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ORIGINAL PAPER

Theoretical investigations on the mechanistic pathway of the thermal rearrangement of substituted N-acyl-2,2-dimethylaziridines

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Abstract The mechanism of the thermal rearrangement of substituted N-acyl-2,2-dimethylaziridines **1** has been studied using quantum chemistry methods. Geometries of reactants, transition states and products have been optimized at the B3LYP/6-311++G(2d,2p) level. Relative energies for various stationary points have been determined and reaction identified by IRC calculations. The results show that thermal rearrangements occur in three ways. Firstly, the transition state $\mathbf{TS_1}$ in which a hydrogen atom of methyl groups migrates from primary carbon to oxygen of amid group to give the N-methallylamide **2**. The second is via the transition state $\mathbf{TS_2}$ in which the attack of oxygen to the tertiary carbon yields the oxazoline **3**. The third is via the transition state $\mathbf{TS_3}$ in which a hydrogen migrate from the secondary carbon to oxygen to give the vinylamide **4**. In order to get insights into the factors determining the exact nature of its interactions with electrophiles, the application of reactivity parameters derived from density functional theory in a local sense, in particular the softness and Fukui function, to interpret and predict the mechanisms of the thermal decomposition of the N-acyl-2,2-dimethylaziridines **1**, has been discussed.

Keywords Density functional theory · Intrinsic reaction coordinate · N-acyl-2,2-dimethylaziridines · Theoretical mechanism · Thermolysis · Fukui functions (FF)

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Introduction

Aziridines are strained three-membered nitrogen-containing heterocycles that have been closely studied due to their great synthetic utility [1–3]. As well numerous synthetic aziridines have found biological applications as antitumor agents, antibiotics and as enzyme inhibitors [4, 5]. The strain energy of aziridine is similar to that of cyclopropane (27 kcal mol^{-1}), reflecting high bond-angle strain [6]. A large number of aziridines reactions involve opening of the ring and thus a release of strain energy but it has been suggested that lowering activation energy in these reactions is not solely due to the release of strain. Significantly, activation of aziridine, due to an electron withdrawing group on the nitrogen atom such as the acyl moiety, is necessary to readily achieve regioselective nucleophilic ring-opening. N-acyl-2,2-dimethylaziridines react with ethanol, water and sodium iodide, to provide products resulting from nucleophilic selective attack on the more substituted carbon atom of the aziridine ring [7–9]. Such heterocycles are also unstable in the presence of Bronsted acids (concentrated and aqueous sulfuric acid) and azaphilic Lewis acids, e.g., [$BF_3.Et_2O$], Zn(II) triflate, silica gel, alumina and acid activated clays), which coordinate to nitrogen atom instead of oxygen one, yielding a mixture of amidoalcohols, allylamides and oxazolines, via aziridinium and tertiary aliphatic carbocation intermediates where heterolytic cleavage of the C-N bond of the aziridine ring can occur [10–16]. In contrast, heating N-*p*-nitrobenzoyl-2-benzylaziridine in toluene, leads to trans-(N-cinnamyl)-*p*-nitrobenzamide [17], which could be explained by the low polarity of toluene that favors intramolecular reaction mechanism, involving a concerted cis-elimination of proton followed by the opening of the aziridine ring. It has also been observed that the thermolysis of N-p-nitrobenzoyl-2-vinylaziridine in toluene gave the *N*-p-nitrophenyldihydro-1,3-oxazepine through ring formation

Scheme 1 Themolysis of N-acyl-2,2-dimethylaziririne **1** into products **2**, **3** and **4**

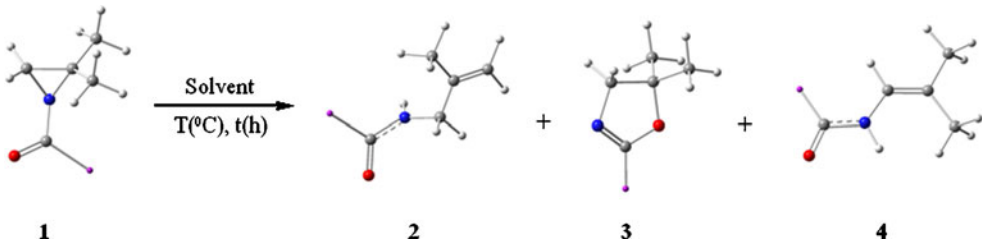
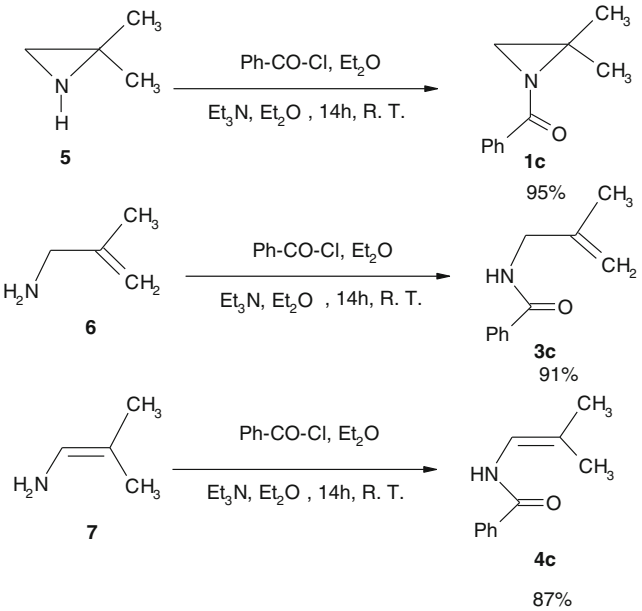


