Theoretical Studies on the Stereochemical Course of 1,3-Dipolar Cycloaddition of Azomethine Ylides Derived from Indol –2,3-dione and Thiazolidine-4-carboxylic Acid

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1,3-Dipolar cycloadditon of azomethine ylides with different dipolarophiles leads to the formation of novel heterocyclic spiro compounds having two or more chiral centers. The theoretical studies (HF/3-21G) on the 1,3-dipolar cycloaddition reaction between ethene and azomethine ylide **A4** derived from isatin and thaizolidine-4-carboxylic acid, indicates that the energy barrier for this addition is about 8 kcal/mol higher than that in simplest azomethine ylide **A1**. HF/3-21G studies on a series of azomethine ylides **A2** and **A3** suggested that the increased barrier is mainly due to stabilization of azomethine ylides arising from aromatic indol nucleus. Semi-empirical studies indicate that the cycloaddition is streocontrolled as the transition states corresponding to only the stericlly allowed paths could be located on the potential energy surface.

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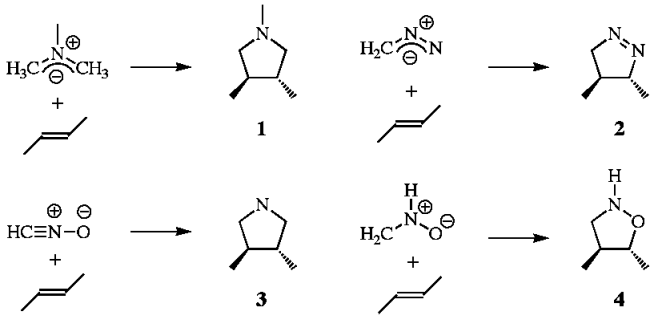
Introduction.

1,3-Dipolar cycloaddition reactions provide a versatile route for the synthesis of a wide variety of heterocyclic compounds [1-3]. The study of 1,3-dipolar cycloaddition has a checkered history, which has been summarized by Houk [4]. The importance attributed to the chemistry of 1,3-dipolar cycloaddition in organic synthesis arises from the formation of spiro-polycyclic heterocycles in a single step process [5]. We have been particularly interested in the azomethine ylide derived from isatin and thiazolidine-4-carboxylic acid [6-8] because such novel spiro compounds may act as useful synthons in the total synthesis of naturally occurring spiropyrrolidine alkaloids [9,10]. Besides the stereochemistry in the addition step is a major challenge. The selectivity challenge is to control the regio-diastereo-, and enantio-selectivity of 1,3-dipolar cycloaddition reactions. This can be controlled either by using chiral dipole or chiral dipolarophiles [11].

In general, 1,3-dipolar cycloaddition [1] of azomethine ylide diazomethane, nitrile oxide and nitrone with alkenes leads to the formation of pyrrolidine **1**, pyrazoline **2**, isoxazoline **3** and isoxazolidine **4** derivatives (Scheme 1). These reactions have been investigated from theoretical point of view in order to understand the reaction course, selectivity and influence of Lewis acid on reaction. Annunziata and co-workers [12] have used a series of PM3 and *ab initio* calculations at RHF/3-21G* level to locate the transition state for reaction of above mentioned dipoles with ethene. These workers have also compared charge distribution with the experimentally observed diastereoselectivities in the corresponding cycloaddition to chiral allyl ethers. Branchadell *et al.* [13] extended the results of diazomethane with ethene at BLYP and B3LYP levels. The results showed that the pyrazoline intermediate is more stable than the reactant and that the Gibbs energy barrier for the nitrogen elimination is larger than the barrier corresponding to the formation of pyrazoline. Kanemasa *et al.* [14] have studied the reaction of chiral lithium-(*z*)-enolates derived from *N*-alkylideneglycinate with α,β-unsaturated esters by theoretical calculations using MNDO and PM3 procedures. Similarly calculations for 1,3-dipolar cycloaddition of phenyl azide with 19 different alkenes have been carried out at HF and DFT levels using 6-31G** basis sets [15]. It was observed that electron withdrawing and electron donating group gave only one product isomer whereas aliphatic and aromatic substituents produce a mixture. The regiochemistry of the diazomethane to ethoxy acetylene and ethyl vinyl ether is reproduced by PM3 calculations [16]. It was reported that these dipolarophiles have opposite regiochemistry in diazomethane cycloaddition. Jorgenson and co-workers [17] have observed a high degree of endoselectivity (endo/exo > 20) in metal catalyzed 1,3-dipolar cycloaddition reactions of nitrones with alkenes.

