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A DFT mechanistic study of the generation of azomethine ylides from the ring-opening reactions of stabilized aziridines and follow-up 1,3-dipolar cycloaddition reactions with acetaldehyde

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ABSTRACT

This work investigated computationally with density functional theory calculations at the M06/6-311G* level, the ring opening reaction of various methyl-, phenyl- and carbonyl- substituted aziridines to obtain azomethine ylides and the subsequent 1,3-dipolar cycloaddition reaction with acetaldehyde leading to 3-methyl and 4-methyl regioisomers and *endo*- and *exo*- stereoisomers. The activation barrier for the electrocyclic ring opening of the parent aziridine is very high (51.3 kcal/mol) but is lowered by at least 15.5 kcal/mol upon methyl and ester group substitutions. In the reaction of 1,3-diphenyl-2,2-methoxycarbonylaziridine **A2** with acetaldehyde, the ring opening step is rate-determining with an activation barrier of 28.9 kcal/mol. The activation barrier for the formation of the 4-methyl isomer from this reaction is at least 7.4 kcal/mol lower than that for the formation of the 3-methyl isomer, which is in accord with the experimentally-observed regioselectivity. Also, the formation of the *exo* isomer is more favoured than the *endo* isomer as the barrier of the former is 2.7 kcal/mol compared to 6.1 kcal/mol for the latter. There is an inverse correlation between the activation barriers for the electrocyclic cleavage of the aziridines and the electrophilicities of the resulting azomethine ylides. The results are rationalized in terms of perturbation molecular orbital theory.

1. Introduction

Azomethine ylides are very reactive intermediates employed in organic chemistry for the synthesis of 5-membered heterocycles [1]. They possess four π-electrons spread over three atoms creating a 1,3-dipole that usually undergoes cycloaddition reactions with olefins and other dipolarophiles to afford cycloadducts such as oxazolidines, pyrrolidines and pyrrolines. The ylide system is a superposition of four resonance structures with the most common representation being that in Scheme 1. The amount of negative charge on each carbon atom is dependent on the nature and number of substituents at these carbons [2].

Several ways of generating azomethine ylides have been developed, including the decarboxylation of amino esters [3]and from imines [4]. Perhaps, among the most convenient methods of generating azomethine ylides is *via* the nucleophilic [5,6], thermal conrotatory and Lewis acid promoted ring opening of aziridines [7–9]. Nielsen [10] has studied thermal ring opening at both the C—C and C—N bonds of parent aziridine, diaziridine and their methyl substituted analogues using high level *ab initio* methods. The energy barriers for the cleavage of these bonds were found to be very high and as such substituted derivatives are usually employed in organic synthesis. It has been shown that the substitution of electron- withdrawing and donating groups on opposite sides of reactive intermediates containing delocalized π-electrons causes stabilization [11]. Also, incorporation into strained bicyclic [2.2.1] systems has been shown to lower the activation energies for these reactions [34]. Based on this, Texier et al. [12] and co-workers reported the trapping of azomethine ylides with aldehydes by heating 1,3-diphenyl-2,2-methoxycarbonylaziridine at 110 °C in toluene. Prior to this, Huisgen [13] had reported the first ring opening of trans-2,3-dimethoxycarbonyl-1-arylaziridine heated in the presence of benzaldehyde. And more recently, Danielson et al. [14] synthesized anti α-amino-β-hydroxy esters by reaction of benzhydryl-protected aziridines with aldehydes (Scheme 2). In all cases, good yields of oxazolidines were obtained and the 1,3-dipole of azomethine ylides were the reactive intermediates. Many other reactions of this nature have been reported [4,15] with reactivity, selectivity and the mechanism of the reaction varying based on the nature and source of the ylide and the nature of substituents on it. Stereocontrol of these reactions may be achieved by choosing the appropriate substrates or using metal complexes as catalysts [16].

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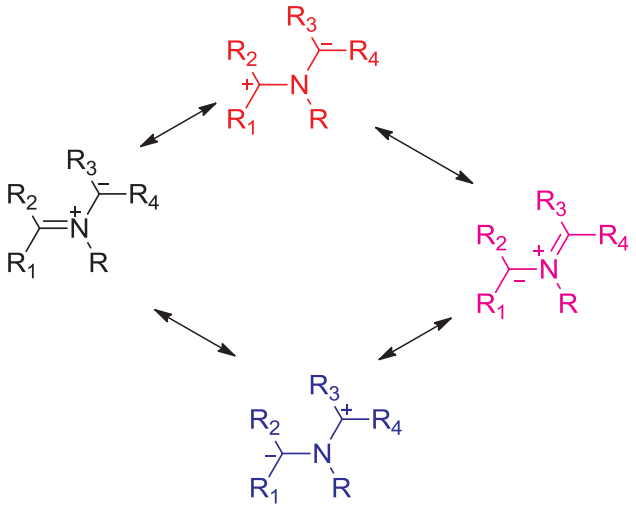
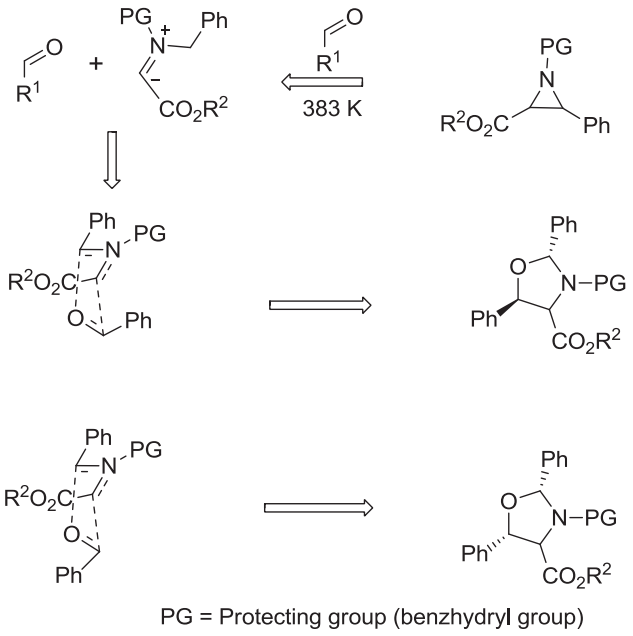


Scheme 1. Resonance structures of the azomethine ylide system.



Scheme 2. Proposed transition state structures for a cycloaddition reaction of benzyhydryl derived azomethine ylide with benzaldehyde by reference 14. Preference for exo-isomer was speculated to be due to steric factors.

Numerous theoretical studies have been devoted to the metal-catalyzed reaction of aziridine derived azomethine ylides with dipolarophiles [17]. Moreover, reactions of both symmetric [18] and unsymmetrical alkenes [19] have been studied vigorously but not much has been done on the reaction involving carbonyls as dipolarophiles. Thus, the factors that govern stereoselectivity and regioselectivity of the reaction of aziridine derived ylides with aldehydes have received less theoretical attention even though there has been a tremendous amount of experimental work done in this area [15]. A theoretical analysis by Houk et al. [20] noted the lack of regioselectivity in unsubstituted azomethine ylides reaction with dipolarophiles due to their symmetry, whereas a study by Khlebnikov et al. [18] has shown that the ring opening step has significant impact on the outcome of the reaction.

As part of our ongoing theoretical studies on reactive intermediates obtained from ring opening reactions [21], this study is aimed at giving theoretical insight into the thermal ring opening of carbonyl-, methyl- and phenyl- substituted aziridines to azomethine ylides and the subsequent reaction with acetaldehyde (Schemes 3 and 4). The free energies of activation ($\Delta G^{\ddagger}$) together with the free energies of formation (ΔG) for the electrocyclic ring opening of the carbonyl-, methyl- and phenyl- substituted aziridines have been calculated and the global electrophilicities of the resulting azomethine ylides computed accordingly. The potential energy surface for the cycloaddition of ylides A**Y1** and A**Y2** obtained from aziridine **A2** (1, 3-diphenyl-2,2-methoxycarbonylaziridine), with acetaldehyde, is subsequently explored. As shown in Schemes 3 and 4, this reaction can take place *via* several paths leading to 3- and 4- regioisomers and also *exo/endo* stereoisomers. As can be seen from the schemes, some of the different pathways lead to the same cycloadduct. For instance, pathways through transition states **TS1exo** and **TS1endo2** lead to the same product **di** even though their energetics differ significantly.