Table 1 Corrections of zero point energy (ZPE), thermal and free energies of aziridines and products at B3LYP/6-311++G(2d,2p) level

	ΔE + ZPE (kcal mol^{-1})	ΔH° (kcal mol^{-1})	ΔG° (kcal mol^{-1})
1a	20,1	19,8	21,0
2a	6,8	6,7	6,5
3a	4,7	3,9	6,1
4a	0.0	0.0	0.0
1b	21,3	20,9	22,3
2b	6,6	6,5	6,4
3b	6,2	5,5	7,1
4b	0.0	0.0	0.0
1c	18,4	18,0	19,4
2c	7,1	7,0	7,1
3c	8,2	7,0	10,1
4c	0.0	0.0	0.0



Scheme 2 Transformations of amines **5**–**7** into N-benzoyl derivatives **1c**, **2c** and **4c**

involving an analogous cyclic transition state [18]. The thermolysis of N-(p-nitrobenzoyl)-6-azabicyclo[3.1.0]hexane in toluene provides a mixture of oxazoline and unsaturated amides [19] in agreement with steric and electronic factors favoring equally in one hand a quasi-six-membered ring transition state, leading to the amide. On the other hand, the formation of a four-membered ring transition state lead to the oxazoline.

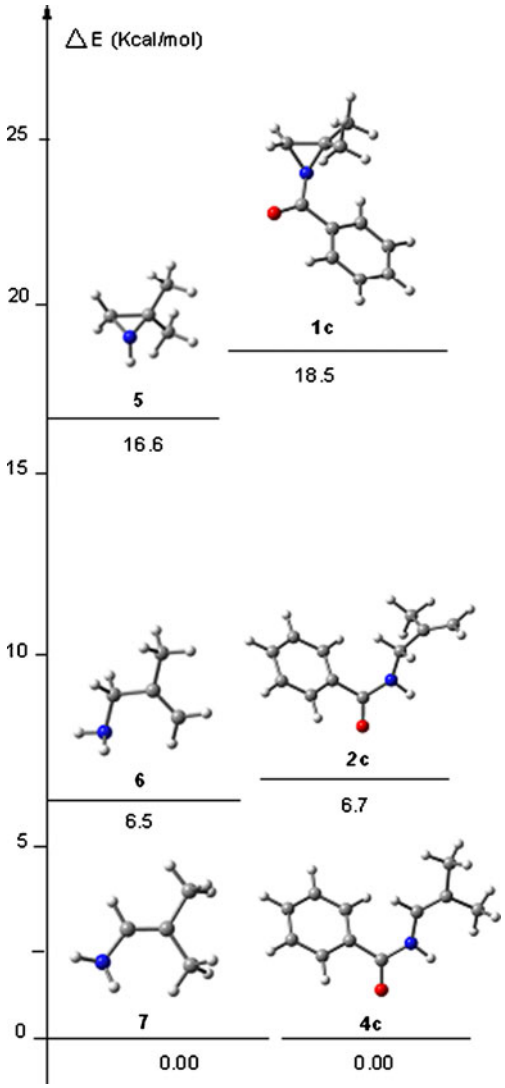


Fig. 1 Energy diagram of amines **5**–**7** into N-benzoyl derivatives **1c**, **2c** and **4c**

Recently, we have proposed an ionic mechanism for the thermolysis of N-acyl-2,2-dimethylaziridines in acetone, butanone and toluene to give methallylamides and/or oxazolines in high yields depending on the nature of the acyl group [20]. The polar nature of the solvent favors then the formation of a zwitterion by heterolytic cleavage of the C-N bond of the heterocycle. The O-amidate of this intermediate either extracts a proton from one of the methyl groups or attacks the tertiary carbonium ion center, leading to the two different products.

Full analysis of the kinetics of these unimolecular thermal processes is complicated by the occurrence of some competitive and consecutive reactions but the characterization of the pathway branching can be used to establish some of the factors controlling the substrate reactivity. Thus, to extend available information concerning N-acyl-2,2-dimethylaziridines, we have examined their thermolysis in toluene [21] which differs in regard to the acyl group, ethyl (**1a**), benzyl (**1b**) and phenyl (**1c**). In fact, compounds **1a** and **1b**, carrying alkyl groups, may not be able to generate any conjugation with the free doublet of nitrogen in contrast to **1c** which carries an aromatic group combined with the carbonyl moiety. In all cases, the exclusive product was found to be the allylamide **2**.

