Theoretical Study on the Epimerization of Azlactone Rings: Keto–Enol Tautomerism or Base-Mediated Racemization?

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Supporting Information

ABSTRACT: Azlactones are versatile heterocycles employed in a diversity of transformations; the main drawback of these cycles consists in the epimerization of the α-carbonyl stereocenter during its preparation. We hereby present a theoretical study to explain how the racemization occurs. Two hypotheses were investigated: the keto–enol tautomerism and the base-mediated racemization, through an enolate intermediate. The results showed that the latter is consistent with the experimental data and can spontaneously occur at room temperature. The same pathway was evaluated for 2-alcoxy azlactone, showing a slower epimerization ratio, consistent with the literature data.

INTRODUCTION

Azlactones (also known as oxazolones) are five-membered ring heterocycles that have recently been employed in several different transformations in organic synthesis (Chart 1).1,2 The versatility of these compounds is related to the presence of different reactive sites, bearing both electrophilic and pronucleophilic moieties, thus allowing its use in the stereo-selective synthesis of α,α-amino acids, complex heterocycles, and natural products.3–6 An important aspect concerning these cycles is the presence of an acidic hydrogen (pK_a ≈ 9), which is attributed to the aromatic character of its enol tautomer.

Although a one-pot procedure for the preparation of azlactone rings has been reported,7 the traditional approach for the attainment of these products consists of two steps: first, acylation of amino acids, followed by intramolecular cyclization mediated by a carboxylic acid activator.8 Furthermore, a very interesting aspect about oxazolones bearing a hydrogen linked to C4 is that, to the best of our knowledge, a racemization-free synthesis has never been achieved when the C2 substituent is an aryl or alkyl group, even when employing a single amino acid enantiomer as the initial substrate.9 In the few reports involving enantiomerically pure oxazolones,10,11 a modification of the C2 substituent of the cycle is necessary to make racemization less likely to occur, affording 2-alcoxy-azlactones by the cyclization of carbamate-protected amino acids.12

The epimerization process is well-known to occur in oxazolones and is widely explored in ring-opening dynamic kinetic resolution (DKR)-catalyzed reactions, in which the racemization process is faster than the subsequent reaction, allowing the isolation of stereenriched products.13,14 Interestingly, almost all of these previous works use a base-derived catalyst, containing one or more basic groups, such as ureas, thioureas, squaramides, and above all, tertiary amines (such as cinchonas).15–21 Despite the epimerization being known for many years, an explanation of the reasons that lead to this high tendency to racemization and the steps in which it occurs are still unclear in the literature.

Recently, our research group has been studying the reactivity of oxazolones in various transformations,12–26 including alternatives for amino acid derivative formation, avoiding an azlactone intermediate and thereby the racemization process.9 Nevertheless, we have been curious about the epimerization process. In this context, we herein present a theoretical study, based on experimental evidences, in an attempt to provide new insights to explain the behavior of the azlactone ring and the nature of this racemization process.

RESULTS AND DISCUSSION

Initially, we decided to perform an experiment to study if the racemization process occurs during the azlactone preparation or after oxazolone use in a further reaction. Therefore, in an
attempt to be able to observe the epimerization process occurrence by crude proton nuclear magnetic resonance (1H NMR) data, L-isoleucine was chosen as an ideal substrate because it contains two stereocenters, and thereby the epimerization of the α-carbonyl hydrogen would result in a pair of diastereomers.

The azlactone synthesis followed the two-step traditional methodology reported in the literature,27 as shown in Scheme 1.

