Origin of Regioselectivity in Photocycloaddition Reactions of 2-Cyclohexenone with Cycloalkenecarboxylates

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The regiochemical results in [2 + 2]photocycloaddition of 2-cyclohexenone (**1**) with 1-cycloalkenecarboxylates (**2**–**4**) significantly changed from head-to-head (hh) to head-to-tail (ht) adducts depending on increments of the ring-size, from four to six, of the carboxylates. The root of the drastic regioselective change was inferred from the transition state (TS) analysis of the triplet reactions, including the back-reaction at the PM5 and B3LYP levels. The TS energy of the first step (TS1) is the most important factor for this reaction. The change in TS energies at hh adducts was larger than that at ht adducts. For more detailed analysis, the TS energies of the hh and ht reactions (at the three reactions) were partitioned to the two reactant deformation (E_{df}) and the interaction (or repulsion, E_{int}) energies. The E_{df} and E_{int} energy changes were found to be dependent on the ring-size of the 1-cycloalkenecarboxylates **2**–**4**. Thus, since the larger ring of **4** has relatively higher TS1 and deformation energies for giving the hh adduct, they may cause the preferential formation of the ht adduct, and result in the significant changes in the ht/hh ratio owing to the ring-size. The root of the significant hh diminution may be the dipole–dipole repulsion between the enone carbonyl and larger carboxylate (**4**) moieties. The improved PM5 and B3LYP/6-31+G(d) calculations are effective and economical for disclosing the origin of regioselectivity in [2 + 2]photocycloadditions.

Photochemical [2 + 2]cycloaddition reactions of α,β-unsaturated carbonyl compounds with alkenes are among the most widely used excited state processes in synthetic organic chemistry.[1] The frontier molecular orbital (FMO) theory has pointed out that the regiochemistry, head-head (hh)/head-tail (ht) ratio of the typical enone–alkene photocycloadditions, mainly depends on the electric property of alkenes.[2] In 1993, Schuster introduced the Bauslaugh–Schuster–Weedon mechanism into the photocycloadditions without the molecular orbital aspect.[3] The origin of the cycloaddition regioselectivity has, however, remained of great interest in this area.

The regiochemical preferences in cyclohexenone–alkene photoadditions were nicely explained by the transition state (TS) analysis using the acrolein–alkenes model and an ab initio MO method of the first biradical producing step.[4] The phenomenon associated with hh vs ht adduct formations from other cyclic alkenones was, however, not similarly addressed. The biradical trapping experiments for the other enone–alkene systems led to the suggestion that reaction regioselectivities are governed by the relative rates of biradical closure vs their return to the starting materials from the biradicals.[5] Regiochemical results obtained by similar biradical trapping experiments for cyclopentenone–allene photoreactions[6] were theoretically analyzed using an ab initio method by Goddard, and the quantitative speculation regarding the biradical species has not coincided with the experimental result by Weedon et al. We suggested that the theoretical aspect is reasonable.[7]

Recently, $^3(\pi–\pi^*)$ [2 + 2]photocycloadditions of many kinds of α,β-unsaturated enone compounds to ethylene have been theoretically studied.[8–11] The CASSCF studies by Robb et al. indicated that the product selectivity is determined by the transition states on concerned energy surfaces, in agreement with the experimental results of Weedon et al. Robb et al. have, however, not described the regioselective aspect. Some contrasting conclusions clearly demonstrate that the origin of the regiochemical control in the [2 + 2]photocycloadditions is still an unresolved issue.

Interesting experimental data of [2 + 2]photocycloaddition of 2-cyclohexenone **1** to 1-cycloalkenecarboxylates **2**, **3**, and **4** are shown in Scheme 1.[12] The ht/hh regioselectivity significantly inverts with increment of the ring-size, from four to six. This significant result was pointed out by Schuster in 1993 and 2003,[3] but no attempts have been made to identify quantitatively the root of the regioselectivity change.