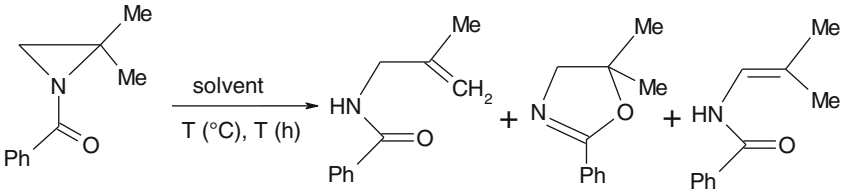
To provide a better understanding of the electronic properties of N-acyl-2,2-dimethylaziridines **1**, we have investigated the substitution effects of carbonyl group on the geometry and the energy as well as on the reactivity of different atomic sites.

In addition, the prediction of the reactivity of different sites is based on the conceptual DFT based local reactivity descriptors (Fukui function [22], local softness [23]). The behavior of aziridines, as electrophiles or nucleophiles species during reaction, depends on the local behavior of these molecules, i.e., on how the atomic sites of the molecule react toward the approch of the reagent.

Computational details

DFT quantum chemical calculations of structures and energies were carried out with the aid of GAUSSIAN 09 set of programs [24]. Geometrical parameters of reactants, transition states (TS) and products for the studied reactions were fully optimized at the hybrid density functional B3LYP [25, 26] level using the 6-311++G(2d,2p) basis. Vibrational frequency calculations were carried out in order to confirm the stationary states, including TS structures. The intrinsic reaction coordinate (IRC) was followed to make sure that no intermediate was formed between reactants and products. To obtain more information on the electronic structures of stationary points, natural bond orbital (NBO), analysis was carried out. Energy profiles calculated along the IRC coordinate for the three aziridines molecules are shown. In order to present all curves on the same scale, the energies of each curve were scaled according to E (product)=0. From density theory, it was possible to define and justify concepts of chemical reactivity such as

Table 2 Formation allylbenzamide **2c**, oxazoline **3**c and vinylbenzmide **4c** by thermolysis of N-benzoyl-2,2-dimethylaziridine **1c**

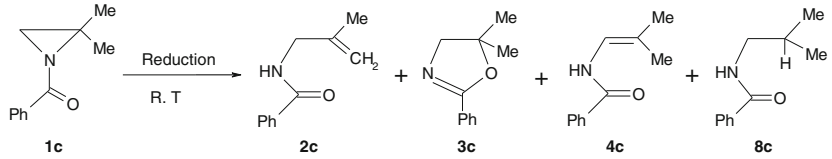


1c **2c** **3c** **4c**

Entry	Solvent	$\varepsilon_{20°C}$	T (°C)	t (h)	**2c** (%)	**3c** (%)	**4c** (%)
1	acetone	20.7	56	19	16	16	0
2	butanone	18.5	56	19	17	8	0
3	butanone	18.5	80	3.30	10	4	0
4	butanone	18.5	80	48	63	23	0
5	toluene	2.4	110	48	98	0	0

For all experiments, the aziridine **1c** was dissolved in 50 mL of anhydrous solvent

Scheme 3 Electrochemical and chemical reduction of N-benzoyl-2,2-dimethylaziridine **1c**



e⁻, Hg, -2,8V, 2h30	14%	31%	2%	18%
Napht⁻, Na^+, 5d	0%	0%	22%	51%

the electronic chemical potential (μ), the absolute hardness (η), the global electrophilicity (ω) and the global softness (S) of the system is defined as the inverse of the global hardness [27–32]. In practice, the condensed Fukui functions (f_k) at the atom k are usually evaluated from differences in atomic charges:

$$f_k^+ = q_k(N) - q_k(N+1) \quad (1)$$

$$f_k^- = q_k(N-1) - q_k(N) \quad (2)$$

and

$$s_k = f_k \cdot S \quad (3)$$

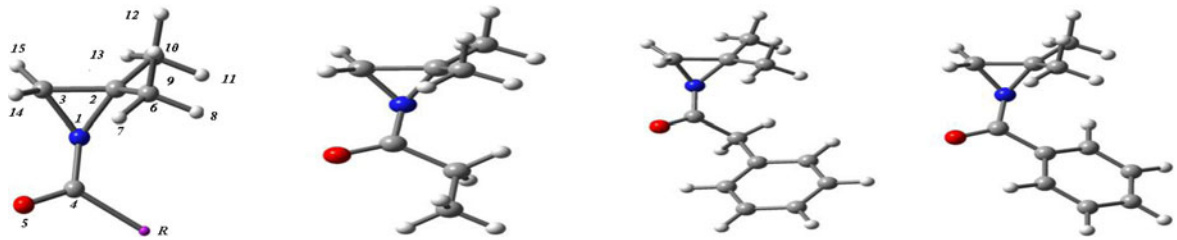
where q_k is the electronic charge of atom k and N is the number of electrons. The two condensed Fukui functions characterize the reactivity preferences of nucleophilic and electrophilic attacks, respectively. In general, the larger the value of a condensed Fukui function, the greater the reactivity of the corresponding atom.

