



Theoretical Study for the [2+2] Cycloaddition Reaction Mechanism of Ketenes and their Derivatives

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ABSTRACT

This study presents the intramolecular [2+2] cycloaddition reaction of ketenes to form cyclobutanones using B3LYP-D3/6-311++G(d,p) level of approximation. The concerted mechanism path was studied in detail. The structures of all intermediates and transition states were located using same level of theory. The influences of the substituents (-H, -CH₃, -NH₂, -F, -OH and -CN) were also discussed. The analysis of stationary points and the energetic parameters indicates that the substituted ketene with -CN group has the highest activation energy; however, ketene with -NH₂ group has the lowest one. Conversely, intramolecular [2+2] cycloaddition records the highest degree of asynchronicity with -NH₂ group and lowest with -CN group. The calculated thermodynamic parameters at room temperature have been listed and analyzed. The global and local properties of reactants involved in the intramolecular [2+2] cycloaddition reactions and the Fukui functions for an electrophilicity and local electrophilicity were also elucidated for carbon centers of each reactant.

Keywords: DFT, [2+2] cycloaddition, Ketenes, Mechanism.

INTRODUCTION

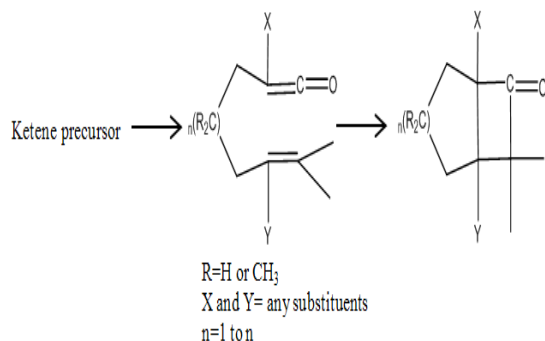
One of the earliest ketenes applications in the synthesis of natural products employed the [2+2] cycloaddition reactions¹. Cyclobutanones are considered a powerful synthetic intermediates involved in processes such as vicinal and geminal alkylation². They are readily prepared by the reaction of olefins with keteniminium salts or activated ketenes³⁻⁴. The intramolecular form of these cycloadditions could offer promising paths for the stereo- and regio- controlled synthesis of polycyclic compounds⁵. The intramolecular stereospecific

cycloaddition of ketenes to olefins is a significant method for the preparation of cyclobutanones⁶ and this is one of the main methods for the carbonyl functionalization of olefins⁷. With ketenes itself, this cycloaddition proceeds in poor yield since ketenes are easily dimerized. Cycloaddition of ketenes containing electron withdrawing groups for instance sulfur, oxygen or halogens are more general⁸. Recent studies obtained very good results with α , β -unsaturated ketenes.

The general form for an intramolecular [2+2] cycloaddition of ketene is presented in Scheme 1. The

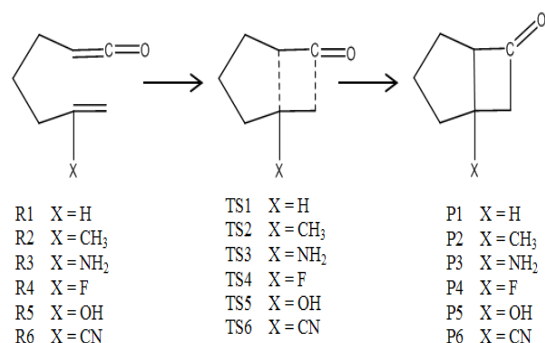


ketene is obtained from the conversion of a ketene precursor. Some of the most common methods used are zinc reduction of α -chloro acid chloride, Wolff rearrangement of α -diazo ketone and base-induced hydrogen chloride elimination from an acid chloride⁹⁻¹¹. Ring opening of cyclobutanones, 1,5-sigmatropic rearrangements of conjugated dienals, pyrolysis of esters, elimination from mixed anhydride and some special cases of photochemical fragmentation processes have been applied with excellent success¹²⁻¹⁶.