We have confirmed that species specificity and regioselectivities in the photocycloaddition of some conjugated cyclic enones and dienones are mainly controlled by the interaction between the FMOs calculated using the PM3-CI level. For example, the peri- ([2 + 2] or [4 + 2]), site- (3,4- or 5,6-addition) and regio-selective photoadducts in the triplet photoreactions of 2-pyrones with electron-deficient or electron-rich alkenes were considered to be formed through the regioselective 3-β or 6-β two-center interactions at the first-step, and periselective ring-closures from the biradical intermediates.[13] Site- and stereoselective [2 + 2]cycloadditions between some 2-pyrone and maleimide at the solid state have also been analyzed by MO

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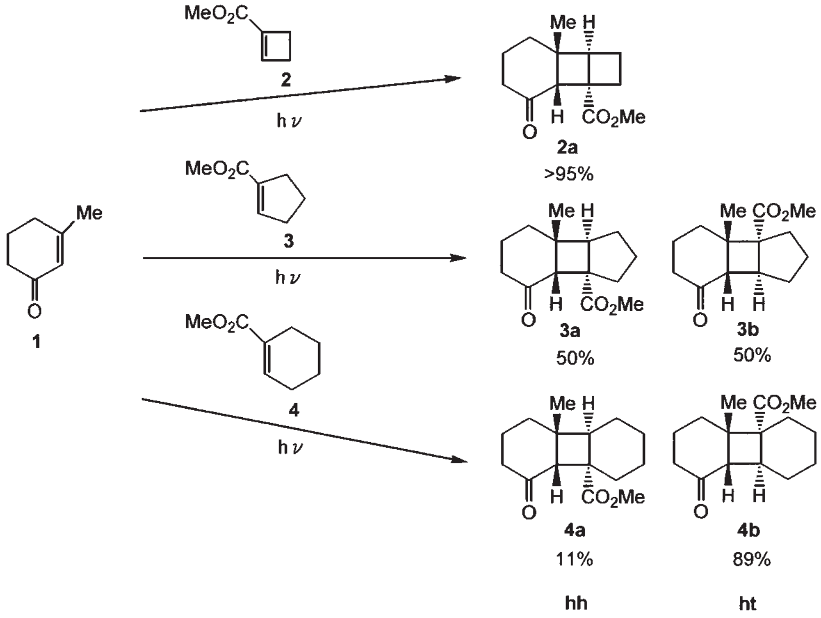

Scheme 1.

TS calculations to proceed via some interactions of the singlet excited state with the ground state.[14] We have, moreover, recognized that the origins of stereo- and face-selectivities in some Diels–Alder reactions are nicely inferred from the TS energy and the deformation energy analyses by use of the new PM5 program together with the DFT method.[15]

We report here an origin analysis of the significant change in ht/hh regioselectivity of the photocycloadditions in Scheme 1. The calculation is performed by the TS analysis and the deformation analysis partitioning the TS energy by use of the PM5 and DFT methods, etc., which may give a simple and straightforward conclusion. We just reported TS analysis on regioselectivity in [2 + 2]photocycloaddition reactions of 3-methoxycarbonyl-2-cyclohexenone with **2–4**, and showed that the hh/ht ratio can be explained in terms of the TS analysis. The origin analysis of the hh/ht ratio was however confused by the existence of the methoxycarbonyl group.[16]

Computational Methods

Geometry optimizations of all molecules were carried out at the improved PM5[17] level in WinMOPAC 3.5 (Fujitsu Ltd[18]) and CIS[19] and B3LYP[20] levels in the Gaussian 98 program.[21] The TS analysis and the deformation energy analysis by partitioning the TS energy to the reactants' deformation energies and the interaction energy[22] were investigated at the PM5 and B3LYP/6-31+G(d) calculations.

Results and Discussion

The photocycloaddition pathway is shown as Fig. 1 (and the surface energies are shown later on). 3-methyl-2-cyclohexenone (**1**) is first excited from the ground state ($^0S_1$) to the triplet state ($^1T_1$) via the singlet excited state ($^1S_1$) by UV irradiation, and reacts with 1-cycloalkenecarboxylates (**2–4**) in the ground state ($^0S_2$). Passing the first transition state (TS1), triplet biradical intermediates (BR) evolve to the singlet state through an intersystem crossing, which affords some [2 + 2]adducts via the second transition state (TS2), competing with the return to the starting materials via the transition state (TS3).