**Scheme 1. Azlactone Preparation Using L-Isoleucine as the Substrate**

![Scheme 1](image)

Although harsh reaction conditions were employed during the first step (extremely acidic or basic conditions), no apparent racemization was detected by 1H NMR (Figure 1A). On the other hand, the intramolecular cyclization step leads to complete epimerization, with a diastereomeric ratio of 1:1 by 1H NMR (Figure 1B). On the basis of these data and the DKR racemization process, we hereby suggest two different possible pathways for the epimerization process: an intramolecular tautomerization of the azlactone ring, which could spontaneously and continuously occur after the cyclization because of the lower pKₐ value of the lactone α-carbonyl hydrogen when compared to that of the N-benzoyl amino acid; a base-mediated racemization, involving a deprotonation/protonation step; it is also worth mentioning that during cyclization, the 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC) urea is formed as a byproduct and that this compound has both the urea and a tertiary amine moiety and might act as the base for the racemization process. This second possibility would also explain why DKR reactions of azlactones were, with one exception,28 only achieved by the use of basic catalysts.

We decided to carry out a theoretical study of both possible pathways. All electronic structure calculations were performed with the Gaussian 09 package.29 Minimum energy conformations for reactants, products, transition states (TSs), and molecular complexes (MCs) were determined in the gas phase on the density functional theory (DFT) level30 with the hybrid B3LYP functional31 and employing the 6-31G(d) basis set. The same level of theory was also applied to the Gibbs free energy prediction and to the vibrational frequency calculations. TSs were optimized using the Berny algorithm32 and confirmed to have only one imaginary frequency. All calculations were performed at a pressure equal to 1 atm and at a temperature of 298.15 K, similar to the conditions usually employed in DKR experimental reports.

Single-point energy calculations using the previously optimized geometries were performed in gas phase, water, and dichloromethane using the B3LYP-D3 functional,33 the 6-31++G(d,p) basis set, and the integral equation formalism polarizable continuum model (IEFPCM) approach.34 ΔG°sol could then be obtained by the sum of the three energy contributions shown in eq 1

\[
\Delta G_{sol}^\circ = \Delta E_{gas} + \Delta G_{T}^\circ + \delta \Delta G_{solv}
\]

in which the terms are, respectively, the electronic energy, thermal correction to the enthalpy and entropy, and solvation Gibbs free energy. To allow a comparison with the experimental data, 1H and 13C NMR were also calculated for azlactone keto and enol isomers. For this purpose, the gauge-independent atomic orbital method35 was employed, using the previously optimized geometries.

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**Figure 1.** (A) 1H NMR of N-benzoyl isoleucine, showing no apparent epimerization; (B) 1H NMR of the azlactone ring, evidencing complete epimerization.
geometries in the gas phase and performing single-point calculations employing the B3LYP/6-31++G(2df,2pd)-IEFPCM-chloroform level of theory. The chemical shift could be obtained employing the following equation

\[ \delta_{ppm} = \delta_{TMS} - \delta_{calc} \]  

(2)

We decided to carry out the studies in two different azlactones: alanine and valine derivatives. To confirm that the optimized geometries were satisfactory, we compared the infrared (IR), \(^1\)H, and \(^13\)C NMR data obtained for the keto tautomer and observed a good correlation with the experimental data (see the Supporting Information). Furthermore, a comparison of the natural bond orbital and the electrostatic potential (ESP) of the keto, enolate, and enol forms has been done, and the results are summarized in the Supporting Information. As expected, it is possible to observe that in general, the enolate bond orders and lengths are an average between the keto and enol tautomers.

The first investigated pathway was the keto–enol tautomerism of the cycle.\(^{36-39}\) During this step, the TS could not be found for any of the azlactones (alanine or valine) employing the B3LYP level of theory. However, by employing the same basis set and changing from DFT to Hartree–Fock or M06-2X, it was possible to obtain the desired TS, with only one imaginary vibrational mode frequency representing the reaction coordinate. Thus, a single-point calculation at B3LYP-D3 was performed employing the optimized TS on the M06-2X level.

The pathway showed a high activation barrier, of more than 75 kcal/mol, incompatible with a reaction that should proceed at room temperature. Besides, no significant differences were observed for the two azlactones (Table 1). Furthermore, the inclusion of the solvation model (for both water and dichloromethane) showed little effect on the overall energies of this reaction.