Results and discussion

Computationally, we selected the three aziridines **1a**, **1b** and **1c** to study their theoretical thermal rearrangement into the corresponding methallylamides **2a**–**c**, oxazolines **3a**–**c** and/or vinylamides **4a**–**c** (Scheme 1).

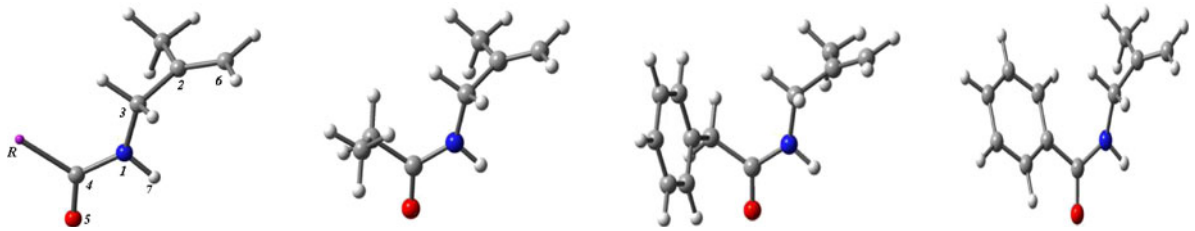
The most stable geometries of these compounds were determined and characterized as minima on the potential

Table 3 Structures and significant distances (Å) of N-acylaziridines **1** at the B3LYP/6-311++G(2d,2p) level



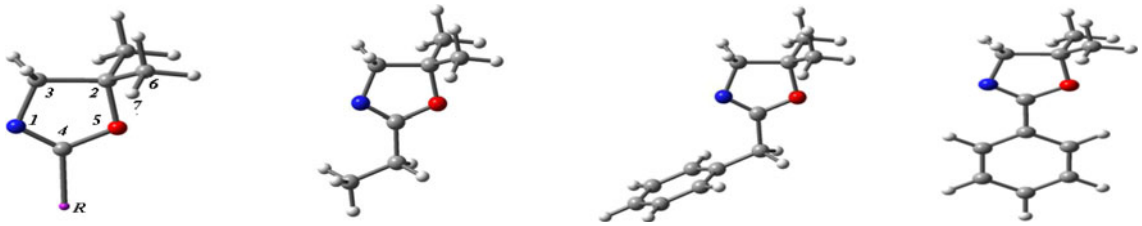
Distances (Å)	1a	1b	1c
dN_1-C_2	1.473	1.472	1.479
dN_1-C_3	1.449	1.448	1.449
dC_2-C_3	1.500	1.502	1.498
dN_1-C_4	1.395	1.390	1.395
dC_4-O_5	1.214	1.213	1.218
dC_2-C_6	1.514	1.512	1.512
dC_6-H_7	1.089	1.089	1.091

Table 4 Structures and significant distances (Å) of N-methallylamides **2** at the B3LYP/6-311++G(2d,2p) level



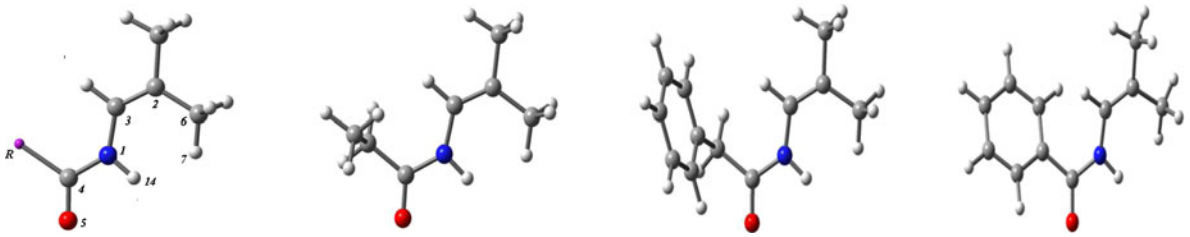
Distances (Å)	2a	2b	2c
dN_1-C_3	1.458	1.460	1.466
dC_2-C_3	1.514	1.513	1.512
dN_1-C_4	1.369	1.366	1.331
dC_2-C_6	1.331	1.331	1.374
dC_4-O_5	1.223	1.223	1.222
dN_1-H_7	1.010	1.010	1.011

Table 5 Structures and significant distances (Å) of oxazolines **3** at the B3LYP/6-311++G(2d,2p) level



Distances (Å)	3a	3b	3c
dN_1-C_3	1,465	1,465	1,467
dC_2-C_3	1,556	1,557	1,556
dN_1-C_5	1,269	1,267	1,268
dC_2-C_6	1,364	1,364	1,362
dC_4-O_5	1,522	1,522	1,522
dC_2-O_5	1,469	1,470	1,473

Table 6 Structures and significant distances (Å) of N-vinylamides **4** at the B3LYP/6-311++G(2d,2p) level



Distances (Å)	4a	4b	4c
dN_1-C_3	1.398	1.400	1.403
dC_2-C_3	1.338	1.338	1.338
dN_1-C_4	1.376	1.372	1.377
dC_4-O_5	1.221	1.222	1.222
dC_2-C_6	1.504	1.504	1.504
dN_1-H_{14}	1.008	1.008	1.009

surfaces. The corrections of zero point energy (ZPE), thermal and free energies of the three aziridines and all products are reported in Table 1. Our theoretical results summarized in Table 1 show that the vinylamide **4** is thermodynamically the most stable.