FMO Analysis. FMO interactions between the triplet excited **1** and the ground state **2**, **3**, and **4** were analyzed as shown in Fig. 2. The energy differences between the HSOMO of **1** and the LUMO of **2**, **3**, and **4** are smaller than those between the LSOMO of **1** and the HOMO of **2**, **3**, and **4**. It is suggested that the HSOMO–LUMO interaction is more effective in all reactions, although the LSOMO–HOMO interaction was thought to be effective in the reactions of 3-methoxycarbonyl-2-cyclohexenone.[16] The coefficient value at the C-3 position of **1** was larger than that at the C-2 position, and the coefficient values at the C-β position of **2**, **3**, and **4** are larger than those at the C-α position. In all reactions, the bonding of the C-3 position of **1** and the C-β position of **2**, **3**, and **4** is preferred, and it is predicted the hh adducts are the main products at the FMO analysis. The smaller ring-size has the marked tendency to lead to the hh adduct because of the large coefficient values at the C-β position (**2** > **3** > **4**), and the HSOMO–LUMO energy difference gradually decreased, following the decreasing ring-size (**2** < **3** < **4**). This tendency might arise at the start of the reaction, because the FMO analysis is an analytical method for the beginning of the triplet reactions.

Transition State (TS) Analysis. Figure 3 shows the initial conditions for the TS analysis, namely, four initial conditions in the first step (TS1), dihedral angles: τ = cis, gauche-in, gauche-out, trans, for head-head and head-tail regioselectivity analysis. Table 1 presents the TS1 energy barriers and dihedral angles τ at the PM5 level; the process starts from the reactant complex of the triplet enone and ground state alkene and gose to the first transition state (TS1), which leads to the triplet biradical intermediates. Some initial conditions gave the same TS1 results. Figure 4 shows the hh and ht geometries of the lowest TS1 for each reaction product of **1** with **2**, **3**, and **4**; the C_3–C_4 or C_2–C_4 distances, 2.15–2.20 Å, are reasonable.

In the **1** + **2** reaction for the hh adduct, the energy of TS ($2a_2$) is larger than that of TS ($2a_1$), by 7 kcal/mol. It is inferred that TS ($2a_1$) is the main TS1 leading to the hh adduct. Three TS1

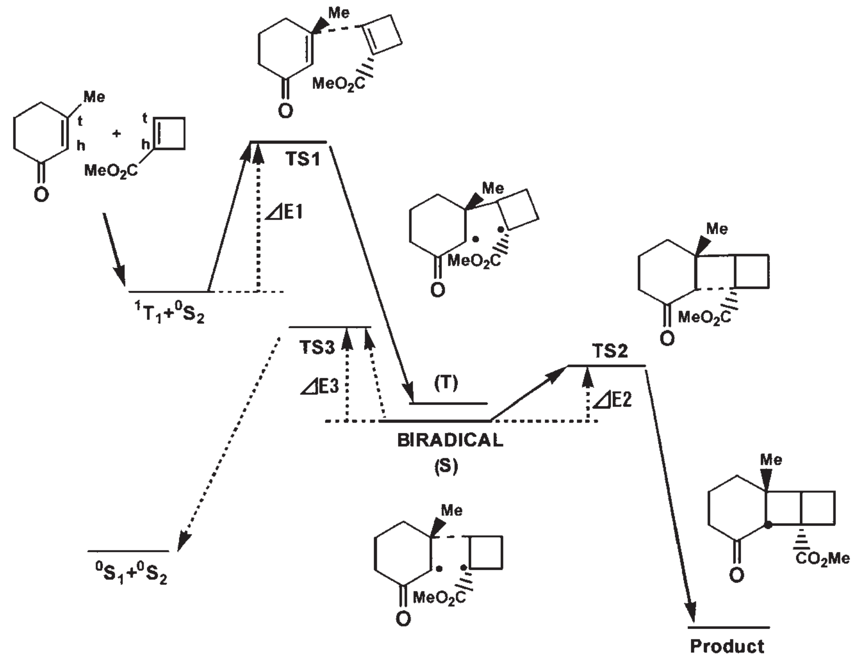

Fig. 1. The triplet photocycloaddition pathway via the biradical intermediate.