Scheme 1



Synthetically, azomethine ylides are unstable species, which can be prepared *in situ*. A number of methods for preparation of azomethine ylides are known [18]. Padwa *et al.* [19] reported the first diastereofacial selective 1,3-dipolar cycloaddition of chiral azomethine ylide with alkene

Table 1

Activation Energies and Stabilization Energies of Different Products at AM1, HF/3-21G and B3LYP/6-31+G* Basis Sets

Products	Energy of activation (E_a) (kcal/mol)			Heat of reaction (kcal/mol)		
	AM1	HF/3-21G	B3LYP/ 6-31+G* //HF/3-21G	AM1	HF/3-21G	B3LYP/ 6-31+G* //HF/3-21G
Py1	5.64	5.80	4.43	-70.29	-83.77	-59.43
Py2	5.85	5.08	5.09	-69.68	-91.49	-64.33
Py3	12.45	15.21	13.08	-53.16	-56.58	-50.75
Py4	14.40	13.83	14.31	-52.43	-67.07	-31.29
Pz1	10.84	8.16	8.56	-73.50	-93.77	-81.20
Pz2	12.08	7.22	9.00	-73.50	-100.06	-92.67
Pz3	18.49	17.90	12.54	-55.91	-67.69	-62.19
Pz4	20.52	18.52	13.89	-55.19	-75.49	-51.53

leading to optically active product. Subsequently Husson and co-workers [20] have extensively investigated 1,3-dipolar cycloaddition of electron deficient alkenes with optically active azomethine ylide derived mainly from (-)-*N*-(cyanomethyl)-phenyl-1,3-oxazolidine. Instead of chiral azomethine ylide, Grigg *et al*. [21,22] have used chiral alkene to study 1,3-dipolar cycloaddition of various azomethine ylides. A study of 1,3-dipolar cycloaddition of azomethine ylides formed by decarboxylation of iminium species derived from the cyclic secondary amino acid and isatin with different dipolarophiles has been recently reported from our laboratory experimently [6-8].

However, the problem of diastereoselectivity in these reactions could not be addressed in detail due to the possibility of formation of a large number of stereoisomers. Thus, a comprehensive study has been undertaken theoretically to locate molecular as well as transition state structures of various diastereomers resulting from 1,3-dipolar cycloaddition reactions of azomethine ylide **A1** and **A4** with different dipolarophiles. The results are presented below.

Computational Details.

All calculations have been carried out using Gaussian 94 [23] and MOPAC6 [24] quantum chemical programs. The molecular and transition state geometries for the reaction of azomethine ylide (abbreviated as amy) **A1**, **A2**, **A3** and **A4** with ethene and ethyne have been performed on Gaussian 94 at HF/3-21G level and AM1 methods. For each transition state, an imaginary frequency has been obtained which substantiates the actual formation of that transition state. For one transition state *viz*. **Py4-TS**, intrinsic reaction coordinate calculation has been carried out and it clearly proves that the transition state structure is indeed on the path connecting the two minima under consideration. The single point energies for these systems have been calculated on B3LYP/6-31+G* basis set. To understand the stereochemical control of the cycloaddition reaction of **A1** and **A4** with methyl acrylate, phenyl acetylene and ethyl phenyl propiolate, AM1 calculations have

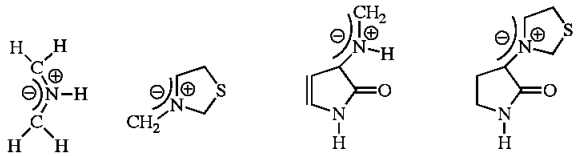


Table 2

Transition State Bond Lengths (Å) of Different Products at AM1 and HF/3-21G Basis Sets