Also, amines **5**–**7** are transformed by benzoylation reaction [33] into their N-benzoylated corresponding to **1c**, **2c** and **4c** in ether and triethylamine at room temperature for 14 h (Scheme 2). Analysis of the results obtained after theoretical calculations allows us to conclude that the N-acyl derivatives

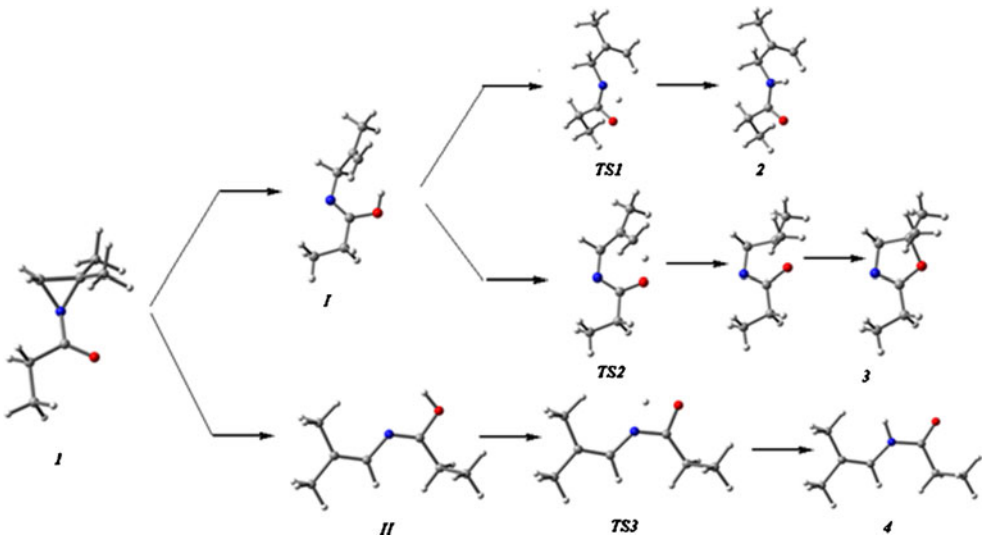


Fig. 2 Reaction way for obtaining transition states (**TS_{1a}, TS_{2a}, TS_{3a}**) and products **2a**, **3a**, **4a** from reactant **1a** at B3LYP/6-311++G(2d,2p) level

1c, **2c** and **4c** have similar energies to those of **5–7** amines (Fig. 1).

In fact, N-benzoyl-2,2-dimethylaziridine **1c** better assess the various effects involved in these reactions. Indeed, this aziridine **1c** leads to a mixture of N-2-methylprop-1-enyl benzamide **2c** and 5,5-dimethyl-2-phenyloxazoline **3c** by heating in acetone, butanone and toluene at different temperatures and for different times. N-2-methylprop-2-enyl benzamide **4c** was not obtained in these experimental conditions (Table 2). The structure of these products **1**–**4** was already confirmed by IR, ^{1}H NMR and ^{13}C NMR and also confirmed by comparing for authentically products.

For a given temperature and time, the same effect is found, the less polar solvent gives more **2c** (Table 2, *entries* 1 and 2). On the other hand, when the reaction time is longer, the conversion is in favor of **1c** (*entries* 3 and 4). The formation of products **2c** and **3c** after heating aziridine **1c** in butanone under reflux for 3.30 h shows that these two products are derived as **1c**. Similarly, the recovery of the oxazoline **3c**, after heating in butanone under reflux for two days, proves that it does not turn into N-methallylamide **2c** under these conditions. However, we have exclusively obtained **2c** by thermolysis of **1c** in toluene for 2 days (*entry* 5). We noticed that the rearrangement of oxazolines **2c** and **3c** was successfully completed in the presence of concentrated sulfuric acid at room temperature. It is interesting to notice that N-vinylamide **4c** was never obtained during the thermal rearrangement reactions. We suggest that product **4c** can be formed from **1c** for longer reaction time. On the other hand, we observed in our previous work that the aziridine **1c** is transformed by electrochemical reduction into a mixture of N-propylbenzamide **8c**, unsaturated amides **2c**, **3c** and oxazoline **4c** whose yields closely depended on both the method of reduction and reaction times [33]. The formation of **4c,** during 5 days, through its chemical reduction reaction, show that allylamide **3c** is the kinetic product whereas the vinylamide **4c** is the thermodynamic one (Scheme 3).