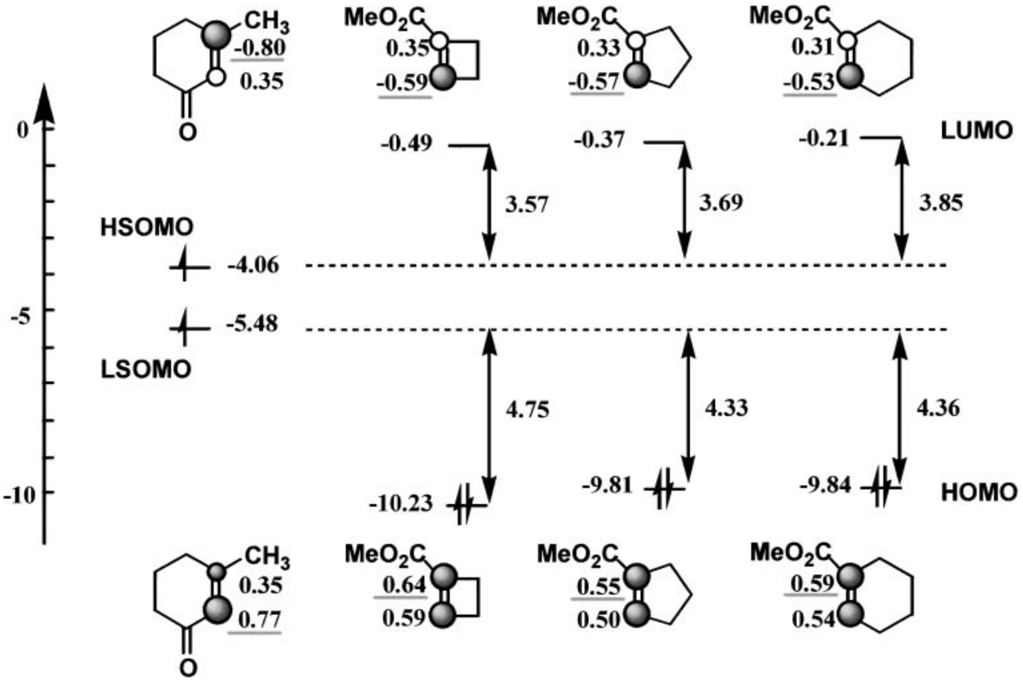

Fig. 2. The FMO coefficients and energy levels (eV) for the triplet excited **1** and the ground state **2**, **3**, and **4** at PM5 level.

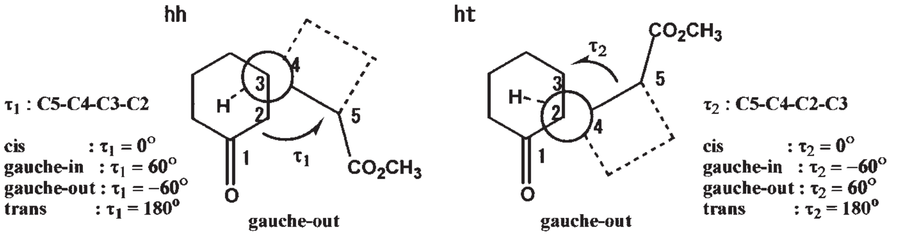

Fig. 3. Four initial conditions at the starting point. Dihedral angles τ = cis, gauche-in, gauche-out, trans, for head-to-head and head-to-tail.

Table 1. The Energy Barriers and Dihedral Angles of TS1 in Regioselective Photoadditions

			Methods and energy barrier ($\Delta E_{\text{act}}{}^{\text{a)}}$/kcal mol^{-1})			τ/°
			PM5	B3LYP/6-31G	B3LYP/6-31+G(d)	
1 + **2**	hh	$2a_1$	11.7	1.8$^{\text{b)}}$	2.8	32.6
		$2a_2$	18.7	16.1	17.0	−174.0
	ht	$2b_1$	11.3	10.2	12.2	70.9
		$2b_2$	10.9	3.3	6.7	−100.3
		$2b_3$	10.6	5.7	8.5	171.7
1 + **3**	hh	$3a_1$	21.8	10.7	9.3	75.5
		$3a_2$	13.6	9.7	6.9	169.3
	ht	$3b_1$	15.4	18.0	15.9	55.7
		$3b_2$	14.4	6.4	4.6	−64.9
		$3b_3$	13.0	12.4	11.5	82.0
		$3b_4$	11.4	6.6	5.4	−172.5
1 + **4**	hh	$4a_1$	16.6	14.2	9.7	64.0
		$4a_2$	19.5	15.2	12.2	−56.1
	ht	$4b_1$	13.4	10.4	6.8	172.4
		$4b_2$	16.6	27.4	23.0	−70.6
		$4b_3$	13.5	25.4	20.7	173.0

a) $\Delta E_{\text{act}} = E(2a_1) - E({}^1T_1 + {}^0S_2)$. b) 1.8 kcal mol^{-1} = −731.503206 a.u. − {−347.775986 a.u. + (−383.730141 a.u.)} = 0.023 a.u.