2. Computational details

All the computations were performed using the Spartan 14 and Gaussian 09 Molecular Modelling programs with density functional theory (DFT) at the M06/6-311G* level of theory [33]. Using Spartan's graphical user interface, molecules (input structures) were constructed and minimized interactively using an appropriate molecular mechanics force field [22]. The geometries were then optimized fully without any symmetry restrictions. Full infrared (IR) frequency calculations were performed to characterize the nature of the optimized stationary points (reactants, transition states, intermediates, and products). Equilibrium geometries (reactants, intermediates, products) were verified by the absence of imaginary frequencies. The transition state structures were located by constraining key internal coordinates along the reaction coordinate (i.e. forming and breaking bonds) and optimizing the remaining internal coordinates. The approximate stationary points located from such a procedure then served as a guess input structures for full transition state optimization. All transition state structures (first-order saddle-points) were shown to have a Hessian matrix with a single negative eigenvalue, characterized by an imaginary vibrational frequency along the reaction coordinate. Intrinsic reaction coordinate (IRC) calculations were performed to ensure that each transition state smoothly connects the relevant minima along the reaction coordinate [29–31].

The global electrophilicities, ω, and ΔN_{max} of the various azomethine ylides were calculated using Eqs. (1) and (2) and the results are shown in Table 1. The electrophilicity index has been used as a parameter for the analysis of the chemical reactivity of molecules. It is a measure of the ability of a reaction substrate to accept electrons [23] and is a function of the electronic chemical potential, $\mu = (E_{HOMO} + E_{LUMO})/2$ and chemical hardness, $\eta = (E_{LUMO} - E_{HOMO})$ as defined by Pearson's acid-base concept [24]. Species with large electrophilicity values are more reactive towards nucleophiles. It is important to note that these equations are based on Koopmans theory [32] which was originally developed for calculating ionization energies from closed-shell Hartree–Fock wavefunctions, but have since been adopted as acceptable approximations for computing electronic chemical potential and chemical hardness.

$$\omega = \mu^2/2\eta \quad (1)$$

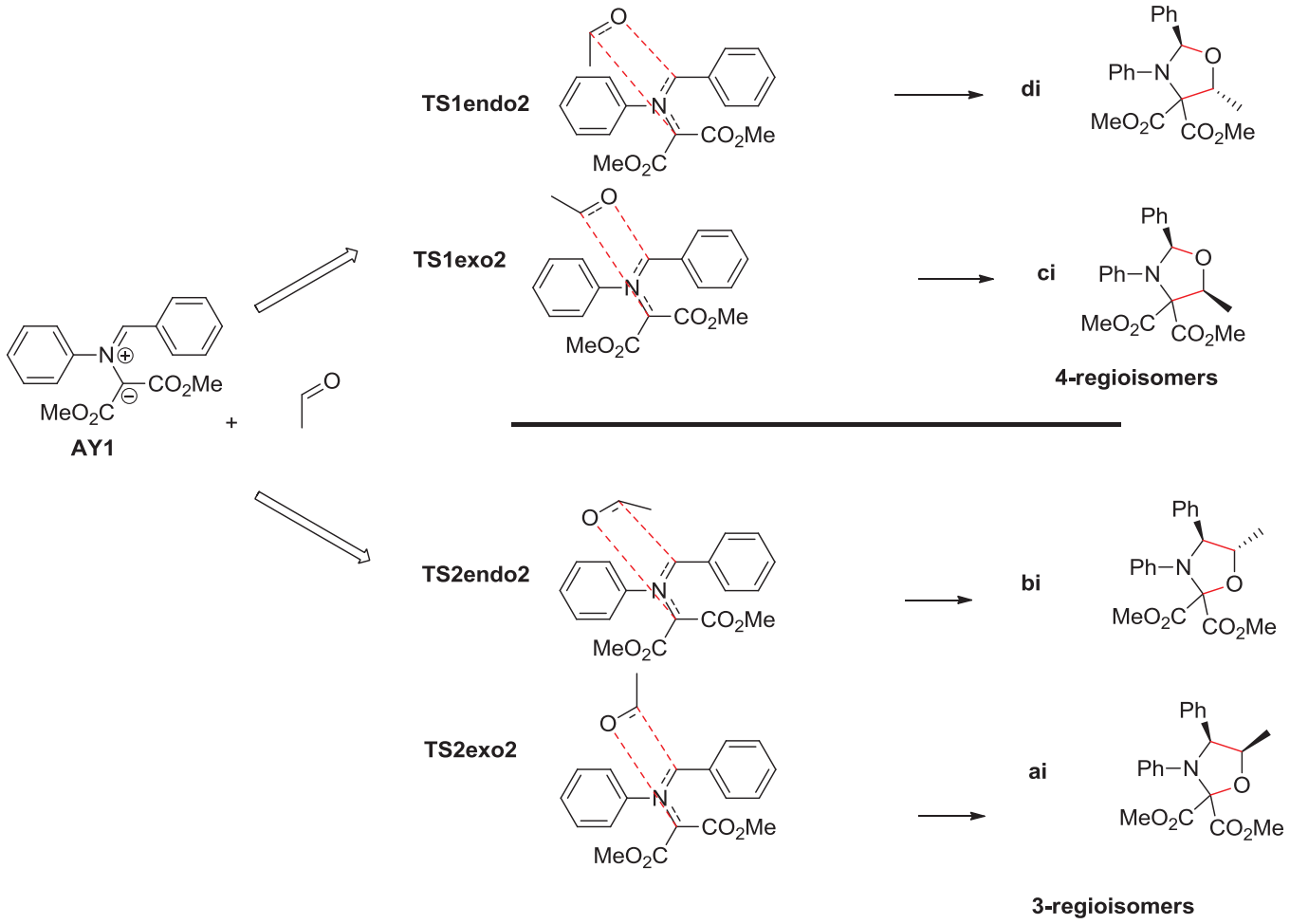
$$\Delta N_{max} = -\mu/\eta \quad (2)$$

The ΔN_{max} parameter measures the maximum electronic charge that the electrophile may accept. Thus species with large ΔN_{max} values would be excellent electrophiles.

