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# Intramolecular competition between alkenes in ketene–alkene [2+2] cycloaddition. A theoretical study

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## Abstract

In this paper, we describe the results of the intramolecular ketene–alkene [2+2] cycloaddition in 2-pent-4-enyl-octa-1,7-dien-1-one, at HF/6-31+G$^*$ and DFT-B3LYP/6-31+G$^*$ computational levels of theory. For this reaction, we have explored the four possible pathways at a supra-antara approach in which four possible products: 5-4-, and 6-4-membered fused [n.2.0] bicycle rings; 6-4-, and 7-4-membered fused [n.1.1] bicycle rings. In all cases, an asynchronous process was found with an appreciable interaction of the ketene central carbon with both carbons from the alkenes. We demonstrated that the reaction is driven towards the formation of 5-4 member rings instead of 6-4 member rings. In addition, the internal molecular orbital HOMO-2 was identified as the molecular orbital with higher nucleophilic reactivity.

*Keywords:* HF/6-31+G$^*$; B3LYP/6-31+G$^*$; Ketene; Intramolecular [2+2] cycloaddition; Molecular orbitals

## 1. Introduction

The intramolecular stereospecific [2+2] cycloaddition of ketenes to alkenes is a valuable method for the syntheses of cyclobutanones and related compounds that derived thereof [1].

Many different ketene–alkene [2+2] cycloaddition mechanisms have been proposed [2] and nowadays two of them are commonly accepted, the first is a stepwise mechanism involving sequential nucleophilic additions via a zwitterionic intermediate [3]; the second is a concerted cycloaddition by a thermally allowed antarafacial process that, according to the frontier molecular orbital (FMO) Theory [4], could be highly asynchronous [2,4]. Experimentally, it is clear that the ketene is the electrophilic component while the alkene is the nucleophilic moiety. Two important consequences can be accounted in the intramolecular ketene–alkene [2+2] cycloaddition: firstly, the regiochemistry of the cycloaddition is determined by the substitution pattern of the double bond [6], in which the internal alkene carbon is more substituted will produce bicyclo[n.2.0]alkanones, while substrates in which the terminal alkene carbon is more substituted will give bicyclo[n.1.1]alkanones (Scheme 1). Secondly, the yield of the reaction will be higher with more nucleophilic alkenes.

In addition, intramolecular ketene–alkene [2+2] cycloadditions favor five-member rings over six-member rings [7,8]. However, the only evidence supporting this affirmation is based on the shorter reaction time.

Solvent effect is important to determine which kind of reaction mechanism is followed on [2+2] cycloaddition. Theoretical calculations on the ketene–imine [2+2] cycloaddition have shown [9] that the stepwise mechanism is driven on polar solvents, whereas the concerted cycloaddition is preferred on apolar solvents. On the other hand, other theoretical calculations of ketene–vinylimide [2+2] cycloaddition have demonstrated that the larger the solvent

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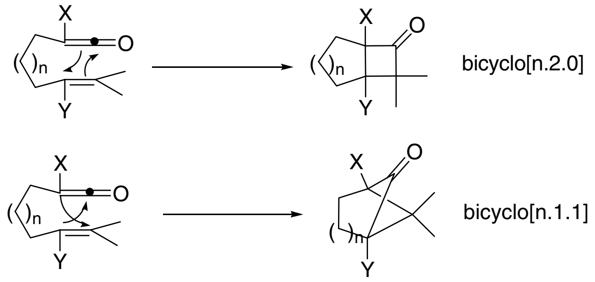
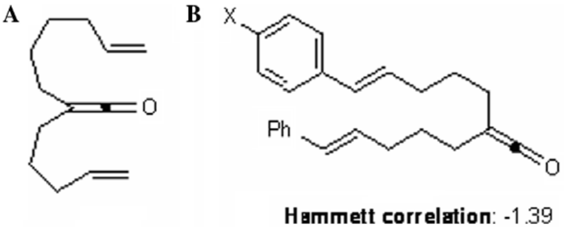


Scheme 1. [2+2] Cycloaddition to form bicyclo[n.2.0] and bicyclo [n.1.1].



Scheme 2. Bélanger models.

dielectric constant, the lower the activation barriers found [10].