leading to the ht adduct are picked since they have similar TS1 values. TS ($2b_3$) has lower energy. By comparison between TS (2a) and TS (2b), the energy barrier of TS ($2b_3$) is 1.1 kcal/mol smaller than that of TS ($2a_1$). This means the TS calculation for the (**1** + **2**) reaction by the PM5 method indicates that one should prefer the ht adduct. The two single-point-energy B3LYP methods, however, show preference of the hh adduct in accordance with experimental results. These differences are shown in Table 2, and are discussed.

In the **1** + **3** reaction, it is inferred that the main TS1 leading to the hh adduct is TS ($3a_2$). TS ($3b_4$) is the main TS1 leading to the ht adduct, and the TS ($3b_4$) is 2.2 kcal/mol smaller than that of TS ($3a_2$). The differences obtained by the two B3LYP methods are similar to the difference obtained by PM5.

In the **1** + **4** reaction, it is inferred that TS ($4a_1$) and TS ($4b_1$) are the main TS1 leading to the hh and ht adducts, respectively.

Table 2 shows the energy difference ($\Delta\Delta E$) between the most stable hh-TS intermediate and the most stable ht-TS intermediate on **1** + **2**, **1** + **3** and **1** + **4** reactions;

$$-\Delta\Delta E = -\{\Delta E(\text{hh}) - \Delta E(\text{ht})\}. \tag{1}$$

The PM5 calculation shows that all of the reactions prefer the ht adducts because the TS1 energy of the ht adducts is smaller than that of the hh adducts in the calculation. The energy differences gradually diminish following the increase of the ring-size. Therefore, we can see the tendency for the cycloalkenecarboxylates of the larger ring to produce the ht adduct in considerable numbers. If the observational errors of the $-\Delta\Delta E$ are about 2.2 kcal/mol, the corrected values of $-\Delta\Delta E$ are 1.12, −0.03, −1.06 kcal/mol on the **1** + **2**, **3**, and **4** reactions, respectively. So the calculation results correspond to the experimental results, that is, the regioselectivity of products changes from hh to ht adducts depending on the increasing ring-size, from four to six, of the carboxylates. The observational error by 2.2 kcal/mol in the PM5 calculation seems to mean that there is balance between the two hh and ht TS positions.[15] The calculated activation energies for the thermal butadiene–ethylene cycloadditions are different by 22.6 kcal/mol even between the CASSCF/6-31G*[23] and B3LYP/6-31G*[24] methods. The result shows energy balancing between reactants and TS molecules is very poor, even as calculated by the CASSCF method of higher level approximations.

Table 1 and Table 2 contain the single-point-energy calculations at B3LYP levels from the PM5 geometry. The calculations of the level of the 6-31+G(d) basis set gave improved results compared with the results of the 6-31G basis set. The calculation results, $-\Delta\Delta E = 3.83$, and −2.89 kcal/mol for **1** + **2**, and **1** + **4** reactions are close to the experimental results of the hh/ht ratio, similarly to the corrected results at the PM5 level. These results show that the TS geometries by PM5 are reasonable, and the TS1 surface energy mainly governs the regioselectivity of ht/hh, significantly depending on the ring-size of the cyclic alkenes.