Calculations for each optimized geometry of the given compounds show that all the reactions have in common bond breakage and hydrogen migration preceding the attainment of a high-energy transition state. Principal parameters for the optimized geometries are given in Tables 3, 4, 5, and 6. During thermolysis, when the reactant is being transformed into its TS, the C_6-H_7, N_1-C_2 distances increase, whereas the N_1-C_4, C_4-O_5 and C_2-C_6 distances decrease. From the first column of Table 3, it is seen that C_2 changes its sp_3 hybridization state to sp_2, whereas C_4 changes from sp_2 hybridization to sp_3.

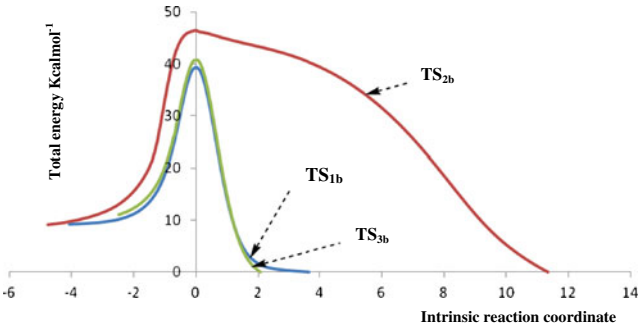


Fig. 4 IRC plots performed for transition states **TS_{1b}**, **TS_{2b}** and **TS_{3b}** obtained during thermal decomposition of N-phenylacetyl-2,2-dimethylaziridine **1b**

Calculations of the IRCs for the possible reaction pathways leads to the description of an initial step involving breakage of the N-C_2 bond of **1** followed by migration of the proton H_7 to oxygen O_5, to give the intermediate **I** (Fig. 2).

The latter **I** is transformed via **TS_1** into allylamide **2** or, after a conformational change, via **TS_2** into oxazoline **3**. Alternatively, heterolytic cleavage of the N-C_2 bond can be followed by abstraction of H_{14} by O_5, then proton migration to give vinylamide **4** via the transition state **TS_3**. Vibrational state calculations show that the imaginary vibrational modes of **TS_1**, **TS_2** and **TS_3** connect with reactant and product, which confirms that **TS_1**, **TS_2** and **TS_3** obtained by the DFT method are reliable. IRC pathways for the thermolysis of N-acyl-2,2-dimethylaziridines **1a, 1b** and **1c** are shown in Figs. 3, 4 and 5.

For the same substituent, the activation energy **Ea_1** for the transition state **TS_1** is lower than the activation energy **Ea_2**

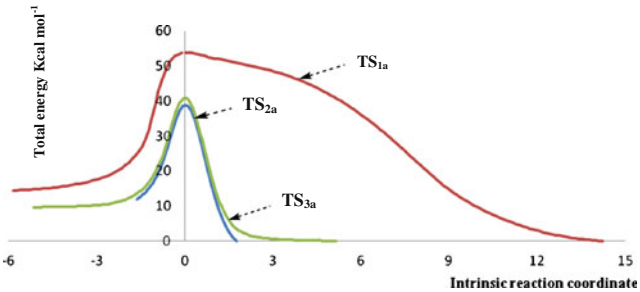


Fig. 3 IRC plots performed for transition states **TS_{1a}** **TS_{2a}** and **TS_{3a}** obtained during thermal decomposition of N-propanoyl-2,2-dimethylaziridine **1a**

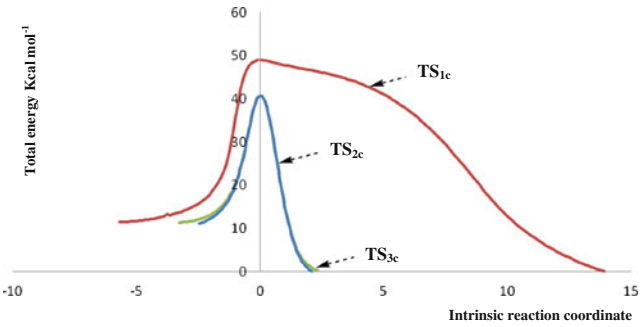


Fig. 5 IRC plots performed for transition states **TS_{1c}**, **TS_{2c}** and **TS_{3c}** obtained during thermal decomposition of N-benzoyl-2,2-dimethylaziridine **1c**

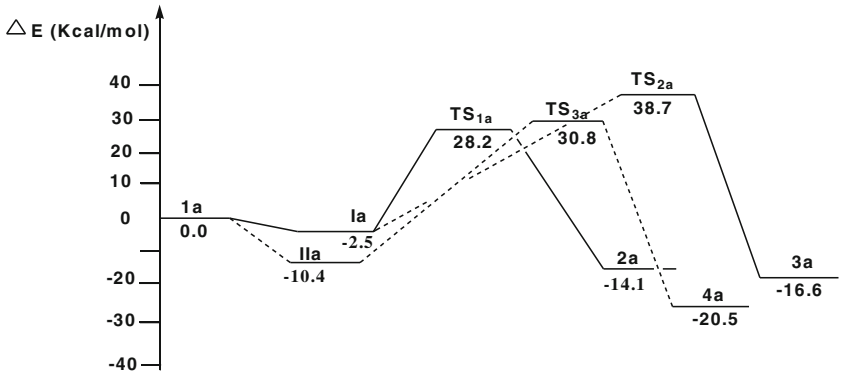


Fig. 6 Energy diagram for the thermal decomposition of N-propanoyl-2,2- dimethylaziridine **1a** into products **2a**, **3a** and **4a** at the B3LYP/6-311++G(2d,2p) level