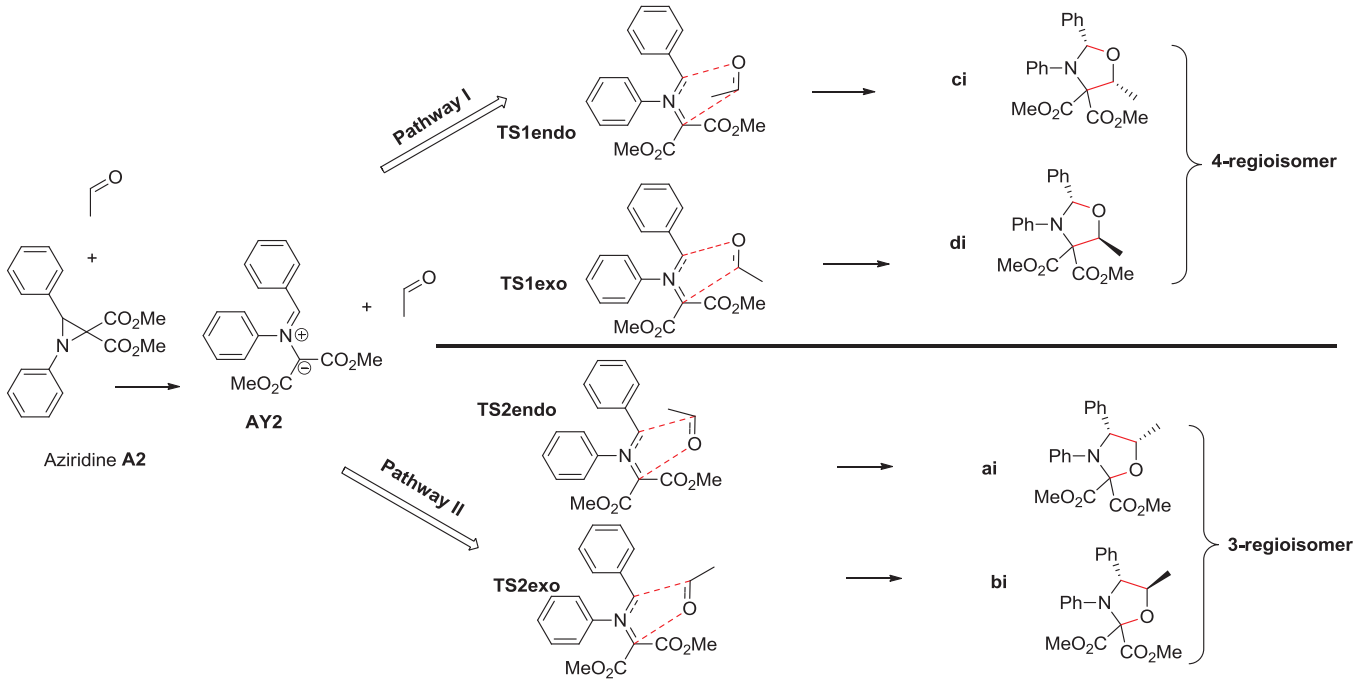
3. Results and discussion

3.1. Electrocyclic ring opening of aziridines

The optimized geometries for the ring opening of parent and substituted aziridines and the relevant computed parameters are shown in



Scheme 3. Reaction scheme for cycloaddition of **AY1** to acetaldehyde.



Scheme 4. Reaction scheme of the ring opening of aziridine **A2** to **AY2** and subsequent cycloaddition with acetaldehyde.

Table 1
Global electrophilicities for various aziridine derived azomethine ylides. Orbital energies are in electron volts (eV).

Ylide	HOMO	LUMO	μ	ŋ	Ω	ΔN_{max}
Y3	−4.36	−0.42	−2.39	3.94	0.73	0.61
Y6	−5.05	−1.60	−3.33	3.46	1.60	0.96
Y4	−5.81	−1.74	−3.78	4.08	1.75	0.93
Y7	−5.61	−1.57	−3.59	4.05	1.59	0.89
Y5	−5.34	−1.65	−3.50	3.70	1.65	0.95
Y1	−4.45	0.51	−1.97	4.96	0.39	0.40
AY1	−5.41	−2.12	−3.77	3.30	2.15	1.14

Fig. 1 and the associated energy profile is shown in Fig. 2.The barrier for the electrocyclic C—C bond cleavage of the parent aziridine **A1**with no substituents on any of the ring atoms is calculated to be 51.3 kcal/mol. At the transition state the C—C bond elongates from a bond distance of 1.473 Å to 2.059 Å. It is important to note that the C—C bond is found to be shorter than a typical carbon-carbon single bond (1.54 Å) which points to the strained nature of the aziridine ring and is characteristic of three-membered rings. With C—C—N bond angle of 59.7° and 60.6° around the N heteroatom, the ring forms a dihedral angle of 102.3° with the hydrogen atom on the nitrogen at the ground state which shows that the H atom is almost perpendicular to the plane of the aziridine ring. But at the transition state, they are near-planar on the nitrogen atom evidenced by a dihedral angle of 0°. The C_1 symmetry found in the ground state is maintained at the transition state as the dihedral angles between the C—C hydrogens are distorted from a planar geometry to 46.1°. These results are quite comparable to that of Nielson [25] who found the barrier height for the ring opening of aziridine to be 49.9 kcal/mol at MP2/6-31G*.

When the N heteroatom of the parent aziridine is substituted with a methyl group to obtain N-methylaziridine, the C—C bond distance increases by 0.005 Å (from 1.473 to 1.478 Å) and the barrier to electrocyclic cleavage is lowered to 49.8 kcal/mol. The dihedral angle on the nitrogen atom also increases from 102.3° to 106.2°with the C—C—N and C—N—C bond angles closing in to 59.3° and opening up to 61.4° respectively. The increase in dihedral angle could be due to steric interactions since the methyl substituent is bulkier than the H atom and as such would interact with the H atoms on the adjacent aziridine carbons. Thus the angle between the ring plane and the methyl substituent would open up.

Among the most commonly used aziridines in chemical synthesis are carbonyl- substituted aziridines. These have been used by Huisgen [13], Texier et al. [26], and Danielson et al. [14] in the synthesis of

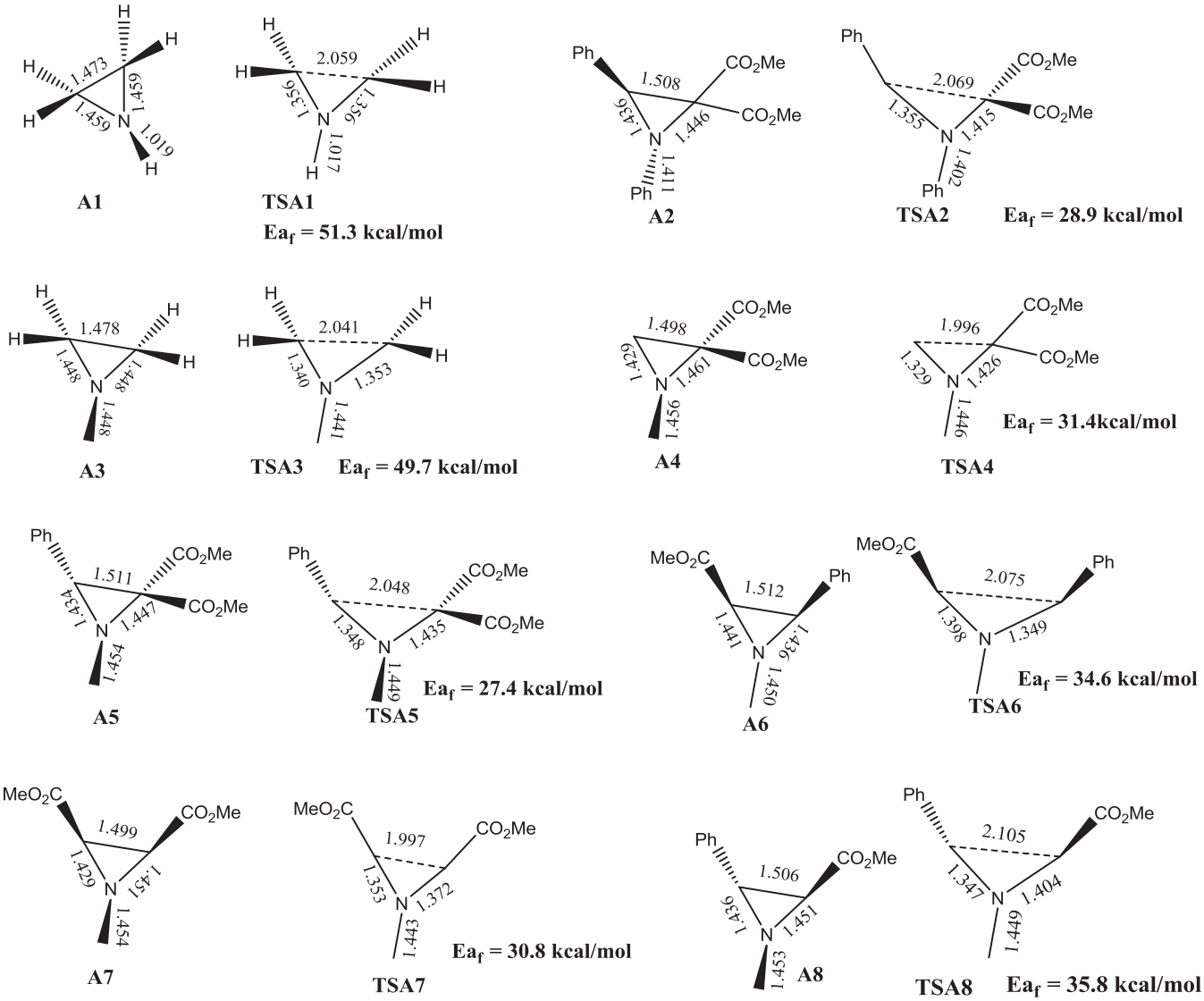


Fig. 1. Values for optimized geometries for the various types of aziridines and their ring-opening transition state structures. Ea_f = Activation energy required for bond breaking.