Deformation Energy Analysis. The TS1 energies are then partitioned to two deformation energies (E_{df}) and the interaction energy (E_{int}), which have been effective for analysis of face-selectivity in the thermal cycloadditions.[15,22] The E_{df} is the energy required to change the reactants' geometry into the transition state geometry. TS energy differences (ΔE_{act}) are partitioned as follows:

$$\Delta E_{\text{act}} = \Delta E_{\text{df-enone}} + \Delta E_{\text{df-alkene}} + \Delta E_{\text{int}}. \tag{2}$$

$\Delta E_{\text{df-enone}}$ and $\Delta E_{\text{df-alkene}}$ are the deformation energies for triplet 2-cyclohexenone and 1-cycloalkenecarboxylate, respectively, and they were calculated as follows.

$$\Delta E_{\text{df-enone}} = E_{\text{TS-enone}} - E_{\text{enone}}. \tag{3}$$

$$\Delta E_{\text{df-alkene}} = E_{\text{TS-alkene}} - E_{\text{alkene}}. \tag{4}$$

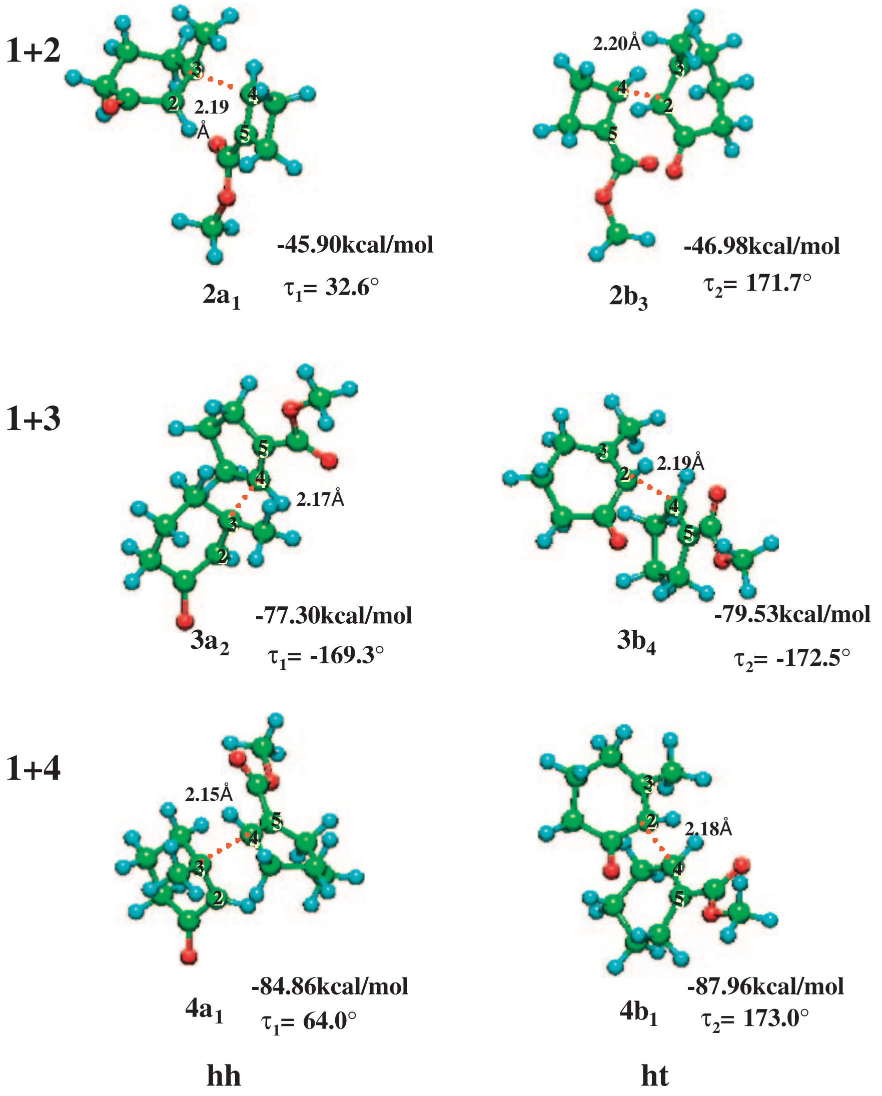

Fig. 4. Transition state (TS1) geometries for the first step leading to biradical intermediates at the [2 + 2]photocycloadditions by the PM5 calculation. TS distances are in Å, dihedral angles (τ) are in degrees.

