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Transition Structures for the Dieckmann Condensation

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Abstract: Transition structures for the Dieckmann condensation have been located using the *ab initio* MO method. The reaction path through **TS-Ia** and subsequent MeOH elimination (**TS-II**) from intermediate (**B1**) leading to enolate (**C**), was found to be more favorable than that through **TS-Ib**, which gave the keto product (**D**), by MeOLi elimination (**TS-III**).
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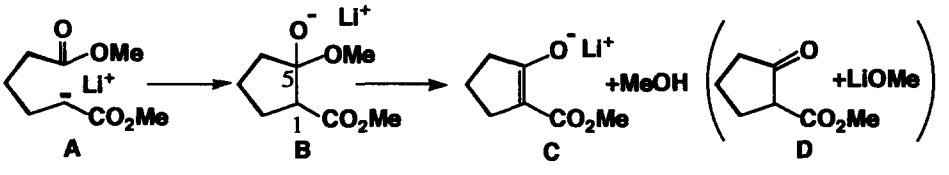
Intramolecular diester cyclization to give cyclic β-keto esters is known commonly as the Dieckmann condensation.[1] An enormous number of examples of constructing various sized carbon ring system using this reaction have been reported.[2] In spite of its wide synthetic utility, transition structures (TSs) for the Dieckmann condensation have not been reported. In this paper, we report *ab initio* TSs and energetic profile for the Dieckmann condensation of **A**, which yields the five-membered β-keto ester (**D**).



Scheme 1

Molecular orbital (MO) calculations were performed using the GAUSSIAN 94 program package.[3] Structures at the stationary points were fully optimized without symmetry constraints using the gradient techniques at the 6-31+G basis set.[4] Electron correlation was considered using the 2nd-order Møller-Plesset perturbation approximation (MP2).[5] The mass-weighted minimum energy path (the intrinsic reaction coordinate (IRC)[6]) calculations at the 6-31+G level on all TSs were also performed.

The Dieckmann condensation of **A** can be considered to proceed through two stages: that is, C-C bond formation leading to cyclized intermediate (**B**) and then subsequent elimination of a MeOM (M=H or Li) species giving the enolate (**C**) or keto product (**D**) (Scheme 1). There are two cyclization modes which give two diastereomeric intermediates, in which the two substituents (CO_2Me and OMe) are either in a *cis* or *trans* relationship.

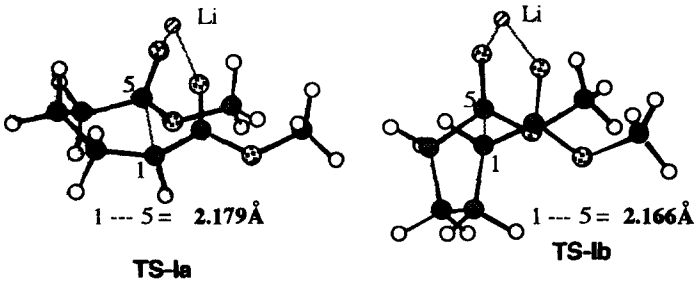


Figure 1. Transition structures (**TS-Ia** and**TS-Ib**) for C-C bond forming step.

Figure 1 shows these two TSs (**TS-Ia** and **TS-Ib**) located at the 6-31+G basis set. **TS-Ia** and **TS-Ib** have structures in which the CO_2Me and OMe substituents are *trans* and *cis* with respect to the forming C_1-C_5 bond, respectively. In both of these TSs, the coulombic interaction between the Li cation and the two ester groups helps to bring the two reaction sites (C_1 and C_5) closer to each other. The potential energy of **TS-Ia** is considerably lower than that of **TS-Ib** by 2.6 kcal/mol (MP2/6-31+G), suggesting that the former path should be the predominant one in the cyclization step. The IRC calculation confirmed that both **TS-Ia** and **TS-Ib** led to five-membered intermediates $\mathbf{B_1}$ and $\mathbf{B_2}$, respectively.

The second stage of the Dieckmann condensation is the elimination of a MeOM (M=H, Li) species from the intermediates ($\mathbf{B_1}$ and $\mathbf{B_2}$). There are two possible mechanisms in which the *trans* intermediate $\mathbf{B_1}$ can give the final products (**C** or **D**). The first involves MeOH elimination to give enolate (**C**) and the other, the elimination of a MeOLi species to give the keto product (**D**). Figure 2 shows the MeOH eliminating TS (**TS-II**), leading to **C**. The TS for MeOLi elimination which directly gives **D** could not be located, suggesting that there is no direct route to **D** from $\mathbf{B_1}$. The activation energy for this MeOH eliminating process from $\mathbf{B_1}$ is only 0.5 kcal/mol (MP2/6-31+G). The cleavage of C_5-OMe bond proceeds with simultaneous C_1-H cleavage (1.306Å for C_1-H distance *vs.* 2.938Å for C_5-OMe); the transition structure can thus be referred to as being a concerted asynchronous rather than synchronous, in which C_5-O and C_1-H bond cleave to the same extent. The distances between O-H_1 and H_1-C_1 are 1.348 and 1.306Å, respectively, indicating the proton abstraction occurs to a considerable extent in the transition state. A similar TS, in which MeOH is released asynchronously from a tetrahedral intermediate to give a carboxylate has been reported in the alkaline hydrolysis of methyl esters.[7]

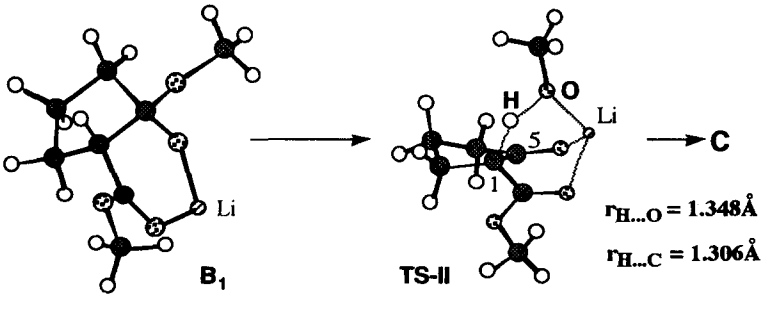


Figure 2. The intermediate ($\mathbf{B_1}$) and the transition structures (**TS-II**) for MeOH elimination step.

