

Ab Initio Transition States for the Reaction of α -Hydroxyl Lithium Ester Enolates with Imine

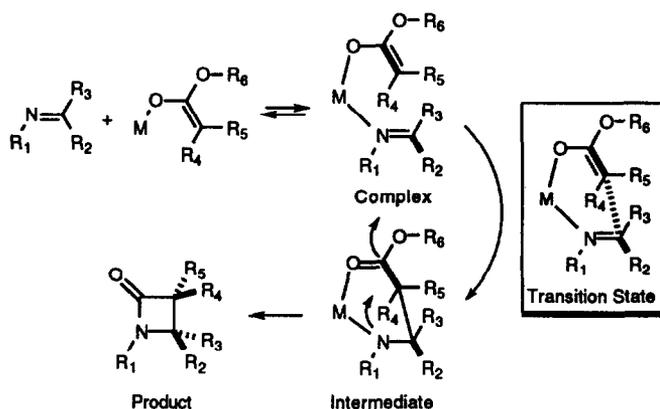
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Abstracts: The transition states for the reactions of α -hydroxyl ester lithium enolates with imine to form β -lactams were located using *ab initio* molecular orbital theory at the RHF/3-21G and RHF/6-31G** levels. MP2/6-31G* energy calculations indicated that the Z-isomer of the ester enolates is much more stable than the E-isomer (5.0-6.9 kcal/mol). This can be rationalized by the coordination of lithium with the α -hydroxyl oxygen. The reaction of the Z-enolate with imine proceeds through a boat-like transition state, which is energetically favored over an envelope-like transition state for the reaction of the E-enolate with imine (9.7 kcal/mol, MP2/6-31G*/RHF/3-21G). A solvent molecule (NH₃) was incorporated into the boat-like transition state at the RHF/3-21G level. Neither the change of basis set nor inclusion of solvents had any significant effect on the transition state geometry.

β -lactams are often the vital structural unit of antibiotic compounds.¹ Due to their recent involvement in the taxol side-chain synthesis, this type of molecules has received widespread attention.² One of the classical methods of constructing β -lactams is by the [2+2] Staudinger cycloadditions.³ The reaction mechanism of various [2+2] systems has been studied theoretically.⁴ An alternate approach to synthesize β -lactams is based on the enolate-imine condensation strategy.⁵ The condensation reaction is mediated by various metals such as Li, Zn, Al and Ti. As shown in Figure 1, formation of β -lactams by this reaction is a two-step process. A six-

Figure 1



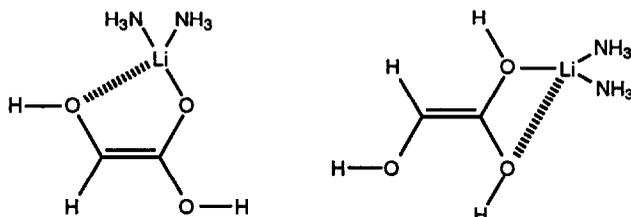
membered transition state similar to that of aldol condensation is postulated in the first step.^{2,5,6} The resulting intermediate then undergoes a nucleophilic cyclization to the β -lactams. Several asymmetric syntheses of chiral β -lactams have been successfully accomplished using the lithium ester enolate-imine condensation chemistry.^{2,5} However, the stereochemistry for the formation of β -lactams can not be predicted with certainty because an

accurate picture of the transition state is not available.

In order to gain a detailed understanding of the mechanism of enolate-imine condensation reaction, we have undertaken *ab initio* molecular orbital calculations. All the calculations were performed with the SPARTAN program on an Iris Indigo workstation running system 4.0.1.⁷ All the transition states are characterized by having one imaginary frequency, which corresponds to the forming and breaking of the dotted C-C bond in Figure 1.

When α -alkoxyl acetates are treated with LDA, both *Z*- and *E*-isomers of the α -alkoxyl lithium ester enolates can be formed. For the saving of computer time, a model system was employed to study the relative stability of these two isomers in the presence of solvents. In this system (Figure 2), alkyl groups and solvents are represented by hydrogen and ammonia, respectively. The geometries of the NH_3 solvated *Z* and *E* lithium ester enolates were optimized with the 3-21G basis set followed by a single point energy evaluation at the MP2/6-31G* level. It is calculated that the *Z*-isomer of α -hydroxyl lithium ester enolate is more stable than the *E*-isomer by 5.0-6.9 kcal/mol.

Figure 2



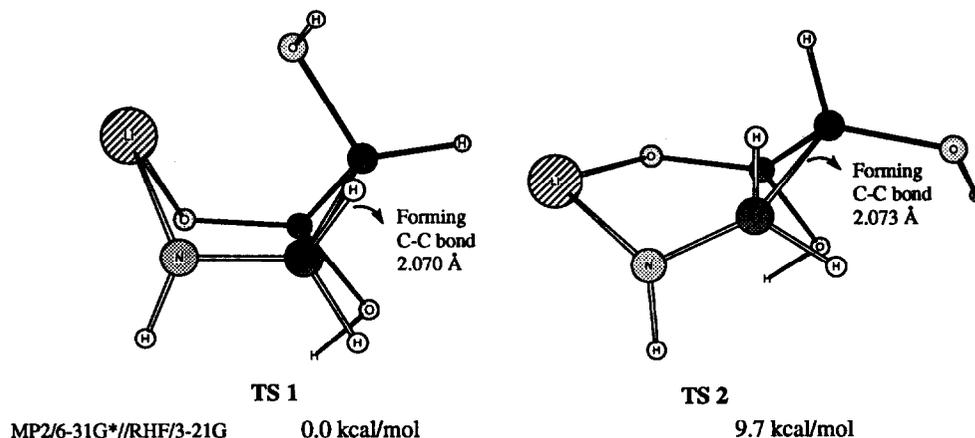
	Z-enolate	E-enolate
RHF/3-21G	0.0 kcal/mol	9.0 kcal/mol
RHF/6-31G**/RHF/3-21G	0.0 kcal/mol	6.9 kcal/mol
MP2/6-31G**/RHF/3-21G	0.0 kcal/mol	5.0 kcal/mol