Recently, Bélanger et al. performed series of competition experiments in the ketene–alkene [2+2] cycloaddition of the substrates A and B describe in Scheme 2 in an apolar solvent (toluene) [11].

They demonstrated that the reaction of A is much faster in the formation of five-four-member bicycles than six-four-member bicycle rings. In the case of the intramolecular ketene–alkene [2+2] cycloaddition in substrates B, they reported the formation of bicyclo[n.1.1]alkanones, in which it is showed that the reaction is accelerated by electron-donating groups, according to the negative value of $\rho$ Hammett constant.

In order to access a best comprehensive explanation for the formation of five-membered bicycles over the six or more membered rings in Belanger substrate A, we carried out a study on the reaction mechanism in gas phase by *ab initio* and DFT calculations of the intramolecular ketene–alkene [2+2] cycloaddition of A, where we considered the four possible products (5-4, two 6-4 and 7-4-membered fused bicycle rings) depicted in Fig. 1 and compared the theoretical with the experimental results.

## 2. Calculation method

All *ab initio* calculations presented here were performed with Gaussian 03 molecular orbital package [12]. Geometry optimizations and frequency calculations were carried out at HF/6-31+G$^*$ [13], the B3LYP density functional [14] in connection with the 6-31+G$^*$ basis set was performed all DFT calculations. The vibrational frequencies calculated for all the systems studied confirmed the nature of the stationary points (for minimum energy all positive frequencies, for transition state one imaginary frequency with the largest contribution from internal coordinates involved in the reaction). Vibrational frequencies were scaled by a standard factor of 0.8929 [15] and 0.95 [16] considering the zero-point energy for HF and DFT calculations.

## 3. Results and discussion

Ketenes are, in general, reactive intermediates. However, in this work, we used a ketene as the starting reagent. Experimentally, acyl chloride compounds (Fig. 2) are used for the generation of ketenes by deprotonation with triethylamine.

The molecular orbitals of the ketene showed that HOMO, HOMO-1 and HOMO-2 have $\pi$ contributions (Fig. 3), in addition, no significant symmetry differences were found for these molecular orbitals through HF and B3LYP calculations. According to our interpretation of the reactivity data obtained by internal molecular orbital, in which either nucleophilic or electrophilic centers are best described by MO's such as HOMO $-$ $n$ or LUMO $+$ $n$, [17] only the last two MO's are important for the [2+2] cycloaddition, since the $\pi$ contributions in HOMO are situated on the ketene group, but the nucleophilic centers are situated on the alkene groups at internal HOMO's: C12=C13 (HOMO-1) and C6=C7 (HOMO-2), respectively. The corresponding internal MO energy values calculated by HF and (B3LYP) are $-0.36333$ ($-0.26283$) and $-0.36636$ ($-0.26561$) eV; in comparison to HOMO energy (HF: $-0.32720$ and B3LYP: $-0.22258$), the gap values for HOMO-1 are 0.03613 (0.04025) and the gap values for HOMO-2 are 0.03916 (0.04303); thus, these molecular orbitals could be accessible in the reaction. If only the molecular orbital energy were the factor to drive the reaction, the [2+2] cycloaddition would form products **2** or **4** mainly because the energy of HOMO-1 is more accessible than the energy of HOMO-2. However, these were not the major products. It is well known that the length and nature of the chain have a great influence on the intramolecular cycloaddition [11]. A three atom chain offers the best compromise between the strain of the product and the activation entropy [7].

In this context, according to the Fig. 1, two types of bicycles could be produced on [2+2] cycloaddition: bicyclo[n.2.0]alkanones (products **1** and **2**) and bicyclo[n.1.1]alkanones (products **3** and **4**) in which the stability order of the products is **1** > **2** > **3** > **4** (Table 1). This result is in agreement with the first consequence reported by Snider and co-workers [6]. Furthermore, the stability of the transition energy can be established in the next order: TS1 > TS3 > TS4 > TS2. The formation of bicycle [3.2.0] **1** is the most favored by both kinetic and thermodynamic controls (see Fig. 4) over bicycle [4.2.0] **2**; in consequence five-member rings are preferred over six-member rings. The results of these reactions, including the electron correlation, showed the same tendency on the stability of products and transition states (Table 1). Unfortunately,