Products	Transition state bond lengths (Å)			
	C1-C3		C2-C4	
	AM1	HF/3-21G	AM1	HF/3-21G
Py1	2.284	2.474	2.284	2.474
Py2	2.183	2.478	2.251	2.491
Py3	2.147	2.243	2.289	2.395
Py4	2.173	2.194	2.265	2.407
Pz1	2.212	2.440	2.212	2.440
Pz2	2.187	2.437	2.234	2.455
Pz3	2.067	2.242	2.261	2.341
Pz4	2.102	2.202	2.227	2.346

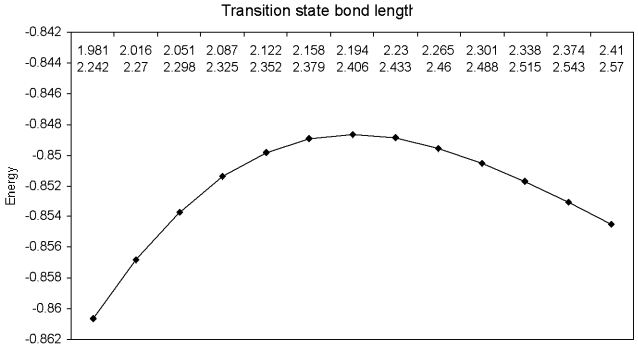


Figure 1. Intrensic reaction coordinate graph for transition state **Py4-TS**.

been carried out using MOPAC6 and Gaussian94 programs. All possible conformations of the products and corresponding transition states for the 1,3-dipolar cycloaddition have been studied by performing complete optimizations at AM1 level. The stereochemical control has been recognized on the basis of the locatable transition states for the 1,3-dipolar cycloaddition paths.

Results and Discussion.

Initially the cycloaddition reaction between azomethine ylide **A1** with ethene has been studied, using HF/3-21G and AM1 methods. The transition state **Py1-TS** (Figure 3) for the above process could be located on the potential energy surface. The reaction has been found to 83.77 kcal/mol (70.29 kcal/mol) (Table 1) exothermic with an energy barrier of 5.80 kcal/mol (5.64 kcal/mol) at HF/3-21G (AM1) level. The transition state bond lengths C_1-C_3 and C_2-C_4 in **Py1-TS** are 2.474 Å (2.284 Å) and 2.474 Å (2.284 Å) (Table 2) at HF/3-21G (AM1) level. These data confirms the concerted, synchronous nature of the cycloaddition reaction. The trends in the AM1, HF/3-21G and B3LYP/6-31+G*//HF/3-21G results are qualitatively comparable (Table 1) suggesting the reliability of the semi-empirical AM1 method.