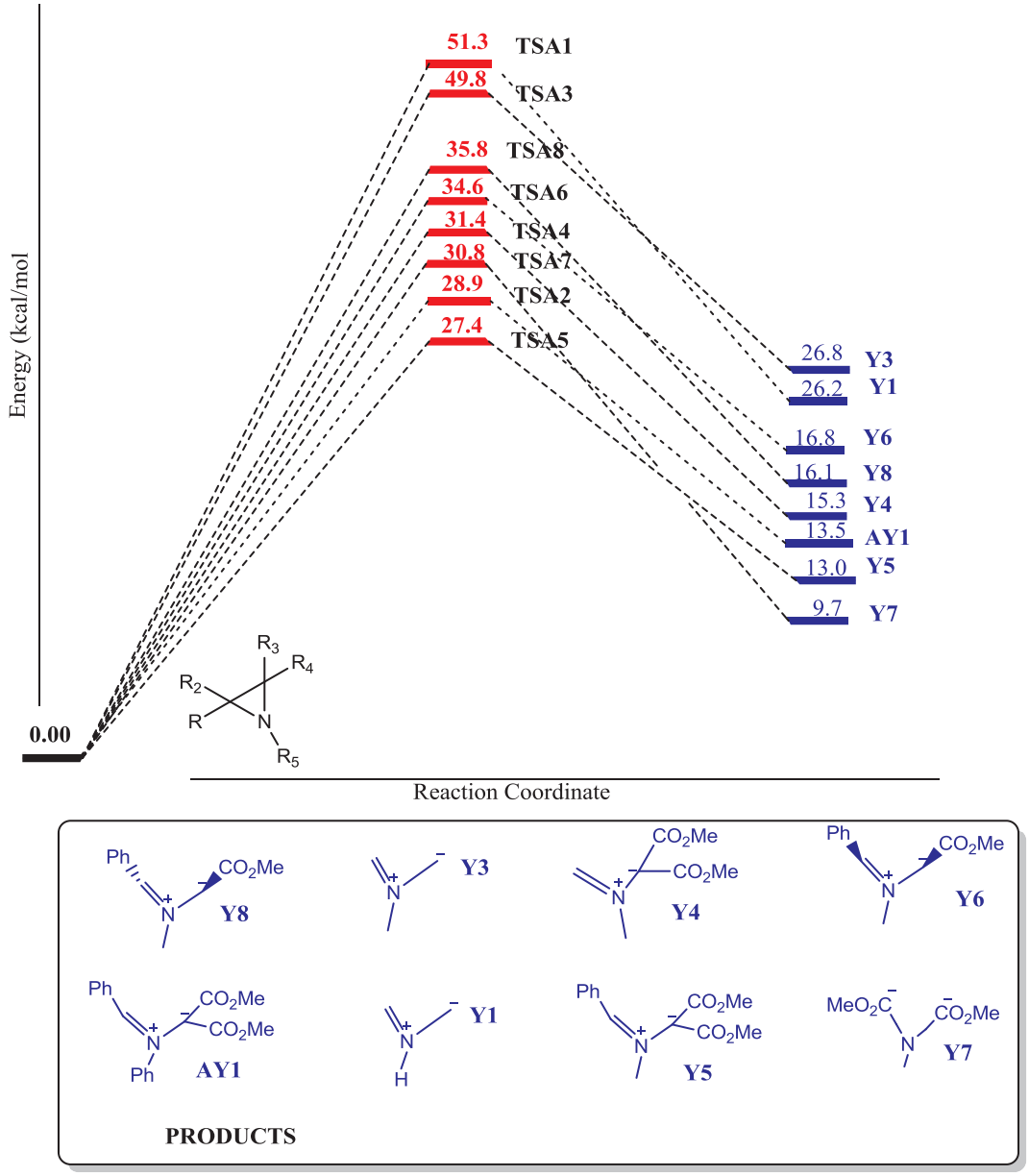


Fig. 2. Potential energy surface for the ring opening reaction of aziridines. All standard Gibbs free energies in kcal/mol.

highly substituted oxazolidines. Thus, we investigated the effects of carbonyl-and phenyl ring substitution on the *N*-methylaziridine carbons. For aziridine **A7** (Fig. 1), which has carbonyl groups on both of the ring carbons, the activation barrier for the ring opening is remarkably lowered to 30.8 kcal/mol (Fig. 2). Thus an energy difference of 19.0 kcal/mol and 20.5 kcal/mol compared to the non-carbonyl substituted *N*-methyl- and parent aziridines respectively. A similar energy of activation (31.4 kcal/mol) is obtained for aziridine **A4** which has two ester substituents on the same carbon. This shows additivity in the substitution effect. The general observation is that the substitution of electron-withdrawing (carbonyl groups) on either of the aziridine carbons significantly lowers the barrier for the conrotatory ring opening of *N*-methyl- and *N*-phenylaziridines. This is because in the transition state for ring opening, the low-lying acceptor orbital of the electron withdrawing substituent overlaps with the high-lying $\sigma^{*\ddagger}$ HOMO of the breaking bond. This results in stabilization and lowering of the activation energy.

For all the aziridines investigated, the Gibbs free energies of formation of the resulting azomethine ylides are found to be endergonic as presented in Fig. 2. These values confirm the unstable nature of azomethine ylides. Interestingly, the reaction energy of the parent ring opening of aziridine **A1** to ylide **Y1** is found be 26.2 kcal/mol which is almost equal to the experimentally determined strain energy (26.7 kcal/mol) [27] for **A1**. The most unstable ylide is the *N*-methyl substituted derivative, **Y3** with a free energy (ΔG) of 26.8 kcal/mol. Since azomethine ylides are used in [3 + 2] cycloadditions and aziridines are among the commonest precursors to them, an experimentally useful aziridine would be the one which has a low barrier of electrocyclic cleavage and a high electrophilicity index of its corresponding ylide. Coincidentally, aziridine **A2** (Fig. 1) which opens to azomethine ylides **AY1** and **AY2** satisfies this requirement (barrier height of cleavage = 28.9 kcal/mol and ω (**AY1**) = 2.15 (Table 1)) and as such has been used experimentally for the synthesis of highly substituted oxazolidines in very good yields and selectivities [26].

A linear regression analysis of the relationship between the activation energies for the ring opening of the aziridines and electrophilicity indices of the resulting azomethine ylides gives an R^2 value of 0.89 with a negative slope of −15.28 (Fig. 3). This indicates a very large negative

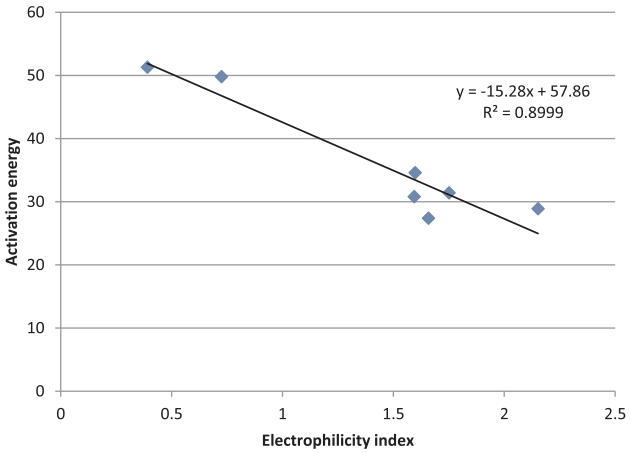


Fig. 3. A plot of activation energy against electrophilicity index.

correlation.