Scheme 1. Preparation of cyclobutanones from ketene precursor

The intramolecular [2+2] cycloaddition of ketene has been investigated experimentally by Marko and Ronsmans, 1985¹⁷. Their studies involved cycloaddition of alkenylketenes R1 (see Scheme 2) derived from unsaturated acid chlorides. However, to the best of our knowledge, the detail information about the reaction mechanism and its stereo- and regioselectivity have not been obtained yet. Therefore, the aim of this paper is to suggest the concerted mechanism of the intramolecular [2+2] cycloaddition of alkenylketenes and its derivatives using DFT method. Herein, electron withdrawing and donating groups are used in order to examine the electronic effect of these substituents on the regioselectivity and the reaction mechanism.



Scheme 2. Proposed Mechanism for the intramolecular [2+2] Cycloaddition reactions

Computational methods

Gaussian 09 package under Linux operation system was used and all studied structures were fully optimized in the gas phase¹⁸. DFT method has been proven to be a convenient method for the study of intramolecular [2+2] cycloaddition reactions and is employed in this study¹⁹⁻²¹. The B3LYP functional is used throughout in combination with 6-311++G(d,p) basis set²²⁻²³. We also considered the D3 correction to take into account for dispersion²⁴. Frequency calculations were performed to ensure that a transition state has only one imaginary frequency and a local minimum has no imaginary frequencies. Intrinsic reaction coordinate (IRC) computations were carried out to verify that the transition states connect the required reactants and products²⁵.

All energies and thermodynamic parameters reported in this research were obtained from the frequency calculations at the same level of approximation. The Gibbs free energies, enthalpies and entropies in the gas phase were obtained with the standard statistical thermodynamics at 1 atm and 298.15 K. The CYLview software was used as a graphical interface²⁶.

The global electrophilicity index (ω) is obtained on the basis of the electronic chemical potential (μ) and the chemical hardness (η) using the equation (1)²⁷.

$$\omega = \frac{\mu^2}{2\eta} \quad (1)$$

The chemical hardness (η) and the electronic chemical potential (μ) quantities may be approached based on the one electron energies of Highest Occupied Molecular Orbital (HOMO) and Lowest Unoccupied Molecular Orbital (LUMO), ϵ_H and ϵ_L , as in equation (2) and (3)²⁸⁻²⁹.

$$\eta \approx \epsilon_L - \epsilon_H \quad (2)$$

$$\mu \approx \frac{\epsilon_H + \epsilon_L}{2} \quad (3)$$

$$N = E_{\text{HOMO}(\text{Nu})} - E_{\text{HOMO}(\text{TCE})} \quad (4)$$

The relative nucleophilicity index (N) obtained in terms of the energies of HOMO $E_{\text{HOMO}(\text{Nu})}$ within the scheme of Kohn-Sham³⁰. This quantity can be defined by using equation (4). Where TCE is tetracyanoethylene and is chosen due to its lowest HOMO energy as a reference³¹.

Condensed Fukui functions and the related local parameters are significant to examine chemical reactivity in the center site of organic molecules³². The Fukui functions are calculated using same level of theory. The Fukui functions for electrophilic attack, f_k^- , and for nucleophilic attack, f_k^+ , allows the identification of the most nucleophilic and electrophilic centers in the organic species.

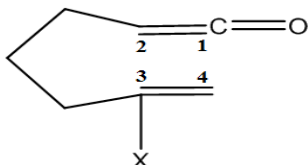


Fig. 1. Schematic structure and atom numbering of reactant involved in intramolecular [2+2] cycloaddition reaction of ketenes