Table 2. The Energy Difference between the Most Stable TS1 of hh and That of ht on Photoreactions

	$-\Delta\Delta E = -\{\Delta E(\mathrm{hh}) - \Delta E(\mathrm{ht})\}$/kcal mol^{-1}			
	PM5		B3LYP/6-31+G(d)//PM5[b)]	Experiment[c)]
	Calculation	Corrected value[a)]	Calculation	
1 + 2	−1.1	1.1	3.8	1.7
1 + 3	−2.2	0.0	−2.3	0.0
1 + 4	−3.3	−1.1	−2.9	−1.2

a) The calculation value plus 2.2 kcal mol^{-1}. b) Single-point-energy. c) ln hh/ht ≒ $-\Delta\Delta E/RT$ (at 298 K).

$E_{\text{TS-enone}}$ and $E_{\text{TS-alkene}}$ are the heat of formation (HOF) of the triplet enone and the ground state alkene at the TS state, respectively. E_{enone} and E_{alkene} are the HOF of $^1T_1$ and $^0S_{2-4}$, respectively. ΔE_{int} is the interaction energy between the enone and alkene (Table 3 and Fig. 5), and the positive value means some repulsion, which may come from the triplet reaction. On the deformation energies of enones, $\Delta E_{\text{df-enone}}$ values at the transition state leading to the hh adducts become larger depending on the increment of the ring-size, from four to six (Fig. 5). On the other hand, such a tendency is not observed at the TS of ht adducts. ΔE_{act} and $\Delta E_{\text{df-alkene}}$ values become relatively larger depending on the increment of the ring-size. Especially, $\Delta E_{\text{df-alkene}}$ of the hh at the **1 + 4** reaction is very large. The phenomenon is different from that in the case of 3-methoxycarbonyl-2-cyclohexenone.[16] Therefore, it is inferred that the hh/ht ratio becomes inverse at the large ring of the carboxylates. ΔE_{int} also becomes

Table 3. Deformation Energy Calculation by the PM5 (kcal mol^{-1})

Reactions			ΔE_{act}	$\Delta E_{df\text{-}enone}$	$\Delta E_{df\text{-}alkene}$	ΔE_{int}
1 + **2**	hh	2a$_1$	11.7	3.4	3.3	5.0
		2a$_2$	18.7	8.1	3.6	7.0
	ht	2b$_1$	11.3	4.0	3.2	4.1
		2b$_2$	10.9	4.9	3.2	2.8
		2b$_3$	10.6	6.6	1.9	2.1
1 + **3**	hh	3a$_1$	21.8	9.2	4.8	7.8
		3a$_2$	13.6	4.2	3.6	5.8
	ht	3b$_1$	15.4	5.6	4.6	5.2
		3b$_2$	14.4	6.6	3.2	4.6
		3b$_3$	13.0	6.0	3.5	3.5
		3b$_4$	11.4	5.5	2.8	3.1
1 + **4**	hh	4a$_1$	16.6	5.0	5.7	5.9
		4a$_2$	19.5	8.7	3.7	7.1
	ht	4b$_1$	13.4	6.2	3.6	3.6
		4b$_2$	16.6	6.4	7.2	3.0
		4b$_3$	13.5	5.5	4.1	3.9