### Table 1. Gibbs Free Energy Variation for the Tautomerism on the B3LYP-D3/6-31++G(d,p)//B3LYP/6-31G(d) Level of Theory for Alanine and Valine (in Brackets) Azlactones

| tautomerism pathway (kcal/mol) | gas phase | CH\(_2\)Cl\(_2\) | H\(_2\)O |
|-------------------------------|-----------|----------------|--------|
| keto                          | 0.0 [0.0] | 0.0 [0.0]      | 0.0 [0.0] |
| TS keto–enol                  | 75.9 [75.8] | 75.5 [79.1]    | 75.5 [79.0] |
| enol                          | 11.2 [12.1] | 11.5 [12.2]    | 11.6 [12.2] |

The second hypothesis consisted in a pathway, in which the enolate is formed from the keto azlactone and then reprotonated, affording the enol tautomer (Scheme 2).\(^{40-43}\) In this case, a base is necessary for the reaction to proceed. Because both the EDC urea and almost all reports of DKR catalysts have a tertiary amine moiety, we choose to work with a model of a tertiary amine: the triethylamine. We also investigated the role of the formation of MCs between the base and the cycle in all steps during the reaction, in an attempt to evaluate the influence of these species in the activation barriers. An interesting observation consisted in the absence of a TS for the reprotonation of the enolate into the enol form for both azlactones (the barrier was lower than \(kT\), in which \(k\) is the Boltzmann constant and \(T\) is the temperature). Thus, to characterize these points, a rigid scan for the proton transfer was performed and corroborated with this proposal (see the Supporting Information).

Some important intramolecular contacts could be observed during the formation of MCs and the TS (highlighted in red—Figure 2). The structure of MC1, TS\(_{\text{keto-enolate}}\) and MC2 showed similar interactions, with considerable differences in C–H (1.10, 1.61, and 2.05 Å, respectively) and N–H (2.40, 1.19, and 1.06 Å, respectively) bond lengths, showing the hydrogen transfer from the heterocycle to the base. The angles between these three atoms have a slight difference in the MC1 (167°) when compared to the TS and MC2 (174° and 176°).

In MC2, the approximation of the positive and negative charged species (formation of an ion-pair) results in further stabilization when compared to the isolated molecules. The MC3, in which the azlactone is in the enol form, is stabilized by the formation of a hydrogen bond with the nitrogen atom of the amine (N–H length 1.67 Å and N–H–O angle 172°).

An overview of the results for the alanine-derived azlactone in dichloromethane is summarized in Figure 2. For the keto tautomer, it is possible to observe a substantial difference between the Gibbs free energy of the isolated species and the MCs (4.4 kcal/mol); the approximation between these reactants reduces the activation energy for the deprotonation from 14.3 to 9.9 kcal/mol, making it a relatively low barrier that can be transposed at room temperature. Furthermore, the MC2 is very close in energy to the TS (only 2.3 kcal/mol), making the reverse reaction spontaneous and thermodynamically favored; it is worth mentioning that during this return, the epimerization process takes place, affording either R or S stereocenters without selectivity. From the enolate, it is also possible for the reaction to continue toward the enol tautomer in a barrierless and spontaneous process, with \(\Delta G\) of −5.5 kcal/mol. The reversibility of this step is also possible under the studied conditions.

This pathway is viable and explains the experimental observations, with reaction barriers that can be transposed at room temperature. The results for Gibbs free energies, enthalpies, and electronic energies for both azlactones are shown in Table 2. This proposal suggests that the DKR catalysts, in addition to the known importance in favoring the stereoselective ring-opening reaction, are also necessary for the racemization process of the azlactone ring.

As shown in Table 2, it is possible to observe that in all comparisons of activation barriers for enolate formation, the racemization process in alanine azlactone proceeds faster than in valine-derived oxazolone when considering the formation of MCs. Another interesting observation is that for both...
azlactones, the reaction activation barriers are 1−5 kcal/mol lower when considering the MC instead of the isolated species. Because of the lower energy barriers, in this path, all steps can occur forward and backward at room temperature; what will drive the keto and enolate tautomers percentage are the differences in the Gibbs free energies. Thus, through the Gibbs distribution calculation shown in eq 3, it is possible to calculate de $%_{keto}$ and $%_{enol}$ forms

$$K = e^{-\Delta G/RT} = \frac{X_{\text{keto}}}{X_{\text{enol}}}$$  \hspace{1cm} (3)$$

with $R = 0.001987$ kcal mol$^{-1}$ K$^{-1}$ and $T = 298.15$ K.