RESULTS AND DISCUSSION

The concerted mechanism of [2+2] intramolecular cycloaddition of R1, R2, R3, R4, R5 and R6 is studied theoretically using B3LYP-D3/6-311++G(d,p) level of approximation. The transition state structures for the intramolecular cycloaddition were first located to examine the possibility of a concerted reaction mechanism. The IRC calculations illustrate the lowest energy pathway connecting the reactant to the cycloadducts (see Fig. 2). This figure illustrates the IRC for the parent (unsubstituted) system. The C2-C3 bond distance was plotted versus the C1-C4 bond distance in a More O'Ferrall-Jencks type diagram (See Fig. 3). The nature of asynchronous between the two forming bonds can be visualized via this diagram, which is clear from the deviation from the diagonal of the curve (dots line) corresponding to points along the actual synchronous (solid line). For the parent system, the C2-C3 bond is suggested to form first and then the C1-C4 bond with asynchronicity degree of 0.11. The degree of asynchronicity of the substituted systems is shown in Table 1.

Table 1: The degree of asynchronicity, Δd , at the transition states of intramolecular [2+2] cycloaddition reactions

	C2-C3	C1-C4	Δd
TS1	2.21	2.16	0.06
TS2	2.27	2.13	0.14
TS3	2.55	1.96	0.58
TS4	2.22	2.12	0.10
TS5	2.38	2.01	0.37
TS6	2.21	2.19	0.02

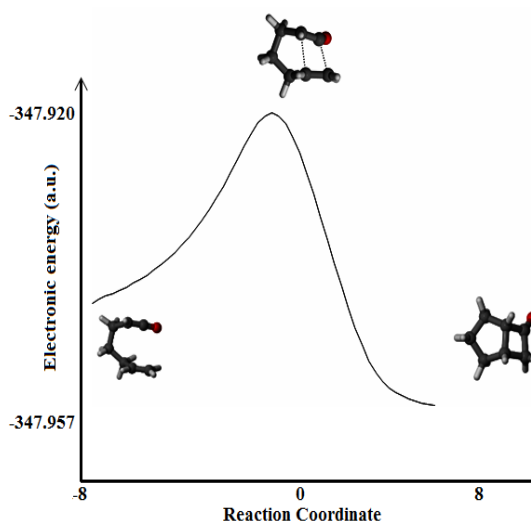


Fig. 2. IRC for parent (unsubstituted) system using B3LYP-D3/6-311++G(d,p) level of approximation

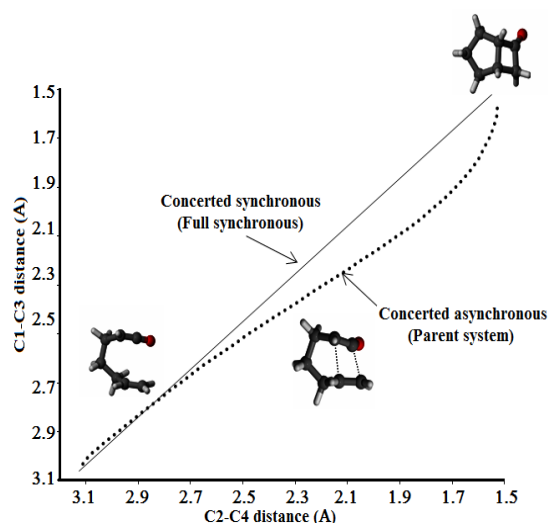


Fig. 3. More O'Ferrall-Jencks diagram explaining the bond formation synchronicity along the reaction coordinate

The geometries of the transition states for a concerted mechanism involved in the intramolecular [2+2] cycloaddition reactions are given in Fig. 4. The intramolecular reactions undergo cycloaddition through highly asynchronous transition states. An analysis of the lengths of the sigma forming bonds at the transition states indicates that the reaction follows asynchronous process. In all cases the length of the formed C1-C4 bonds are shorter than the formed C2-C3 bonds. The TS3 has larger Δd among all transition states and TS6 has the smallest degree and the formation of the most favorable transition states is more asynchronous.