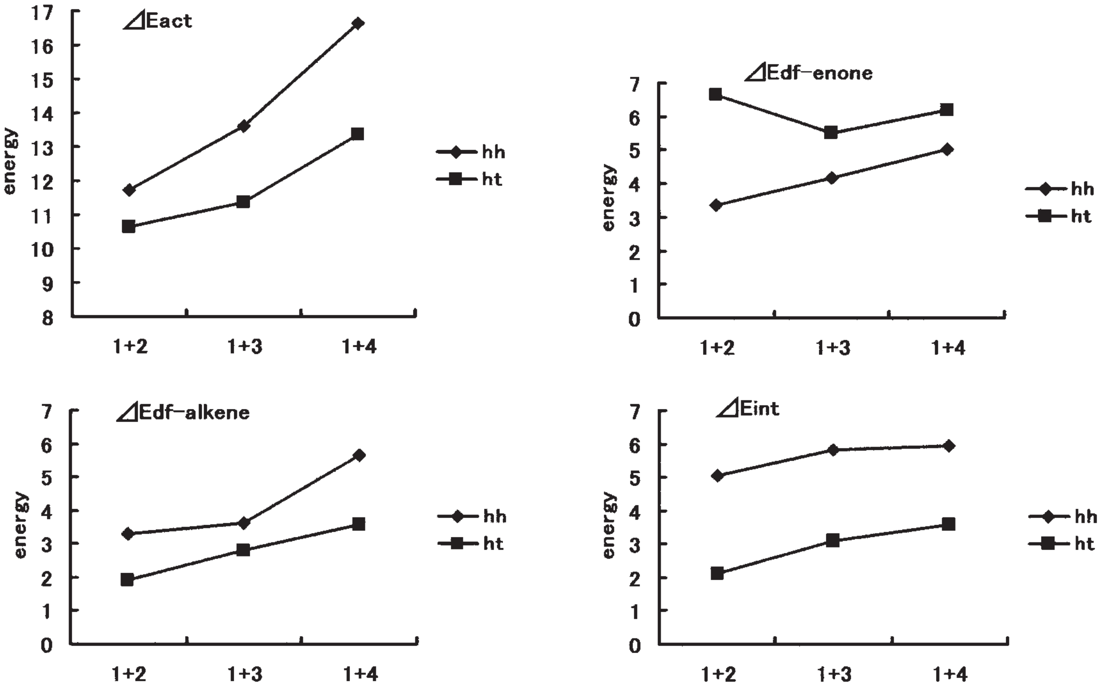

Fig. 5. Relative comparison in energy shift following the ring-size increasing, from four to six, cycloalkenecarboxylate (**1** + **2**, **3**, **4**). Activation energies (ΔE_{act}), deformation energies ($\Delta E_{df\text{-}enone}$, $\Delta E_{df\text{-}alkene}$) of enones and alkenes, and interaction energies (ΔE_{int}).

larger, which means larger repulsion. Such repulsion may electrically come from the approach between C=O on **1** and carboxylate on **4** for the hh adducts, and it is inferred to give the ht adduct, mainly. The increment of the approach repulsion on the hh adducts at the hh adducts at the larger cycloalkene may also cause the larger repulsion $\Delta E_{df\text{-}enone}$ at the TS gauche geometry.

Table 4 shows the transition state energies leading from the biradical intermediates to the products (TS2) and that leading back to the reactants (TS3) on the calculation of the PM5 method. The TS2 energies are only a few kcal/mol. On the other hand, the TS3 energies are over 10 kcal/mol. In these triplet reactions, it is inferred that the second-step reactions forming cyclobutanes may occur as soon as the biradical intermediates are formed.

Conclusion

The factors causing the significant regioselective change in the triplet [2 + 2]photocycloaddition of 2-cyclohexenone (**1**) with 1-cycloalkenecarboxylates (**2**–**4**) were quantitatively analyzed. The results of the FMO analysis at the initial approach showed that all the reactions produce the biradicals leading to

Table 4. The Analysis of TS2 and TS3 in the Photocycloaddition Pathway (Fig. 1) by the PM5 (kcal mol^{-1})

Reactions			TS2	TS3	Rotation
1 + **2**	hh	2a$_1$	a)	18.0	
	ht	2b$_1$	1.2	11.1	3.9
		2b$_2$	2.9	14.3	3.9
		2b$_3$	2.6	14.8	3.9
1 + **3**	hh	3a$_2$	a)	12.1	5.6
	ht	3b$_4$	0.8	12.0	6.2
1 + **4**	hh	4a$_1$	a)	10.2	
	ht	4b$_1$	2.2	10.3	4.3

a) Not converged.

hh adducts, where the smaller ring-size has the marked tendency to lead to the hh adduct. The TS analysis at the PM5 calculation gave results that showed that the reactions produce the biradicals leading to ht adducts. The TS1 energy differences gradually diminish following the increment of the ring-size. The correction by 2.2 kcal/mol of the observational error at the PM5 level and the B3LYP/6-31+G(d)//PM5 calculation showed the product change from hh to ht adducts depending on increment of the ring-size of the carboxylates. By calculation of the partitioned deformation energy, in the reaction of **1** with **4**, the larger repulsion is inferred to come from the approach between C=O on **1** and carboxylate on **4** for the hh adducts, and to give mainly the ht adduct. Consequently, the improved PM5 and B3LYP/6-31+G(d)//PM5 calculations showed that the TS1 surface energy and the alkene deformation energy mainly govern the regioselectivity of the ht/hh ratio, significantly depending on the ring-size of the carboxylates.

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