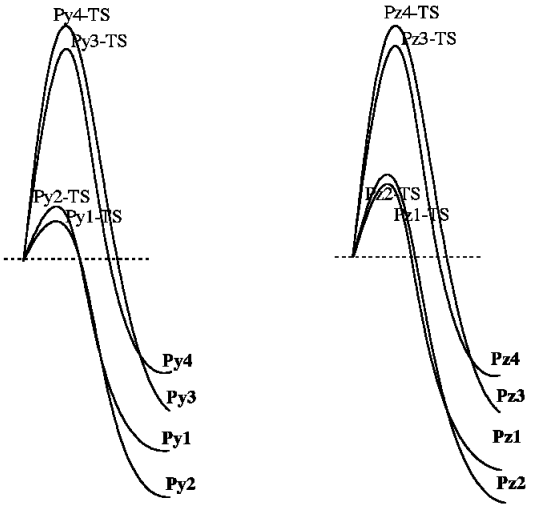


Figure 2

The quantum chemical study of the reaction between amy **A1** and ethyne through the transition state **Pz1-TS** showed this reaction also to be highly exothermic 93.77 kcal/mol (73.50 kcal/mol) with an energy barrier of 8.16 kcal/mol (10.84 kcal/mol) at HF/3-21G (AM1) level. In **Pz1-TS** the newly forming C-C bond lengths are 2.440 Å (2.212 Å) at HF/3-21G (AM1) level. Encouraged by the consistency of the results, the cycloaddition reaction between azomethine ylide **A4** derived from isatin and thiazolidine-4-carboxylic acid with ethene and ethyne have been studied using HF/3-21G and AM1 basis sets. The transition state bond lengths C1-C3 and C2-C4 in **Py4-TS** are 2.194 Å (2.173 Å) and 2.407 Å (2.265 Å) at HF/3-21G (AM1) level. It may be noted that one of the transition state bond lengths (C2-C4) in **Py4-TS** is longer than the other (C1-C3). This suggested that cycloaddition path is concerted but not asynchronous. This non-synchronous path is also observed in **Pz4-TS** where bond lengths are 2.202Å (2.102 Å) and 2.346 Å (2.227 Å) at HF/3-21G (AM1) level. Intrinsic reaction coordinate calculation for **Py4-TS** showed that the transition state structure estimated

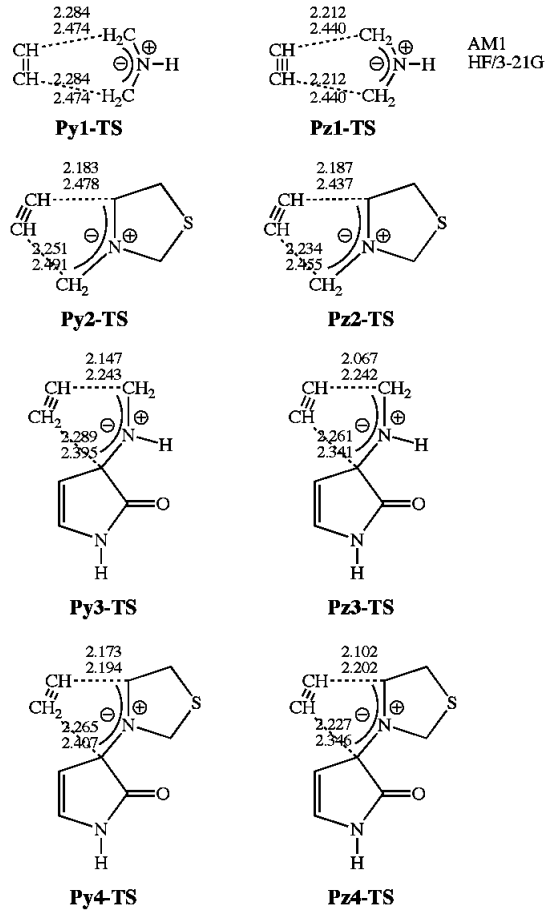
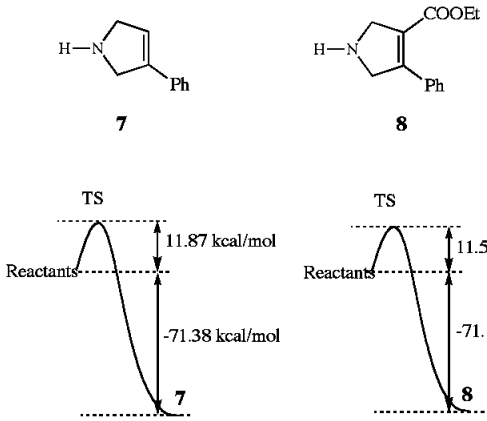


Figure 3. Important geometric parameters for the transition states **Py1-TS** to **Pz4-TS** (***AM1***, HF/3-21G).

is indeed on the path connecting the two minima. The results of intrinsic reaction coordinate calculations have been compiled for 13 points on the path connecting the two minima and a graph between energy and transition state bond distance is shown in Figure 1.