3.2. Ring opening of 1,3-diphenyl-2,2-methoxycarbonylaziridine (A2) and follow-up1, 3-dipolar cycloaddition reaction of the resulting azomethine ylides (AY1 and AY2) with acetaldehyde

The optimized structures of 1,3-diphenyl-2,2-methoxycarbonylaziridine **A2**, the transition state and the resulting azomethine ylide **AY1** and **AY2** are presented in Fig. 4. The optimization shows that the C—C bond distance increases from the equilibrium value of 1.508 Å to 2.069 Å at the transition state of the electrocyclic ring opening. This indicates a significantly late transition state. This transition state structure has the same symmetry as the ground state structure (C_1). The aziridine **A2** has the phenyl substituent on the carbon-C_1 being in the axial position and *trans* to the *N*-phenyl substituent to minimize steric crowding. But once the ring is opened, there is a possibility of the phenyl substituent rotating downwards to assume a *pseudo*-S-ylide configuration. The optimized structures for both the *pseudo*-S (**AY2**) and *pseudo*-U (**AY1**) form of the ylide are presented in Fig. 4. The optimizations indicate that the *pseudo*-S (**AY2**) form is the most stable thermodynamically by 2.1 kcal/mol. This could have severe implications for diastereoselectivity since these reactions are usually performed at high temperatures (110–120°) and the *pseudo*-U (**AY1**) isomer could

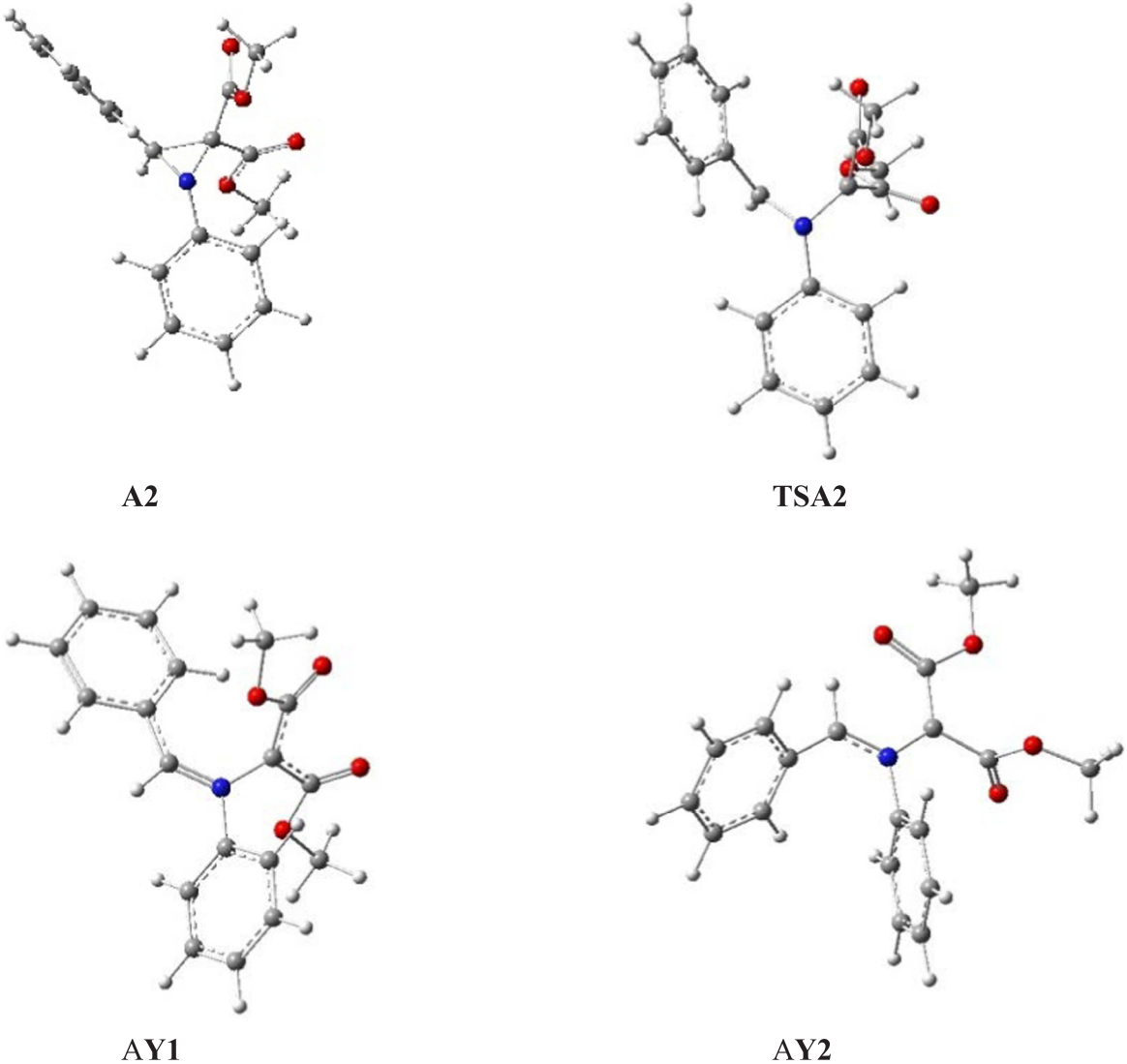


Fig. 4. Optimized stationary points along the potential energy surface for the ring opening reaction of aziridine **A2** to azomethine ylides **AY1** and **AY2**. Atomic color code (Red = Oxygen, Blue = Nitrogen, Gray = Carbon).