The result of the percentage of each species is shown in Table 3. It is possible to observe that only the keto tautomer can be detected in significant amounts, with only traces of the enol form. This observation is consistent with the experimental data obtained by IR, $^1$H, and $^{13}$C NMR (available in the Supporting Information), which shows only the presence of the keto tautomer. Furthermore, theoretical calculations for a wide scope of different C2- and C4-substituted azlactones were carried out, showing the same behavior (in all cases, the $%_{keto}$ is higher than 99.999%), and the results are available in the Supporting Information.

Finally, both pathways were also evaluated in dichloromethane, considering a 2-alcoxy-substituted azlactone (data available in the Supporting Information). The results showed a similar behavior, considering the tautomerism hypothesis (a barrier of about 78 kcal/mol in both the gas phase and in dichloromethane) not viable to occur at room temperature. In this case, the base-mediated pathway for the deprotonation of the keto azlactone showed no TS and a reaction Gibbs free energy of 20.3 kcal/mol in dichloromethane on the B3LYP-D3 level of theory, about 8−9 kcal/mol higher than in 2-phenyl substituted azlactones. This observation was expected and explains why the epimerization process is less likely to occur in 2-alcoxy azlactones, as reported in the literature. 10,11

Table 2. Results for the Base-Mediated Pathway for Both Azlactones (The Values for Valine Are Given in Brackets)

|                      | base-mediated pathway (kcal/mol) | gas phase | dichloromethane | water |
|----------------------|----------------------------------|-----------|-----------------|-------|
|                      | $\Delta E$ | $\Delta H$ | $\Delta G$ | $\Delta E$ | $\Delta H$ | $\Delta G$ | $\Delta E$ | $\Delta H$ | $\Delta G$ |
| B + keto             | 0.0 [0.0] | 0.0 [0.0] | 0.0 [0.0] | 0.0 [0.0] | 0.0 [0.0] | 0.0 [0.0] | 0.0 [0.0] | 0.0 [0.0] | 0.0 [0.0] |
| MC 1                 | $-7.6 [-8.8]$ | $-6.1 [-7.5]$ | $3.1 [12.9]$ | $-6.3 [-7.7]$ | $-4.8 [-6.3]$ | $4.4 [2.3]$ | $-6.0 [-7.4]$ | $-4.6 [-6.0]$ | $4.6 [2.6]$ |
| TS keto−enolate      | 6.6 [5.4] | 5.8 [4.6] | 19.1 [18.4] | 1.7 [1.0] | 0.9 [0.2] | 14.3 [13.9] | 0.8 [0.1] | 0.0 [0.7] | 13.4 [13.1] |
| MC 2                 | 4.7 [3.9] | 6.9 [6.1] | 19.5 [18.4] | $-2.7 [-3.4]$ | $-0.6 [-1.2]$ | 12.0 [11.0] | $-4.2 [-4.8]$ | $-2.0 [-2.6]$ | 10.6 [9.6] |
| BH$^+$ + enolate     | 99.3 [98.9] | 100.1 [99.8] | 100.1 [100.1] | 17.1 [17.8] | 17.8 [18.6] | 17.8 [19.0] | 7.3 [8.1] | 8.0 [9.0] | 8.1 [9.4] |
| MC 3                 | $-6.4 [-5.7]$ | $-5.1 [-4.4]$ | 5.6 [5.9] | $-5.5 [-5.0]$ | $-4.3 [-3.7]$ | 6.5 [6.6] | $-5.3 [-4.9]$ | $-4.1 [-3.5]$ | 6.7 [6.7] |
| B + enol             | 12.8 [13.6] | 12.5 [13.4] | 11.2 [12.1] | 13.1 [13.7] | 12.8 [13.4] | 11.5 [12.2] | 13.1 [13.7] | 12.8 [13.4] | 11.6 [12.2] |