The energy barrier for reaction of azomethine ylide **A4** with ethene has been found to be 13.83 kcal/mol (14.40

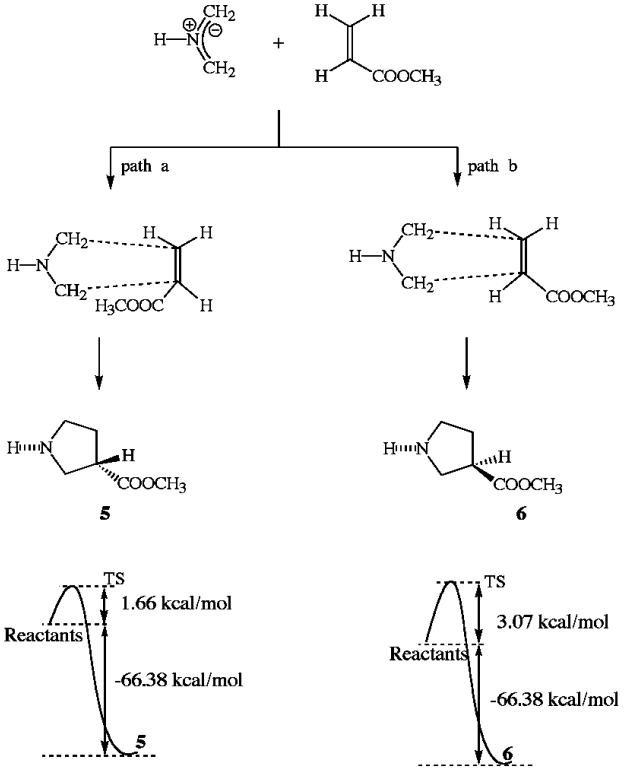
kcal/mol) and with ethyne 18.52 kcal/mol (20.52 kcal/mol) at HF/3-21G (AM1) level with 67.07 kcal/mol (52.43 kcal/mol) and 75.49 kcal/mol (55.19 kcal/mol) exothermicity at HF/3-21G (AM1) level respectively. The energy required for the reaction of ethene with amy **A4** (13.83 kcal/mol) is much larger than that with amy **A1** (5.80 kcal/mol). Similarly the energy barrier for the reaction of ethyne with amy **A4** (18.52 kcal/mol) is also much larger than that with amy **A1** (8.16 kcal/mol) (Figure 2). This indicates that the isatin based azomethine ylide requires higher activation energy compared to the simple amy **A1**. The increase in energy barrier can be attributed either to i) the increase in the steric strain due to thiazolidine nucleus or ii) the delocalisation of π electron cloud on to the indole nucleus. To confirm this, calculations have been carried out on the two model systems using azomethine ylide **A2** and azomethine ylide **A3**. The activation energy for reaction of amy **A2** with ethene **Py2-TS** and ethyne **Pz2-TS** has been found to be 5.08 kcal/mol (5.85 kcal/mol) and 7.22 kcal/mol (12.08 kcal/mol) respectively at HF/3-21G (AM1) level. Also the activation energy for reaction of amy **A3** with ethene **Py3-TS** and ethyne **Pz3-TS** has been found to be 15.21 kcal/mol (12.45 kcal/mol) and 17.90 kcal/mol (18.49 kcal/mol)



respectively at HF/3-21G (AM1) level (Table 1). From Table 1, it may be concluded that there is negligible change in activation energies for the reaction of amy **A1** and amy **A2** with ethene and ethyne while there is a sharp increase in activation energy for the reaction of between amy **A1** with ethene and ethyne and amy **A3** with ethene and ethyne. This can be explained by the fact that there is greater stablization of azomethine ylide **A3** due to delocalization of dipolar charge into the five membered ring. This observation may be extended to conclude that the azomethine ylide **A4** is stabilized by the indole nucleus instead of thiazolidine ring, which results in an increase in activation energy for the reaction path. The trends observed in the energetics of the cycloaddition reactions are similar at HF/3-21G and AM1 levels, supporting the reliability of AM1 method, further studies have been carried using AM1 method only.