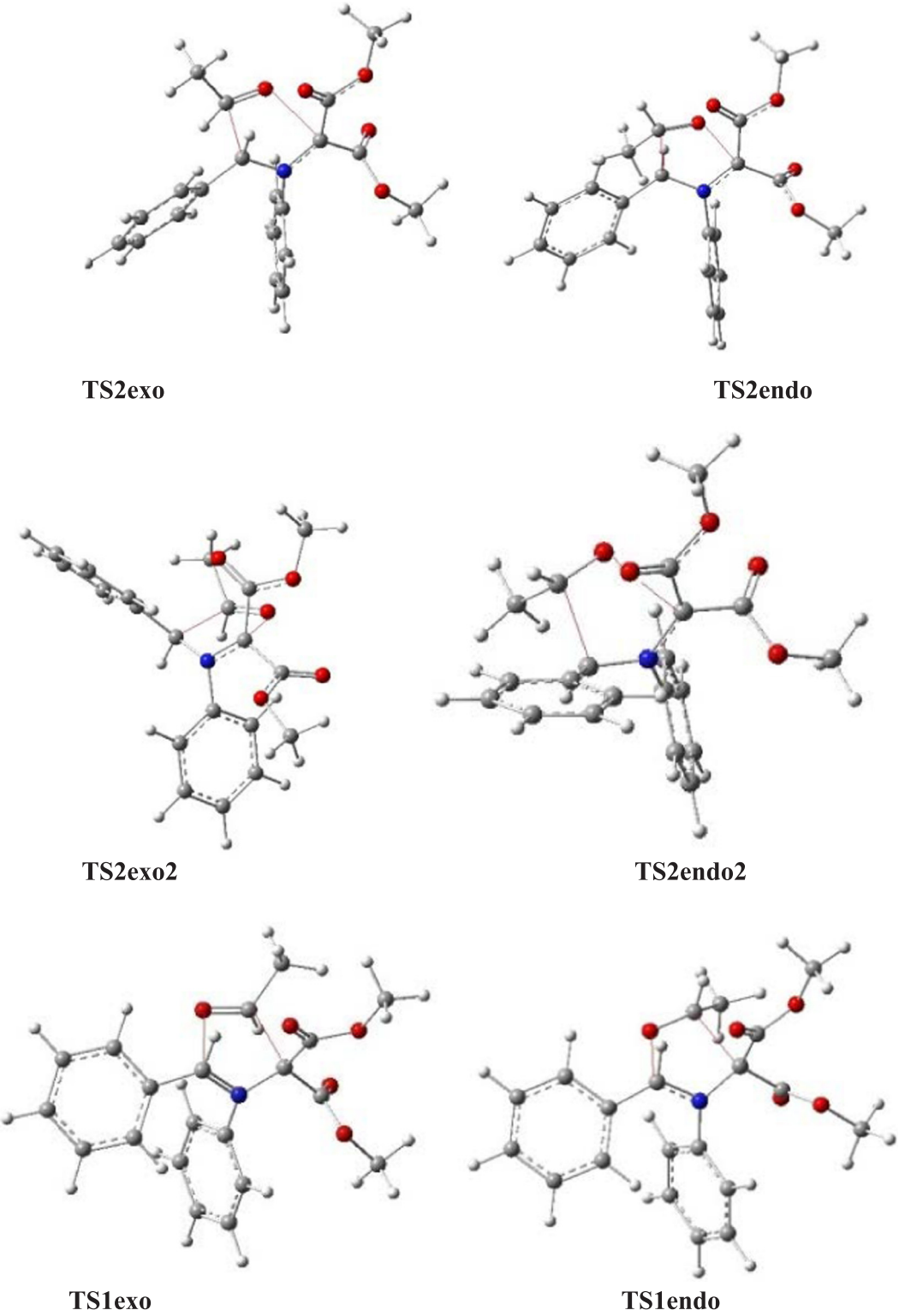


Fig. 5. Optimized transition state structures along the potential energy surface of the cycloaddition reaction of ylides **AY1** and **AY2** with acetaldehyde. Atomic color code (Red = Oxygen, Blue = Nitrogen, Gray = Carbon).

readily interconvert to the *pseudo*-S (**AY2**) form before reaction with an incoming dipolarophile. Thus if the subsequent reaction after the ring opening reaction has an activation barrier less than that for the isomerisation of *pseudo*-U (**AY1**) *to pseudo*-S (**AY2**) then the reaction would most likely yield cycloadducts of the **AY1** configuration only. Moreover, there would be four possible stereoisomers instead of two (*endo/exo*) in the reaction of A**Y1** and A**Y2** with acetaldehyde. Nevertheless, this study has shown **AY1** to be quite unstable and its cycloaddition to acetaldehyde is relatively of higher energy (Figs. 6 and 7).

3.2.1. Regioselectivity

There are two possible regioisomers each from the reaction of A**Y2** and A**Y1** with acetaldehyde; 3- and 4-regioisomers where 3 and 4 denotes the position of the methyl group of the incoming aldehyde at the

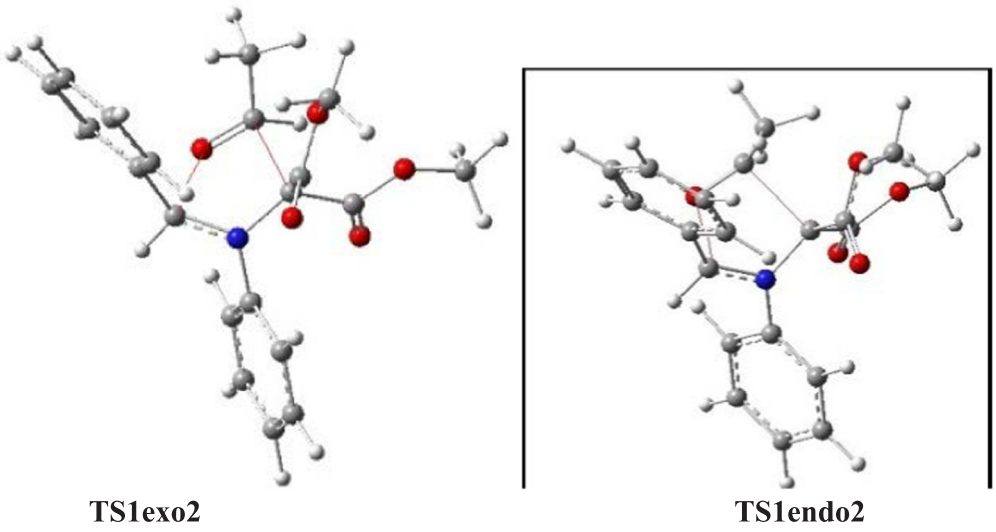


Fig. 5. (*continued*)

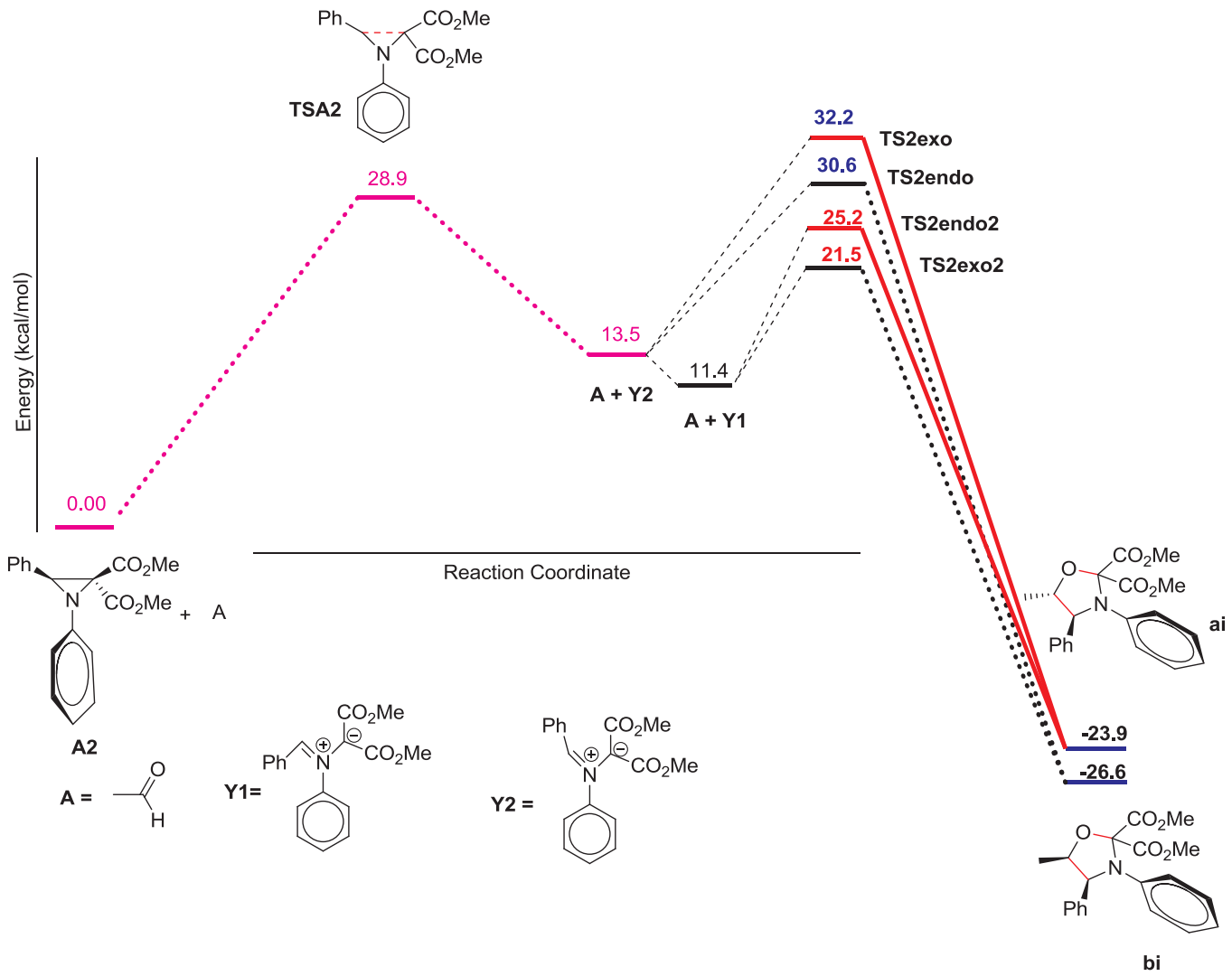


Fig. 6. Potential energy surface diagram of the ring opening reaction of aziridine **A2** and follow-up 1,3-dipolar cycloaddition reaction between azomethine ylides **AY1** and **AY2** with acetaldehyde to form 3-methyl oxazolidines. All standard Gibbs energies are in kcal/mol.

