

duct is obtained via two consecutive steps, 1, 5-acyl shift and 1, 5-H shift. Then, both mechanisms were investigated theoretically and the result revealed that the path b is energetically favorable.

Computation Methodology

All stable structures and transition states were fully optimized and then harmonic vibrational frequencies were performed at B3LYP/6-31G* level of theory. Intrinsic reaction coordinate (IRC) analyses were also conducted to validate the transition states obtained. Computations were carried out with the Gaussian 98 program package.

Results and Discussion

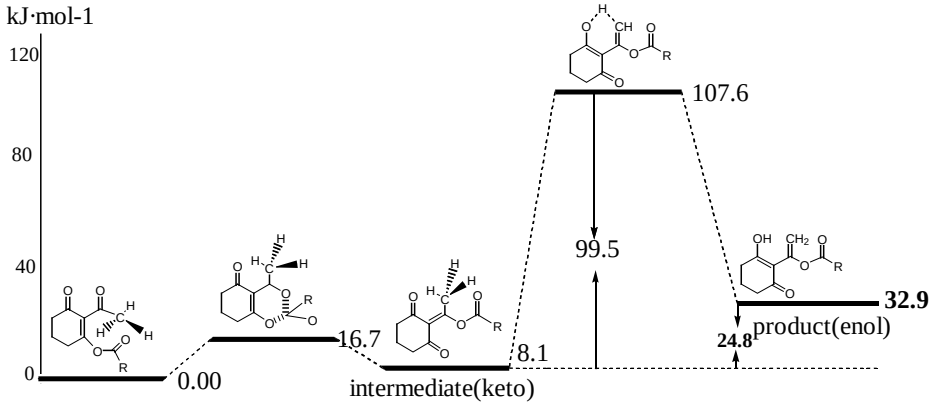
1, 3-H shift in path a is normally considered as a rate-determining step, so its barrier height in the title compound is computed, the results of which is 280.0 $kJ \cdot mol^{-1}$ (all energies reported throughout this paper refer to the zero-point energy corrected values) in vacuum. But as shown in **Figure 1**, the potential energy surface for path b in vacuum, the energies barriers for 1, 5-acyl shift and 1, 5-H shift are 16.7 and 99.5 $kJ \cdot mol^{-1}$, respectively, which means that 1, 5-H shift is rate-determining step in path b and its energies barrier is much lower than that for 1, 3-H shift in path a, so path b is more favorable than path a in vacuum. The reason for this is that the transition state of 1, 5-H shift with steric favorable six-member cycle is more stable than that of 1, 3-H shift with steric unfavorable four-member cycle.

Besides, it is of considerable interest to study the catalytic role of triethylamine on H-shift, since experimentally the reactant is synthesized in triethylamine. The H-shift energy barrier can be lowered due to interaction between the shift H of reactant and the N of triethylamine, which could facilitate the H-shift process[8,9]. For simplicity, 1, 3-H shift in aldehyde and 1, 5-H shift in But-2-enal were explored. The active energies for

the two H-shifts both in vacuum and triethylamine were calculated, which are 124.1 kJ·mol^{-1}, 122.9 kJ·mol^{-1} for 1,5-H shift and 290.0 kJ·mol^{-1}, 165.0 kJ·mol^{-1} for 1, 3-H shift, respectively. It showed that the solvent catalytic effect reduces substantially the barrier height for 1, 3-H shift, but has little influence on 1, 5-H shift. To shed more light on solvent catalytic effect on 1, 3-H shift in titled compound, the barrier height for 1, 3-H shift of path a in triethylamine was also calculated, which is 142.6 kJ·mol^{-1}, much lower than 280.0 kJ·mol^{-1} in vacuum. It indicates that, as the same as in aldehyde, the solvent catalytic effect is great on the activate energy for 1, 3-H shift in the title reaction. It is understood by the fact that there is a proton transfer between proton donor, methyl and strong proton acceptor, triethylamine, which form an ion-pair transition state[9], whose harmonic vibrational frequencies computation verified that the single imaginary frequency exist actually between atom C of methyl and N of triethylamine. Further, IRC computation confirmed that the ion-pair transition state connect the corresponding reactant and product indeed. It is also reasonable that N atom of triethylamine could capture proton easily from the steric unfavourable four-member cycle transition state of 1, 3-H shift than the steric favourable six-member cycle transition state of 1, 5-H shift, which lead to prominent diminishment of activate energy for 1,3-H shift. However, the barrier height for 1, 3-H shift of path a is still higher than that for 1, 5-H shift, alternatively, path b is preferable reaction mechanism.

From the viewpoint of thermodynamics, as shown in **Figure 1**, the product enol is 24.8 kJ·mol^{-1} thermodynamically less stable than intermediate keto in vacuum, which conflicts notably with the fact that isomerizated enol can be easily obtained. The reason may be attributed to two factors. First, the enol can be stabilized by intermolecular hydrogen bond between N of triethylamine and H of hydroxyl in product, Which is further verified by calculated intermediate binding energy, 14.5 kJ·mol^{-1}, with counterpoise correct for BSSE. Second, the enol with low dipole moment 3.03 Debye, is more favorable to exist in non-polar triethylamine than the intermediate keto with dipole moment 3.27 Debye. Additionally, the effect of the substituent group on tautomeric equilibrium between keto and enol is under systemical concerns.

Figure 1 Potential energy surface of path b in vacuum



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