To understand the stereochemistry of the cycloaddition reaction between azomethine ylide **A1** and azomethine ylide **A4** with different dipolarophiles *viz.* methyl acrylate, phenyl acetylene and ethyl phenyl propiolate we have carried out the AM1 calculations using the MOPAC6 package. The transition state of concerted 1,3-dipolar cycloaddition reactions is controlled by frontier molecular orbitals (FMO's) of dipoles and dipolarophiles [25,26]. The HOMO-LUMO and LUMO-HOMO energy gaps of amy **A1**, amy **A4** and dipolarophiles are listed in Table 3. From the Table it may be concluded that $HOMO_{dipole}$-

Scheme 2



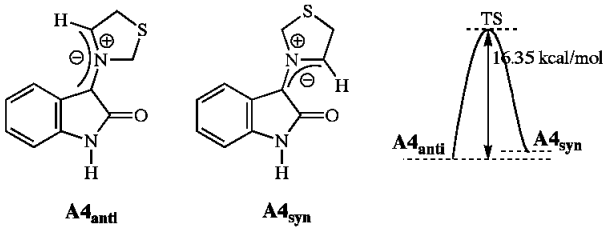


Table 3

$HOMO_{dipole}$-$LUMO_{dipolarophile}$ (H-L) and $LUMO_{dipole}$-$HOMO_{dipolarophile}$ (L-H) Energy Gaps Between Dipole and Dipolarophiles

Dipole/	**A1**		**A4$_{anti}$**		**A4$_{syn}$**	
dipolarophlile	H-L	L-H	H-L	L-H	H-L	L-H
Methyl Acrylate	7.76	11.95	8.06	10.12	7.97	1016
Phenyl acetylene	7.75	12.49	8.05	8.45	7.96	8.49
Ethyl Phenyl propiolate	7.16	10.60	7.46	8.77	7.37	8.81

C-atom *i.e.* a pair of enantiomers could be possible. We have been successful in locating the transition states and minima for both the isomers **5** and **6** (Scheme 2). Both the products **5** and **6** have almost the same heat of reaction -25.14 kcal/mol and -23.76 kcal/mol respectively thereby suggesting thermodynamically equal stability of both the isomers. However, transition state calculations indicated that when -$COOCH_3$ group is towards N-H (path a, Scheme 2), activation energy is slightly lower (-1.66 kcal/-mol) as compared to when -$COOCH_3$ group is away from the N-H group (-3.07 kcal/mol) (path b, Scheme 2). This may probably be due to secondary orbital interaction

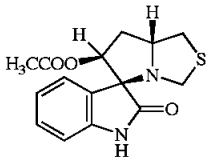
Table 4

ΔH_f-R, ΔH_f-TS, ΔH_f-P, E_a, Stablization Energy and Transition State Bond Lengths of amy **A1** and amy **A4** with Different Dipolarophiles (AM1 results)

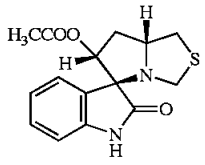
Product	ΔH_f Reactant (kcal/mol)	ΔH_f TS (kcal/mol)	ΔH_f Product (kcal/mol)	Energy of activation (E_a) (kcal/mol)	Stablization energy (kcal/mol)	Transition state bond lengths (Å) C1-C3	C2-C4
5	-26.810	-25.144	-93.195	1.660	-66.385	2.42	2.26
6	-26.810	-23.762	-93.196	3.078	-66.386	2.42	2.27
7	119.691	131.569	48.373	11.878	-71.318	2.31	2.16
8	32.132	43.686	39.053	11.554	-71.185	2.29	2.21
9a	-14.669	2.162	-57.926	16.831	-43.257	2.35	2.10
9b	-14.669	3.428	-57.047	18.08	-42.388	2.36	2.11
10	131.832	157.627	82.583	25.795	-49.25	2.39	2.05
11	44.273	70.163	2.172	25.890	-42.101	2.38	2.12

$LUMO_{dipolarophile}$ difference is lower than $LUMO_{dipole}$ - $HOMO_{dipolarophile}$ difference confirming the dominant FMO approach of concerted cycloaddition reactions.