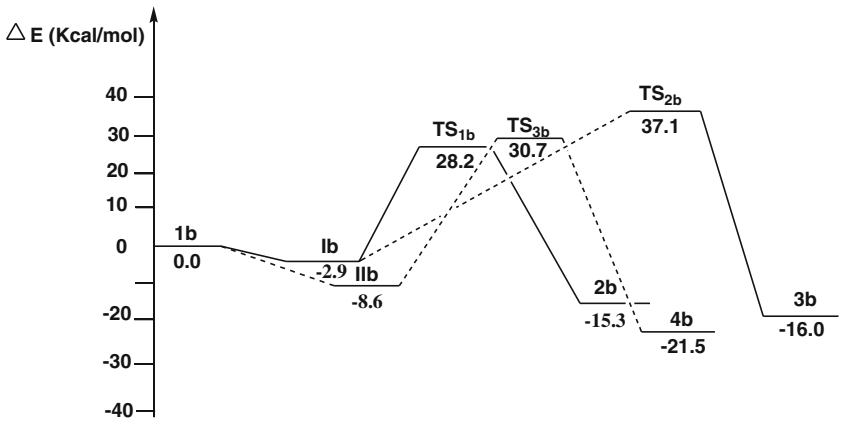


Fig. 7 Energy diagram for the thermal decomposition of N-phenylacetyl-2,2-dimethylaziridine **1b** into products **2b**, **3b** and **4b** at the B3LYP/6-311++G(2d,2p) level

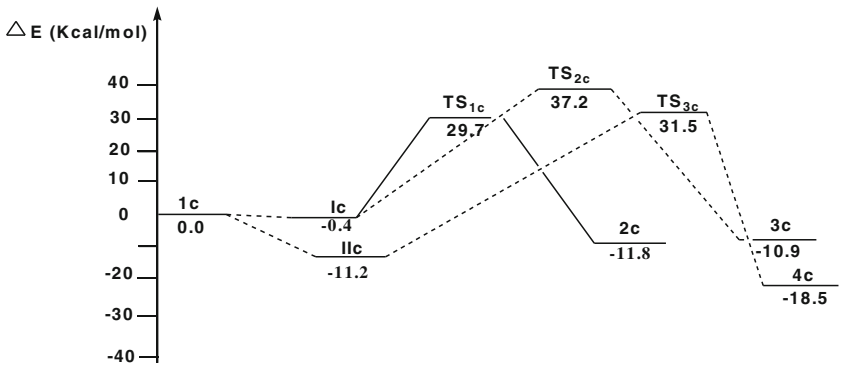


Fig. 8 Energy diagram for the thermal decomposition of N-benzoyl-2,2-dimethylaziridine **1c** into products **2c**, **3c** and **4c** at the B3LYP/6-311++G(2d,2p) level

and **Ea$_3$** respectively for the transition state **TS$_2$** and **TS$_3$** (Figs. 6, 7 and 8). This enables us to say that the allyamide **2** is preferred over oxazoline **3** and vinylamide **4**. The vinylamide **4**, thermodynamically preferred over the allylamide **2**, is not obtained by thermolysis of the aziridine **1**.

DFT/B3LYP calculations using the program Gaussian 09 show that the preferred conformation of the aziridines **1a-c** results in the allylamides **2a-c** as kinetic products whereas the vinylamides **4a-c** are thermodynamic ones [25]. From the values reported in Tables 8 and 9, the reactivity order of the N-acyl-2,2-dimethylaziridines (**1a:** R= CH_3CH_2, **1b:** R= $PhCH_2$ and **1c:** R= Ph) for the electrophilic case is:

$$O_5 > N_1 > H_{14} > H_8 > H_{15} > C_2; O_5 > N_1 > H_{14} > H_8 > C_2 > H_{15} \text{ and } O_5 > N_1 > H_{14} > H_8 > H_{11}$$

The nucleophilic reactivity order was:

$H_{11}>H_8>H_7>H_{12}>H_{13}>H_9; H_{11}>H_8>H_7>H_{12}>H_{13}>H_9$ and $C_1>H_9>H_{13}>H_7>H_{15}$ for the same order of substitution as in the electrophilic case. The f_k^+ and s_k^+ descriptors are used to predict the most favored N-acyl-2,2-dimethylaziridines **1** site for nucleophilic attack. Similarly, for electrophilic attack, we have utilized f_k^- and s_k^-. We noted that electron populations, adopted for computing reactivity descriptors in the present study, were obtained from natural bond orbital (NBO) analysis. From Tables 7, 8 and 9 results, it is found that f_k^+ and the corresponding s_k^+ display very similar trends. According to the values of f_k^+ and s_k^+ for the N-acyl-2,2-dimethylaziridines **1**, the H atoms of one of the two methyl groups are highly the preferred sites for nucleophile attack. Both f_k^+ and s_k^+ results show that the H_{14} and H_{15} atoms of the methylene group are less reactive. It is clear from the values of f_k^- and s_k^- that O_5 atom should be the most reactive site toward an electrophilic attack of molecule (Tables 8 and 9). The evaluated f_k^- and s_k^- value for the O_5 atoms in the N-propanoyl-2,2-dimethylaziridine molecule **1a** is 0.326 and 1.379 which are 0.164 and 0.652 less than those of O_5 in the N-phenylacetyl-2,2-dimethylaziridine molecule **1b**. However, the data from Tables 8 and 9 indicated clearly that the evaluated surface reactivity descriptors are considerably influenced by the nature of substitutents.

Table 7 Reactivity descriptors for substituted N-acyl-2,2-dimethylaziridines **1** at the level B3LYP/6-311++G(2d,2p)

	E_{HOMO} (u.a.)	E_{LUMO} (u. a.)	S	η	μ	ω
CH_3CH_2	−0.25348	−0.01688	4.23	6.43	−3.68	1.05
$PhCH_2$	−0.24671	−0.02417	4.49	6.05	−3.69	1.13
Ph	−0.25544	−0.05699	5.04	5.40	−4.25	1.67

Table 8 Values of the Fukui function considering NBO charges according to Eqs. (1 and 2) for substituted N-acyl-2,2-dimethylaziridines **1**

	1a		**1b**		**1c**	
	f_k^-	f_k^+	f_k^-	f_k^+	f_k^-	f_k^+
N_1	0.276	0.003	0.105	0.002	0.203	0.008
C_2	0.032	0.002	0.017	0.006	0.027	0.218
C_3	0.007	0.003	0.005	0.009	0.004	0.010
C_4	−0.014	0.005	−0.007	0.011	−0.012	0.140
O_5	0.326	0.023	0.162	0.025	0.226	0.126
C_6	−0.007	−0.043	−0.003	0.018	−0.006	−0.002
H_7	0.027	0.096	0.006	0.060	0.017	0.191
H_8	0.043	0.115	0.028	0.083	0.036	0.028
H_9	0.005	0.049	−0.004	0.020	0.004	0.210
C_{10}	−0.003	0.028	−0.004	0.030	0.003	−0.006
H_{11}	0.041	0127	0.003	0.122	0.033	0.024
H_{12}	0.029	0.095	0.011	0.101	0.018	0.003
H_{13}	0.014	0.079	−0.073	0.075	0.012	0.200
H_{14}	0.057	0.045	0.034	0.040	0.045	0.028
H_{15}	0.033	0.021	0.016	0.016	0.026	0.182

Conclusions

In the present study on the N-acyl-2,2-dimethylaziridines, the thermolysis reaction is proposed in both hydrogen migration and cyclization mechanisms. The reaction paths (intrinsic reaction coordinate IRC) of the thermolysis of these three heterocycles were carried out by means of density functional theory at

Table 9 Values of the local softness considering NBO charges according to Eq. (3) for substituted N-acyl-2,2-dimethylaziridines **1**

	1a		**1b**		**1c**	
	s_k^-	s_k^+	s_k^-	s_k^+	s_k^-	s_k^+
N_1	1.167	0.013	0.471	0.009	1.023	0.040
C_2	0.135	0.008	0.076	0.027	0.136	1.099
C_3	0.030	0.013	0.022	0.040	0.020	0.050
C_4	−0.059	0.021	−0.031	0.049	−0.061	0.706
O_5	1.379	0.097	0.727	0.112	1.139	0.635
C_6	−0.030	−0.182	−0.013	0.081	−0.030	−0.010
H_7	0.114	0.096	0.027	0.269	0.086	0.962
H_8	0.182	0.486	0.126	0.373	0.181	0.141
H_9	0.021	0.207	−0.018	0.090	0.020	1.058
C_{10}	−0.013	0.118	−0.018	0.135	0.015	−0.032
H_{11}	0.173	0.537	0.013	0.548	0.166	0.121
H_{12}	0.123	0.402	0.049	0.453	0.091	0.015
H_{13}	0.059	0.334	−0.328	0.337	0.061	1.008
H_{14}	0.241	0.190	0.153	0.180	0.227	0.141
H_{15}	0.140	0.089	0.072	0.072	0.131	0.917

the B3LYP/6-311++G(2d,2p) level. Calculations show that the preferred conformation of the aziridines results in the allylamides as kinetic products although the vinylamides are thermodynamically favored. It seems that the Fukui functions have practical advantages over other electronic indices for understanding chemical reactions, especially reactions in which both bond breaking and forming occur.

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