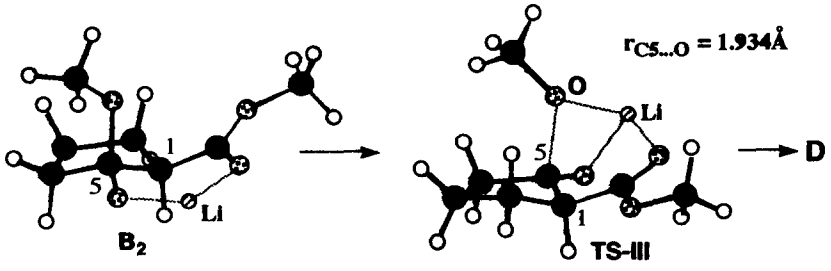


Figure 3. The intermediate ($\mathbf{B_2}$) and the transition structures (**TS-III**) for MeOLi elimination step.

However, in the reaction path of the *cis* intermediate $\mathbf{B_2}$ only the MeOLi eliminating TS (**TS-III**) could be located because of the *trans* relationship between the OMe and the adjacent methine proton (Fig. 3). The activation energy for **TS-III** from $\mathbf{B_2}$ was calculated to be 2.2 kcal/mol. IRC calculation confirmed that **TS-III** is the saddle point between the intermediate ($\mathbf{B_2}$) and the keto product (**D**). Although the MeOH eliminating TS from $\mathbf{B_2}$ could not be located, the keto product (**D**) would give enolate (**C**) after abstraction of the methine proton by attack of the LiOMe liberated (Fig. 4).[8]

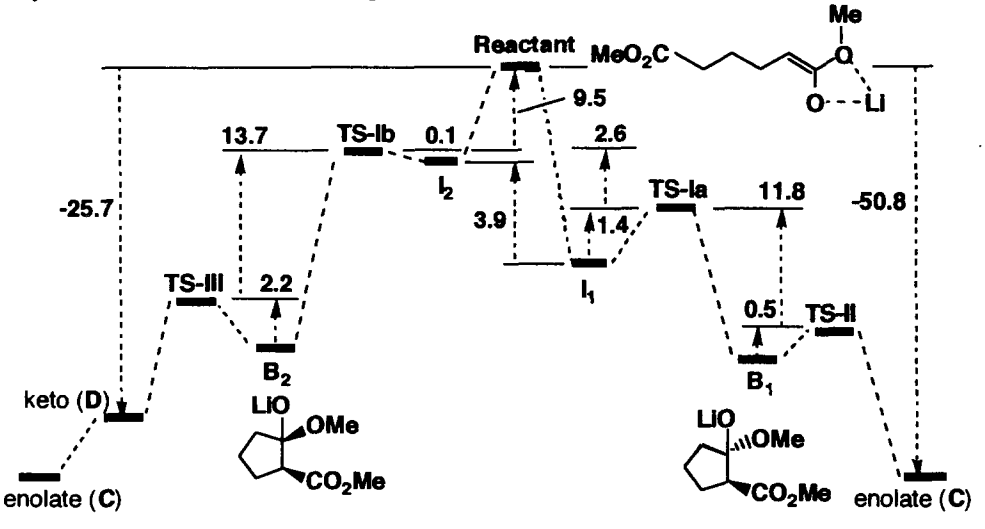


Figure 4. Energy diagram (MP2/6-31+G//RHF/6-31+G) of the Dieckmann condensation.

The present paper reports the reaction path for the Dieckmann condensation reaction. **TS-Ia** is energetically more favorable (2.6 kcal/mol at MP2/6-31+G//6-31+G level of theory) than **TS-Ib**, suggesting that the cyclization step proceeds through the former, which gives the *cis* intermediates $\mathbf{B_1}$. The final enolate product (**C**) can be formed through **TS-II** by a MeOH elimination process. The reaction occurs preferentially through the reaction path (reactant -> **TS-Ia** -> Intermediate ($\mathbf{B_1}$) -> **TS-II** -> enolate product (**C**)) rather than the path (reactant -> **TS-Ib** -> Intermediate ($\mathbf{B_2}$) -> **TS-III** -> keto product (**D**)). As the results, the enolate (**C**) is always involved in the Dieckmann condensation and the keto product (**D**) is energetically unfavorable in the presence of LiOMe.

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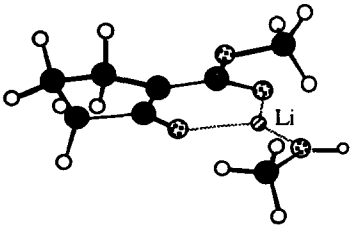
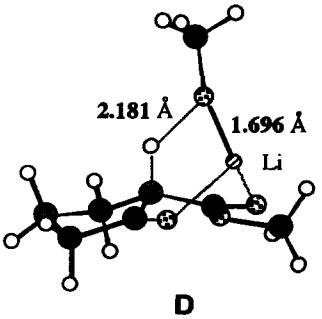
8. The 6-31+G optimized enolate (**C**) and keto (**D**) structures are as follows.



C



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