Reaction of azomethine ylide **A1** with methyl acrylate may result in the formation of a product with one chiral resulting from partial overlapping of these two groups (called *endo approach*) thereby stabilizing the system. Hence it may be concluded that instead of steric hindrance it is the e*ndo approach* of -$COOCH_3$ group, which results in the lower activation energy. With phenyl acetylene and



9a



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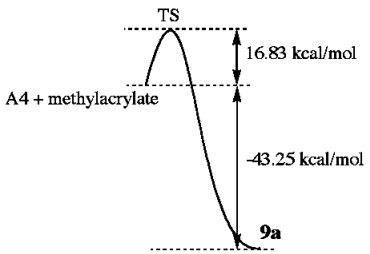
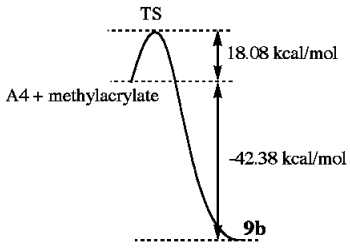
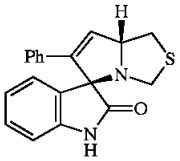




ethyl phenyl propiolate however, a single product **7** and **8** respectively are possible.

It is observed that the activation energy for the reaction of amy **A1** with methyl acrylate (1.66 kcal/mol) is lower



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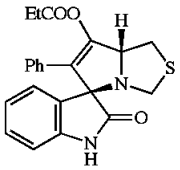

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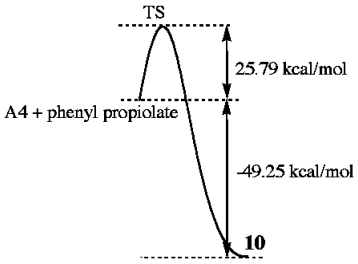

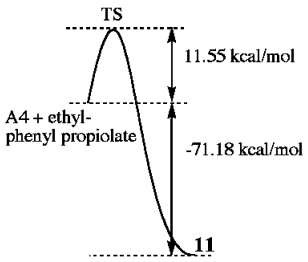

than that with ethene (5.64 kcal/mol). This is due to the electron withdrawing nature of the -$COOCH_3$ group, which accelerates the cycloaddition reaction. However, the activation energies for the reaction of amy **A1** with phenyl acetylene (11.87 kcal/mol) and ethyl phenyl propiolate (11.55 kcal/mol) are higher than that with ethyne (10.84 kcal/mol) which may be due to steric hindrance of the phenyl group. Also the activation energy of **8** is slightly lower than **7**, which is again due to the electron withdrawing nature of -$COOC_2H_5$ group. The results are summarized in Table 4.

Next we extended these calculations to azomethine ylide **A4** derived from isatin and thiazolidine-4-carboxylic acid with different dipolarophiles. Geometry optimization of azomethine ylide **A4** indicated that it has an almost planar structure. The thiazolidine ring, instead of having envelope shape, is planar and lies in the same plane as that of isatin. It exists in two isomeric forms. One in which C=O group and –CH of dipole are *anti* (azomethine ylide, $\mathbf{A4_{anti}}$) and in which these are *syn* (azomethine ylide, $\mathbf{A4_{syn}}$). Both the isomers have almost the same heat of reaction indicating formation of both isomers in solution, however transition state calculation indicated that they can interconvert into each other and are separated by an energy barrier of 16.35 kcal/mol.