This energy difference mainly results from coordination of lithium with the neighboring oxygen. In the *Z*-enolate, the coordination is within a less strained five-membered ring geometry and is therefore favored. While in the *E*-enolate, the coordination is imposed within a strained four-membered ring system and is therefore disfavored. The *Z/E* energy difference will be even larger in real systems than in the model system, because the favorable hydrogen bonding interaction in the *E*-enolate will no longer exist. Therefore, the *Z*-enolate of α -alkoxyl lithium ester should be formed predominantly as the thermodynamic product.

In searching for the transition state for the reaction of the *Z*-enolate with imine, we first omitted solvent molecules from the reaction. A boat-like transition state, **TS 1**, was located at the RHF/3-21G level. Numerical frequency calculation at the same level of theory confirmed it is a saddle point on the reaction potential surface. The transition state was further optimized at the RHF/6-31G** level and no significant geometric changes were observed. The coordination of lithium with the α -hydroxyl oxygen observed in the reactant remained in the boat-like transition state. When the α -hydroxyl group is switched from the axial position to the equatorial position, its coordination with lithium is no longer possible and an envelope-like transition state, **TS 2**, was obtained at the RHF/3-21G level. This is the transition state for the reaction of the *E*-isomer of α -hydroxyl lithium ester enolate with imine. MP2/6-31G**/RHF/3-21G calculation indicated that the boat-like transition state, **TS 1**, is lower in energy by 9.7 kcal/mol than the envelope-like transition state, **TS 2**. The calculation suggests that the *Z*-enolate

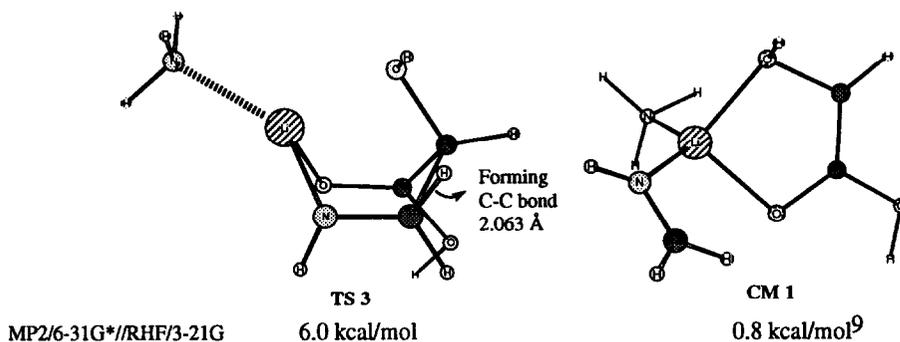
prefers to be involved in the α -alkoxy lithium ester enolate-imine condensation reactions over the E-enolate. The experimentally observed cis- β -lactam should be formed via the boat-like transition state.

Figure 3



A solvent molecule can be placed next to lithium in the boat-like transition state, **TS 1**, as crystallography studies showed that lithium could be tetra-coordinated.⁸ The resulting transition state is situated on a relatively flat potential surface due to flexibility associated with solvents. Searching of the H₂O solvated transition state was not successful at the RHF/3-21G level. On the other hand, the transition state, **TS 3**, with NH₃ as the solvent model was obtained at the RHF/3-21G level. Optimization of the transition state towards the reactant side gave rise to the complex, **CM 1**. According to MP2/6-31G**/RHF/3-21G calculations, Formation of the complex is slightly endothermic (0.8 kcal/mol) and the overall reaction barrier is relatively low (6.0 kcal/mol). Interestingly, the NH₃ solvated transition state, **TS 3**, is also a boat conformation. Its geometry almost superimposes that of the solvent free transition state, **TS 1**. The solvent molecule is distant from the reaction center in **TS 3** and its interaction with substituted groups or chiral auxiliary groups can be neglected.

Figure 4



Therefore, the solvent free boat-like transition state, **TS 1**, can be used to model the stereochemistry for the formation of chiral β -lactams. Calculations on large systems using semi-empirical methods to predict the

stereoselectivities for the reaction of chiral α -alkoxyl lithium ester enolates with imines are in process. Parallel studies on the reaction of α -amino lithium ester enolates with imines are also underway.¹⁰

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9. The energies are relative to that of the reactants (0.0 kcal/mol).
10. The transition state for the reaction of Z-LiOC(OH)=CHNH₂ with CH₂=NH was located at RHF/3-21G and RHF/6-31G* levels. No significant geometrical changes were observed when the α -hydroxyl group (axial) in **TS_1** was replaced by an amino group.

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