Table 3. Results for the Base-Mediated Pathway for Both Azlactones

|                      | alanine-derived azlactone | gas phase | CH$_2$Cl$_2$ | H$_2$O |
|----------------------|---------------------------|-----------|--------------|-------|
| $\Delta G_{k\rightarrow e}$ | 11.2 kcal/mol | 11.5 kcal/mol | 11.6 kcal/mol |
| $K$                  | $6.16 \times 10^{-9}$ | $3.71 \times 10^{-9}$ | $3.14 \times 10^{-9}$ |
| $%_{\text{enol}}$    | <0.001                   | <0.001     | <0.001       |
| $%_{\text{keto}}$    | >99.999                  | >99.999    | >99.999      |

|                      | valine-derived azlactone | gas phase | CH$_2$Cl$_2$ | H$_2$O |
|----------------------|--------------------------|-----------|--------------|-------|
| $\Delta G_{k\rightarrow e}$ | 12.1 kcal/mol | 12.2 kcal/mol | 12.2 kcal/mol |
| $K$                  | $1.35 \times 10^{-9}$ | $1.14 \times 10^{-9}$ | $1.14 \times 10^{-9}$ |
| $%_{\text{enol}}$    | <0.001                   | <0.001     | <0.001       |
| $%_{\text{keto}}$    | >99.999                  | >99.999    | >99.999      |
**CONCLUSIONS**

In summary, the study reported here pointed out the mechanism behind the epimerization process experimentally observed in azlactones. NMR experimental evidences showed that no racemization occurs during the acylation step, occurring only during or after the intramolecular cyclization. On the basis of these observations, a DFT study employing the B3LYP-D3/6-31+G(d,p)//B3LYP/6-31G(d) level was carried out. According to the obtained data, we suggest that the epimerization process takes place in a base-mediated equilibrium after the formation of the oxazolone heterocycle. Even byproducts, such as the EDC ureda, can act as a base in this process, which explains the isolation of racemic azlactones right after the intramolecular cyclization step. When the same pathway was evaluated toward 2-alcoxy azlactone, the barrier for the epimerization process is 8.9 kcal/mol higher when compared to a 2-phenyl oxazolone, which corroborates with the experimental observations that these azlactones have a slower epimerization ratio. Besides, an alternative pathway for the racemization, involving the direct keto-enol tautomerism of the α-carbonyl hydrogen was studied, and because of the high barrier, it is not viable to happen at room temperature.

Furthermore, the percentages of keto and enol tautomers were calculated for a wide scope of azlactones and are in perfect accordance with the experimental data, showing only the presence of the keto form. The reaction barriers showed great influence of the formation of MCs between azlactones and the base.

Finally, we hereby suggest a new role for the catalysts involved in DKR reactions, in which, in addition to influencing the ring-opening reactions in a stereoselective manner, these catalysts are also necessary to mediate the racemization process.

**EXPERIMENTAL SECTION**

**General Methods.** All purchased chemicals were used as received without further purification. Solvents were dried following standard procedures. Thin-layer chromatography (TLC) was performed on TLC plates (silica gel 60 F254) and visualized under ultraviolet light (254 nm). The chemical shifts were reported in ppm relative to the solvent residual peak. The 1H NMR spectra were recorded at 500 MHz, and 13C NMR spectra were recorded at 125 MHz on a Bruker DPX-500 MHz spectrometer. IR spectra were recorded on a Perkin-Elmer 1720 FTIR spectrometer in the region of 4000–400 cm−1, as a KBr pellet. All electronic structure calculations were performed with the Gaussian 09 package as described above. Azlactone Synthesis. The azlactone heterocycle was prepared and purified according to the literature protocols. 16

**ASSOCIATED CONTENT**

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**Notes**

The authors declare no competing financial interest.

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