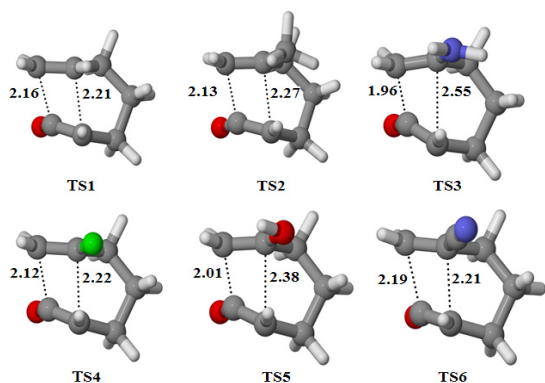


Fig. 4. Optimized geometries of the transition states involved in the intramolecular [2+2] cycloaddition reactions using B3LYP-D3/6-311++G(d,p) level of approximation

The relative electronic energies of the transition states and their corresponding products in the gas phase are presented in Fig. 5. As shown from these figures, the TS6 has higher energy than the other transition states. In contrast, TS3 has the lowest energy among all transition states. It is worth to realize that the P2 product is more stable than the others, due to their lowest electronic energies. From the observed data of activation energies and degree of asynchronicity, the transition states that have higher activation energies have the lowest degree of asynchronicity.

The thermodynamic parameters of the studied reactions in the gas phase at 1 atm and 298.15 K are collected in Table 2. The same trends of relative energies can be seen for enthalpy and Gibbs free energy values. An analysis of Table 1 indicates that the values of Gibbs free energy for products are negative, which refer to that the reactions are possible to occur. It is also shown that the transition states and products are found to be disfavored entropically. The activation enthalpy and activation Gibbs free energy at all levels of theory are found to be positive and very close. The overall cycloaddition reactions are exothermic and this indicates the stability of the products.

HOMO and LUMO energies in eV at B3LYP-D3/6-311++G(d,p) level of theory are computed for reactants and products and listed in Table 3. It is worth to realize that the energy gap for the parent molecules is higher than the other derivatives which indicates the stability of this product. Product P3 has narrow energy gap with 5.57 eV. The energy gap has

become narrow with $-\text{NH}_2$ and $-\text{CN}$ (4.45 and 4.60 eV, respectively). The wider energy gap was found for reactants R4 and R5.

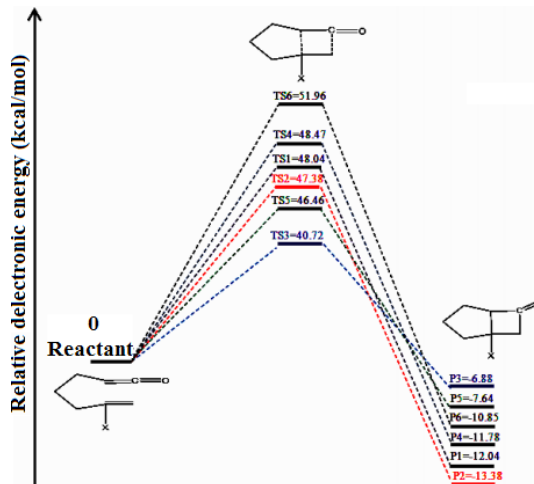


Fig. 5. Energy profile for the intramolecular [2+2] cycloaddition reactions using B3LYP-D3/6-311++G(d,p) level of approximation. The energies are given relative to reactants (kcal/mol)

Table 2: Thermodynamic parameters for transition states and products at B3LYP-D3/6-311++G(d,p) level of theory in (kcal/mole) for ΔH and ΔG and in (cal/mol.K) for ΔS

	ΔH (kcal/mol)	ΔG (kcal/mol)	ΔS (cal/mol.K)
P1	-14.10	-10.31	-12.71
P2	-15.28	-11.25	-13.50
P3	-8.15	-4.62	-11.84
P4	-13.01	-9.39	-12.16
P5	-8.77	-5.39	-11.33
P6	-12.05	-8.52	-11.85
TS1	46.94	50.72	-12.69
TS2	46.29	50.24	-13.25
TS3	39.59	43.19	-12.07
TS4	47.51	50.97	-11.60
TS5	45.42	48.96	-11.88
TS6	51.07	54.42	-11.26