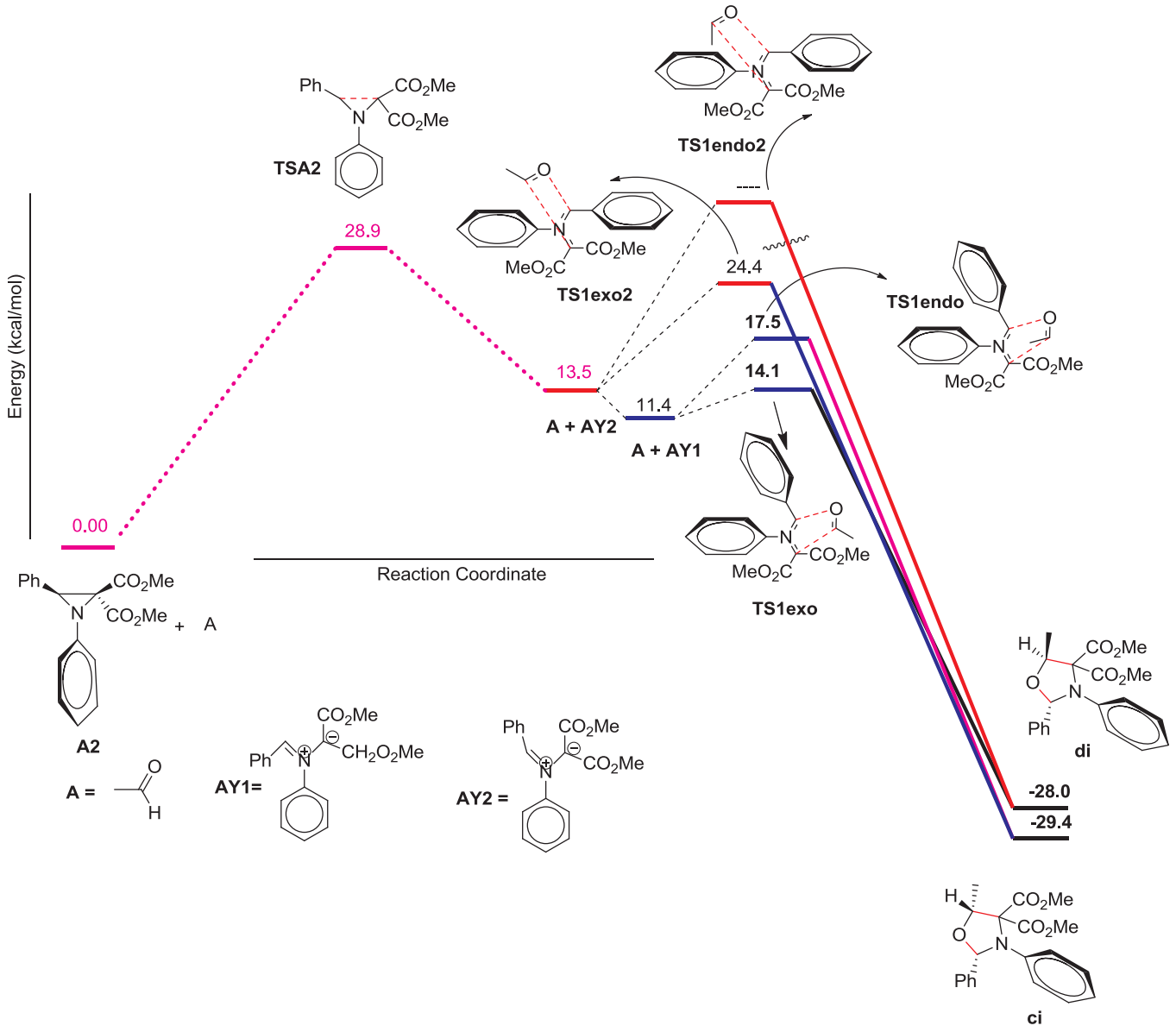


Fig. 7. Potential energy surface diagram of the ring opening reaction of aziridine **A2** and follow-up 1,3-dipolar cycloaddition reaction between azomethine ylides **AY1** and **AY2** with acetaldehyde to form 4-methyl oxazolidines. All standard Gibbs energies are in kcal/mol.

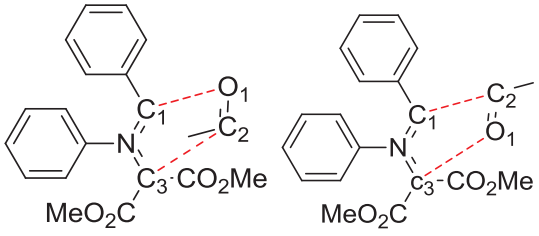


Fig. 8. Labels of atoms at the transition states.

pericyclic transition state and in the cycloadduct. Fig. 7 shows **TS1exo**, **TS1endo**, **TS1exo2** and **TS1endo2** leading to the 4-regioisomer with the cycloaddition occurring along the C_1-O_1 and C_2-C_3 reaction coordinates whiles Fig. 6 shows **TS2exo**, **TS2endo**, **TS2exo2** and **TS2endo2** leading to the 3-regioisomer along the C_2-C_1 and C_3-O_1 coordinates (Fig. 8). The gas phase optimized structures of the transition states and their associated relevant computed parameters are displayed in Fig. 5 and Table 2 respectively. Since these reactions are usually performed in organic solvents and at elevated temperatures (110 °C), the calculations were repeated at 110 °C with benzene as solvent so as to investigate the effects of solvent and temperature on the energetics of the reaction. These energies are included in Table 2.

Generally, it is observed that the acetaldehyde approaches the 1,3-dipole of the azomethine ylide in a near planar manner assuming a dihedral angle of 3.0° for the most stable transition state, TS1exo.

The 3-regioisomer is unfavourable due to relatively high barrier heights for this kind of cycloaddition. The transition state with the highest barrier height among the 4 possible 4-methyl- regioisomers has activation energy of 10.9 kcal/mol while the lowest barrier amongst the 3-methyl regioisomers is 10.1 kcal/mol. Thus, clearly the 4-methyl regioisomer would be favoured. This accounts for the complete regioselectivity in this reaction. It is worthy of note that **TS1endo2** could not be located. But even though its corresponding product is the experimentally favored, comparing it to its corresponding 3-isomer (**TS2endo2**) makes it likely to have a relatively high activation energy.

Table 2 also shows that solvent effects do not affect the selectivity of the reactions, it slightly changes the activation barriers in some instances. It is also seen that even though cycloadditions are very

Table 2
Activation energies (Ea_f) and geometrical parameters of transition states located along the potential energy surface of the cycloaddition reaction between **AY1** and **AY2** with acetaldehyde. All bond distances are in agstroms (Å). *Dihedral angle (C_1 O_1 C_2 C_3). **Energetics 110 °C with benzene as solvent. All Gibbs energies in kcal/mol.