Methyl acrylate may approach either of the azomethine ylide ($\mathbf{A4_{anti}}$ and $\mathbf{A4_{syn}}$) with formation of products having three chiral centers. Therefore a total of 8+8 = 16 isomers could be possible. Out of these 16 possibilities only eight have the concerted mechanism, the other eight are not possible from the reaction under consideration. Hence we have carried out the geometry optimization and transition state calculations for these eight possibilities. Results showed that all the eight isomers have almost same ΔH_f, indicating that thermodynamically all are equally stable. Obviously the next question was which one of these eight isomers is kinetically controlled. For this purpose we have carried out transition state calculations of all the eight isomers. However we have been successful in locating the transition state geometries in case of only two isomers, **9a** and **9b** thereby indicating that this reaction is of great stereospecific control. Attack of methyl acrylate on azomethine ylide $\mathbf{A4_{syn}}$ results in inward movement of thiazolidine ring towards isatin ring and the transition state could not be located even in a single case. This may be due to the fact that there is steric hindrance between the isatin ring and thiazolidine ring that makes it unstable and hence fails to produce transition state geometry. Thus the only possibility is attack on azomethine ylide $\mathbf{A4_{anti}}$ in which attack by methyl acrylate results in the outward movement of the thiazolidine ring leaving only four structures for consideration. Out of the four structures we have been able to locate transition states in case of **9a** and **9b** only. This can be explained on the basis of FMO's. $HOMO_{dipole}$ - $LUMO_{dipolarophile}$ energy gap is lower than $HOMO_{dipolarophile}$ - $LUMO_{dipole}$ and hence for the reaction to occur the favoured path is $HOMO_{dipole}$ and $LUMO_{dipolarophile}$. Both HOMO and LUMO of dipole show uneven distribution of electronic density along C-N-C dipole. In the HOMO of amy $\mathbf{A4_{anti}}$ the orbital coefficients on C-N-C dipole are 0.595(C1) and 0.529(C2). Similarly in the LUMO of methyl acrylate the orbital coefficients are 0.737(C1) and 0.541(C2). Thus there is better orbital overlap between C1 of azomethine ylide $\mathbf{A4_{anti}}$ and the C1 of methyl acrylate. This results in the formation of product **9a** and **9b**. The activation energy

for **9a** (16.83 kcal/mol) is lower than **9b** (18.08 kcal/mol) due to *endo approach* of $COOCH_3$ group and hence **9a** should be in enantiomeric excess of **9b**.

Parallel to methyl acrylate, phenyl acetylene and ethyl phenyl propiolate also attack the azomethine ylide **A4**, but the product formed has only two chiral centers and therefore a total of 4+4 = 8 isomers are possible in each case. Out of these isomers it has been possible to optimize the transition state geometry of only one isomer **10** and **11** in each case respectively suggesting the predominant formation of these isomers. Attack of phenyl acetylene and ethyl phenyl propiolate on $\mathbf{A4_{syn}}$ results in inward movement of thiazolidine ring and the transition state could not be located. Thus the only possibility is attack on $\mathbf{A4_{anti}}$ which results in outward movement of ring leaving only two structures for consideration in each case. Of these we have been able to locate the transition states for regio-isomers **10** and **11** in each case. This can be explained on the basis of FMO approach and *endo approach* of phenyl acetylene and ethyl phenyl propiolate. In the HOMO of amy $\mathbf{A4_{anti}}$ the orbital coefficients on C-N-C dipole are 0.595(C1) and 0.529(C2). Similarly in the LUMO of phenyl acetylene and ethyl phenyl propiolate the orbital coefficients are 0.35(C-bearing phenyl group) and 0.20(C-bearing H) and 0.38(C-bearing phenyl group) and 0.20(C-bearing -COOEt) respectively. Thus there is better orbital overlap between C1 of azomethine ylide $\mathbf{A4_{anti}}$ and the C bearing the phenyl ring. This results in the formation of regioisomers **10** and **11**. The reaction of amy **A4** with phenyl acetylene is found to be 49.25 kcal/mol exothermic with an energy barrier of 25.79 kcal/mol. Similarly with ethyl phenyl propiolate it is 42.10 kcal/mol exothermic with an energy barrier of 25.89 kcal/mol. All the results are summarized in Table 4.

Conclusions.

One of the transition state bond length in **Py4-TS** is longer than the other. This suggested that, when a spiro center is being formed, the cycloaddition path is concerted but not synchronous. From Table 1, it may be concluded that amy **A4** is stabilized by the delocalisation of dipolar charge into the indole nucleus. The dominant FMO approach for the cycloaddition reaction between amy **A1** and **A4** with methyl acrylate, phenyl acetylene and ethyl phenyl propiolate is $HOMO_{dipole}$ and $LUMO_{dipolarophile}$ because this energy gap is lowest. Structure **9a** should be in enantiomeric excess than **9b** due to the *endo approach* of $COOCH_3$ group. It lies near to the isatin nucleus. It should be possible to isolate the streoisomers **9a, 9b, 10** and **11** in case of reaction of azomethine ylide **A4** with methyl acrylate, phenyl acetylene and ethyl phenyl propiolate and the experimental work in this direction is currently in progress in our laboratory.

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