Table 3: HOMO energies, LUMO energies and energy gap (in eV unit) for reactants and products at B3LYP-D3/6-311++G(d,p) level of theory

	E_H	E_L	$E_L - E_H$
R1	-6.45	-1.28	5.17
R2	-6.41	-1.27	5.14
R3	-5.75	-1.30	4.45
R4	-6.43	-1.16	5.27
R5	-6.27	-1.03	5.25
R6	-6.50	-1.90	4.60
P1	-6.83	-1.05	5.78
P2	-6.78	-0.95	5.83
P3	-6.59	-1.02	5.57
P4	-7.11	-1.32	5.79
P5	-6.87	-1.07	5.80
P6	-7.45	-1.58	5.88

A good explanation for the regioselectivity in intramolecular [2+2] cycloaddition reactions may be obtained by calculating Fukui functions, where the transition structure associated with the rate-determining steps mostly involves the formation of one single bond between the most nucleophilic and other electrophilic sites in the [2+2] cycloaddition reagent pair. The global and local properties of reactants involved in the intramolecular reactions are gathered in Table 4. The nucleophilic site in all reactants are at C2 atom, which has the highest

value of the Fukui function for an electrophilic attack f_k^- , except R3 in which C4 atom has the highest value. The highest value of local electrophilicity (ω_k) is located at C1 carbon atom, except for R6 where C4 has the highest value. The C4 carbon atom in R6 is considered the most powerful electrophile as the most favorable site for nucleophilic attack based on the local electrophilicity, $\omega_k = 0.635$ eV, and the Fukui function, $f_k^+ = 0.4158$.

CONCLUSION

The B3LYP-D3/6-311++G(d,p) level of approximation was used to investigate the concerted mechanism of the intramolecular [2+2] cycloaddition reaction of ketenes to obtain cyclobutanones as a cycloadducts. Different substitution groups were used to study their effect on the stability of the reaction products. The highest activation energy was found with CN group and lowest with NH_2 group. All cycloadducts were found to be stable thermodynamically. The global and local properties including Fukui functions were studied for carbon centers of each reactant.

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Conflict of interest

We as authors declare that there are no conflicts of interest with any person and organization related to this article.

Table 4: The Global and Local properties of reactants involved in intramolecular [2+2] cycloaddition reactions

	ω	N	site (k)	f_k^-	f_k^+	ω_k	Nk
R1	1.45	3.04	C1	0.1195	0.3306	0.389	0.322
			C2	0.472	0.0477	0.056	1.273
			C3	0.0016	0.0019	0.002	0.004
			C4	0.0004	0.0042	0.005	0.001
R2	1.43	3.08	C1	0.0933	0.2984	0.351	0.254
			C2	0.3683	0.0429	0.050	1.004
			C3	0.0127	0.0015	0.002	0.035
			C4	0.024	0.0006	0.001	0.065
R3	1.40	3.74	C1	0.0028	0.3443	0.380	0.010
			C2	0.0069	0.0461	0.051	0.023
			C3	0.1247	0.0004	0.001	0.423
			C4	0.4054	0.0012	0.001	1.377
R4	1.37	3.06	C1	0.1164	0.3717	0.416	0.317
			C2	0.4631	0.0304	0.034	1.259
			C3	0.0022	0.0021	0.002	0.006
			C4	0.0035	0.0019	0.002	0.010
R5	1.27	3.21	C1	0.1155	0.3747	0.386	0.332
			C2	0.4476	0.0285	0.029	1.285
			C3	0.0082	0.0014	0.001	0.024
			C4	0.02	0.0011	0.001	0.057
R6	1.92	2.99	C1	0.1148	0.0083	0.013	0.303
			C2	0.4673	0.002	0.003	1.233
			C3	0.0014	0.2547	0.389	0.004
			C4	0.0019	0.4158	0.635	0.005

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