Ab initio Computational Study of the Stereocontrolled Intramolecular Hetero-Michael Addition to 2, 3-Disubstituted Tetrahydropyrans.

Reference: M. A. Ramirea, J. M. Padron, J. M. Palazon, V. S. Martin. *J. Org. Chem.* **1997**, *62*, 4585.

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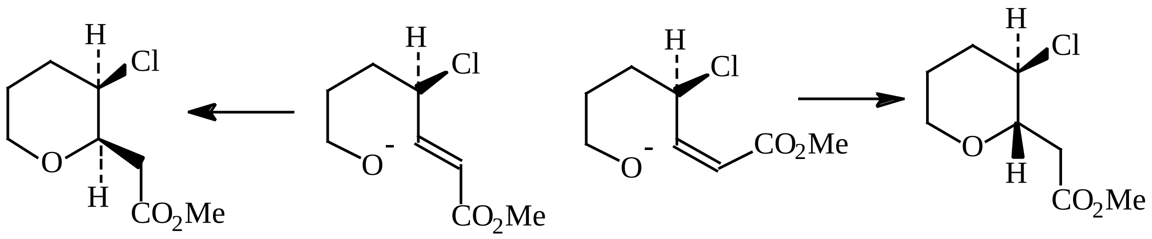
I. Introduction

Intramolcular hetero-Michael addition is the key step to build a tetrahydropyran unit. An important feature of this reaction is that the product is stereocontrolled. For example, under aprotic condition using NaH as base, 7-hydroxy-4-substitued-(E)-2, 3-unsaturated ester (**1**) yields the *cis*-substitued tetrahydropyran (**2**) while the Z isomer (**3**) yields the *trans* product (**4**) (**Scheme 1**). This research is forcused on the study of the influence of the stereochemistry by the chiral center (on position γ) and the double bond geometry of the unsaturated ester.



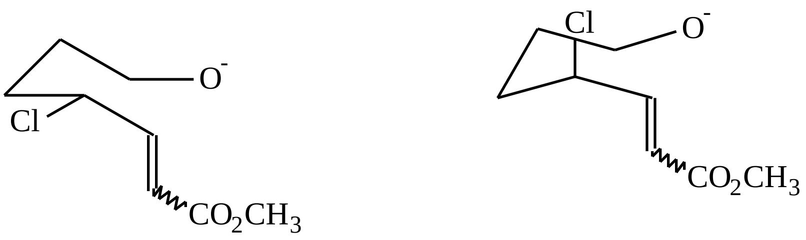
cis (**2**)   (E) (**1**)   (Z) (**3**)   *trans* (**4**)

Scheme 1. Influence of double bond geometry on the stereochemistry in the intramolecular hetero-Michael addition.

It is necessary to find the reaction path, transition state and potential energy surface which determine the stereoselective product. In this paper, a computation study at the ab initio level of the (E), (Z) unsaturated esters (**1**, **3**) leading to the 2, 3-disubstitued tetrahydropyrans (**2**, **4**) has been performed. The obtained results are in good agreement with the experimental observations.

II. Computation Results

A. The transition states: Transition states assume a chair-like 6-member ring. On this hypothesized chair-like “ring”, the chiral inductor (Cl on the position γ) occupies either equatorial or axial position, so does the α,β-unsaturated system. The total number of possible TSs is 4, denoted as eq-ax, eq-eq, ax-eq and ax-ax approach mode (**Figure 1**). Preliminary analysis of the TSs is carried out by semiempirical calculations with studying the reaction coordinates by AM1 Hamiltonian. Final energies of TSs are calculated exclusively by ab initio methods using 3-21G basis set (**Table 1**). The starting geometries are those obtained for the TSs available using AM1. The most stable TS for E isomer (**1**) is eq-ax mode leading to the *cis* product which is consistent with experiment results. The structure of this TS is shown in **Figure 2**, the distance of $O^{-} \cdots\cdots C(=C)$ is 2.502A. For Z isomer (**3**), the most stable TS is eq-eq mode and the favor product is *trans.*



Cl=“equatorial”, π-system = “axial”

Approach= **eq-ax,** *cis* product

Cl=“axial “,π-system = “axial “

Approach= **ax-ax,** *trans* product

Cl=“ axial”, π-system = “equatorial

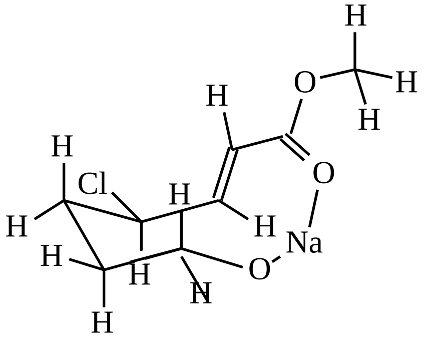
Approach= **ax-eq,** *cis* product

Cl=“equatorial “, π-system = “equatorial “

Approach= **eq-eq,** *trans* product

Figure 1. Basic geometryies of possible transition states in the hetero-Michael addition.

B. The energy of product. The energy of products are calculated the same way as the transition states. The most stable product is the one in which both the chiral the chiral center inductor (Cl) and the and the ester enolate are located *trans* (ax-ax) (**Table 2**).



O^{-}···C(=C): 2.502A, Na···O(=C): 2.002A, Na···O ring: 2.157A, O-···C=C(CO): 115.96°, C=C-C=O: 14.35°

Figure 2. Geometry of most stable transition state obtained using 3-21G for the E ester.

Table 1. Energies of Transition States.

Geometry	product config.	approach	E(hartree)
E	*cis*	**eq-ax**	-1149.74006
		ax-eq	-1149.72634
	trans	ax-ax	-1149.73796
		eq-eq	-1149.72903
Z	*cis*	eq-ax	-1149.70716
		ax-eq	-1149.72240
	trans	ax-ax	-1149.71961
		eq-eq	-1149.73466

Table 2. Energies of products.

product config.	approach	E(hartree)
cis	ax-eq	-1149.765
	eq-ax	-1149.768
trans	eq-eq	-1149.764
	ax-ax	-1149.774

III. Questions

1. From the distance of O^{-} ······· C(C=C) in the most stable TS of reactant (**1**) (**Figure 2**), Do you know whether this transition is reached in early or late stage in the reaction coordinate? (**ICR**)

2. This reaction is thermodynamically controlled or kinetic controlled? (**RQD**)

3. The transition states shown in **Figure 1** is directly adopted from the original paper. The structure shown is not strictly correct, why (don't consider the chelation of metal ion)? (**FAR**)

4. Calculate the ratio of *cis* product to *trans* product when (**1**) is used as starting material and the reaction is done at -78 °C? Experimently, this ratio is 15:1. (**SCL**)

5. The coordination of the metal ion with the oxygen of the nucleophile and that of the carbonyl ester is very important in the calculation of the transition state energy. No TSs can detected without considering the cation. Can you suggest some modifications to the experiment which can confirm the validation of this kind of computational results? (**FAR**)

IV. Group Dynamic

We have group meeting twice a week in our lab. Each meeting will last for half an hour. Being a group, we can search large amount of paper. Before we decide a the selection, we read about 10 papers from 3 journals. The problem is that lots of terms and principles are strangers to us because we just began this class. However we benefit from talking with each other. We want to engage in the future group project.