			4-isomer		3-isomer		
	$Ea_{f(gas\ phase)}$	$Ea_{f(benzene)}$**	C_1-$O_{1(gas)}$	C_2-$C_{3(gas)}$	C_3-$O_{1(gas)}$	C_2-C_1	D*
TS1endo2	–	–	–	–			–
TS1exo2	10.9	15.2	2.093	2.187			12.5°
TS1endo	6.1	8.1	2.167	2.107			23.7°
TS1exo	2.7	4.2	2.267	2.083			3.0°
TS2endo2	13.8	21.6			2.263	2.054	1.4°
TS2exo2	10.1				2.339	2.038	0.8°
TS2endo	17.1	16.3			2.357	2.070	10.8°
TS2exo	18.7	12.6			2.281	2.072	6.2°

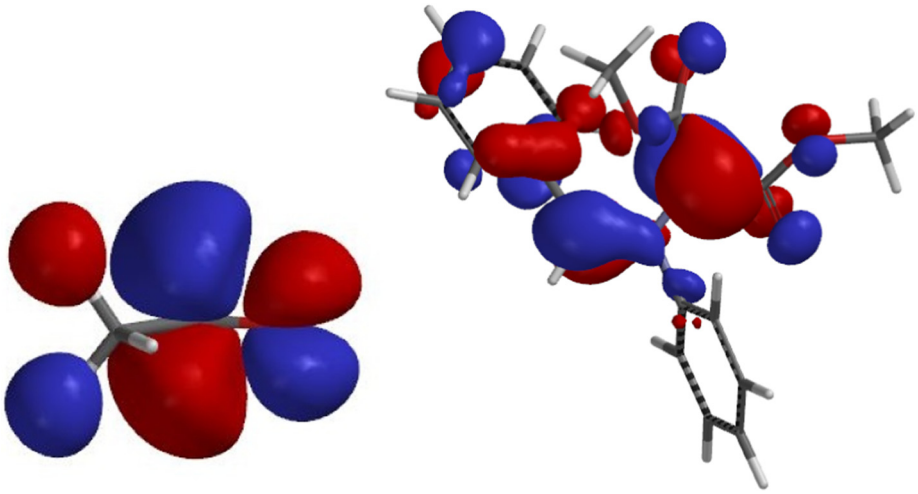


Fig. 9. Graphical representations of the HOMOs and LUMOs of AY1 and acetaldehyde respectively.

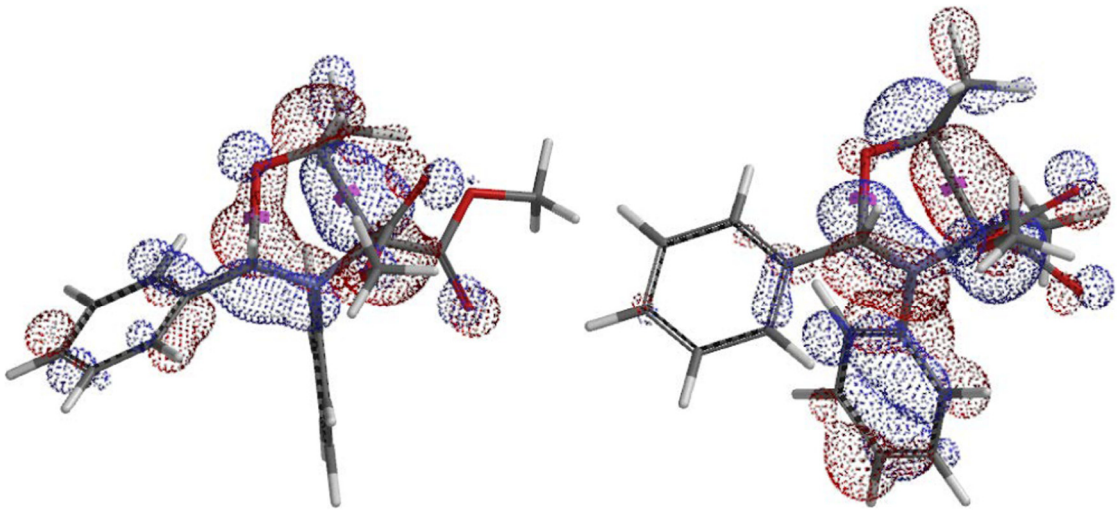


Fig. 10. Graphical representation of the HOMOs of **TS1endo** and **TS1exo**.

sensitive to entropic effects, and thus temperature effects, the Gibbs free energies of activation at 25 °C and 110 °C are not very different. Thus the gas phase energetics at 25 °C are sufficient for the reactions studied.

To delineate the origins of this kind of regioselectivity, perturbation molecular orbital (PMO) theory is invoked [28]. Fig. 9 displays a graphical depiction of the HOMOs and LUMOs of the dipole and dipolarophile respectively. By natural bond order (NBO) analysis, the molecular orbital coefficient of the anionic C-terminus of the 1,3-dipole is higher (0.589) than that for the neutral terminus (0.556). Similarly, orbital coefficients of the dipolarophile are higher at the carbonyl center (0.539) as compared to the carbonyl oxygen (0.439). By the rules of PMO, the cycloaddition will happen in such a way as to unite the atoms with the highest molecular orbital coefficients since this would lead to the greatest stabilization. Therefore the carbonyl carbon (C_2) will prefer to bond with the dicarboxylate substituted carbon C_3 of the azomethine ylide (Fig. 8) whiles the oxygen (O_1) will bond to the

phenyl substituted carbon C_1.

3.2.2. Stereoselectivity

As can be seen from Schemes 3 and 4, for each regioisomer, there are 4 possible transition states leading to 2 stereoisomers from this reaction. Figs. 6 and 7 show the potential energy surface for the formation of these stereoisomers. **TS1exo** is the most favorable transition state with an activation barrier of 2.7 and 4.2 kcal/mol in the gas and solvent phases respectively, leading to the formation of the *exo* diastereomer **di**. Thus these calculations predict **di** to be the major cycloadduct both in the gas and solvent phase while the minor cycloadduct would be **ci** since the activation barrier for the formation of this diastereomer is 6.1 kcal/mol (gas phase) and 8.1 kcal/mol under solvent conditions. Even though Texier et al. [26] reported in their experimental work the formation of two diastereomers in 95:5 ratios, there was no mention of the nature of these diastereomers. Nevertheless, these results agree well with the experiment of Danielson et al. [14] who studied a similar reaction using benzaldehyde instead of acetaldehyde.

Again, using molecular orbital theory the preference for the *exo* isomer can be rationalized. Evaluation of the HOMOs of **TS1exo** and **TS1endo** which are associated with the two σ-bonds of the isomers being formed shows a delocalization along the methyl substituent on the incoming acetaldehyde in the *endo* approach with a HOMO-LUMO gap of 4.53 eV (Fig. 10). And since this reaction is a normal electron demand 1,3 – dipolar cycloaddition reaction, it would be expected that the *endo* isomer would be preferred due to secondary orbital interactions at the transition state. But this is not observed because for the *exo* attack (**TS1exo**), the HOMO-LUMO gap is lowered significantly to 4.42 eV (difference of 2.4 kcal/mol) which causes the free energy of activation for the formation of **di** to be lower. However, an inspection of the thermodynamic stabilities of the cycloadducts **di** and **ci** show the **ci** is slightly more stable (−29.4 kcal/mol**)** than the **di** (−28.0 kcal/mol**)** stereoisomer. This, together with the stereoelectronic effect in **TS1endo**, shows that though the secondary orbital interactions are present, it is overcome by steric factors in the reaction.

4. Conclusions

The following deductions can be made based on the results obtained from this study.

1. The conrotatory ring-opening reactions of aziridines involve very high activation barriers. However, *N*-methyl substitution and the presence of carbonyl groups on the aziridine carbons lower the activation barrier for these ring opening reactions (Fig. 2).
2. The lower the activation barrier for ring opening, the more electrophilic the resulting azomethine ylide and by careful substitution of electron donors and acceptors at the appropriate positions, the electrocyclic conrotatory ring opening of aziridines are enhanced.
3. In the cycloaddition reaction of 1,3-diphenyl-2,2-methoxycarbonylaziridine with acetaldehyde, the ring opening of the aziridine is the rate-limiting step. The barriers for the formation of 3-methyloxazolidines are higher (10.1 kcal/mol for the most favorable 3-methyl regioisomer) compared to that of the 4-methyloxazolidines (2.7 kcal/mol for the most favorable isomer) in this 1,3-dipolar cycloaddition reaction, which explains the experimentally observed regiospecificity (Figs. 6 and 7).
4. The *exo* approach of the dipolarophile (acetaldehyde) in the 1,3-dipolar cycloaddition of 1,3-diphenyl-2,2-methoxycarbonylaziridine **A2** derived azomethine ylides with acetaldehyde is preferred over the *endo* approach due to steric factors in the transition states.
5. The energetics of the cycloaddition reactions at 25 and 110 °C are not very different. Thus temperature effects do not seem to play a significant role in the course of these reactions.
6. And finally, these results have been rationalized in terms of perturbation molecular orbital theory.

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