FULL PAPER

The Effect of Position Replacement of Functional Groups on the Stepwise character of 1,3-Dipolar Reaction of a Nitrile Oxide and an Alkene

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It is a well-known fact that by changing the 1,3-dipolar cycloaddition (1,3-DC) reaction mechanism from concerted to stepwise, the stereospecificity is lost; since in synthesizing the required heterocyclic molecules that reaction is a requisite, it is important to study the concertedness of that reaction. Several papers on this subject have already stated that the existence of electron withdrawing groups (EWG) or electron donor groups (EDG) on dipole or dipolarophile leads to a high-energy differentiation between the dipole HOMO and dipolarophile LUMO (or *vice versa*) as well as the emergence of an intermediate in the reaction pathway. This paper seeks answering the question of when an EWG on dipole and an EDG on dipolarophile could be a factor in making the reaction mechanism stepwise, and does repositioning of functional groups in replacing dipole and dipolarophile switches the reaction mechanism from stepwise into concerted or *vice versa*?

Keywords: Stepwise, Concerted, Reaction mechanism, Functional group effect, 1,3-Dipolar cycloaddition reaction, Reaction pathways.

Introduction

A large number of alternatives are available that reveal the ability of changing the mechanism of 1,3-dipolar cycloaddition (1,3-DC) reaction from its usual and most probable state, *i.e.*, concerted model into the stepwise pathway [1 – 3]. The concertedness of the 1,3-DC reaction mechanism makes this reaction more valuable in synthesizing the required chiral molecules and components, for when the mechanism of this process becomes stepwise, and as an intermediate emerges in the course of the reaction routes, the stereospecificity loses [4][5] thoroughly. In addition, the stepwiseness of this reaction leads to lose of stereospecificity, and it creates unwanted stereoisomers, such as enantiomers or diastereomers as their side products [6][7]. On the other hand, development of those side products could bring along some problems and difficulties which are caused by some factors, such as expensive ingredients, high-energy consumption, longer time, and more importantly the difficulties that appear in the subsequent efforts to separate or isolate the side products [8][9].

Although they have the same physical and chemical properties [8 – 10], the separation of the stereoisomers, either the enantiomer or the diastereoisomer, is usually a difficult, expensive, and time-consuming task, as frequently reported by the researchers on organic synthesis. In most examples, the mechanism of the 1,3-DC reaction is normally concerted and there is no medium in the reaction pathways [11][12]; therefore, by controlling several alternatives and applying them on the reaction conditions, the researcher could safely ensure the concertedness of the mechanism. On the other hand, neglecting certain conditions could lead to the emergence of an intermediate between the reactants and the products, which in turn would pave way to a rival stepwise pathway showing itself alongside the usual concerted route [13][14].

Huisgen (in 1963) was the first chemist who clearly commented on the mechanism of 1,3-DC reaction. He hypothesized that the reaction mechanism proceeds concertedly *via* a transition state that directly links the reactants to the cycloaddition final product [15]. Few years later, in 1968, *Firestone* proposed the possibility of a diradical intermediate existence in the reaction pathway, that is, between the reactants and the cycloaddition products [16]. Based on the proposed diradical intermediate, he was able to create a two-step model for the mechanism of 1,3-DC reaction.

Subsequently, in 1976, in response to the *Firestone*'s proposal, *Huisgen* published a paper titled 'Concerted nature of 1,3-dipolar cycloadditions and the question of diradical intermediates' that insisted on the concertedness of the reaction mechanism [17]. The debate was followed by several independent research teams followed by many reports which admitted the possibility of the concerted model [18][19]. Finally, in 1986, *Huisgen* reported unusual examples of thiocarbonyl ylide dipolar reactions in a series of research papers [20 – 22].

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He found out that by making a large HOMO–LUMO gap between an electron-rich thiocarbonyl ylide dipole and electron-poor dicyano-substituted dipolarophile, the reaction lost its stereospecificity in the cycloaddition products. He concluded that an (*E*)-alkene dipolarophile would be responsible in the development of both *cis*- and *trans*-products [20]. *Huisgen* suggested that the large difference noticed in the electron negativity between an electron-rich thiocarbonyl ylide dipole and an electron-poor dicyano-substituted dipolarophile would lead to the emergence of a relatively stable zwitterionic intermediate as the reaction coordinates.

Following the *Huisgen*'s thiocarbonyl ylide dipolar cycloaddition examples in 1986, various research teams rigorously thought of ways to find new examples of 1,3-DC reactions with a stepwise mechanism. For example, in 1989, *Huisgen* presented the 1,3-DC reactions of thione *S*-methylides to dimethyl 2,3-dicyano fumarates as well as to 2,3-dicyano maleates in this framework. A preceding *cis-trans*-isomerization of the unsaturated dipolarophiles during the cycloaddition showed that the example was not stereospecific either [23]. Since then, many other examples of stepwise dipolar cycloadditions of *Huisgen*'s thiocarbonyl derivatives have been reported [24 – 27]. Perhaps, it is an indication that the nature of the thiocarbonyl ylide, compared to other 1,3-dipoles, possesses high potential in making 1,3-DC reactions mechanism stepwise. Therefore, there is a possibility that the nature of the dipole plays an important role in the concertedness of the 1,3-DC reaction mechanism.

Sauer (1999) reported a nonstereospecific 1,3-DC reaction of a group of azomethine ylide derivatives and enamines [28]. Their results showed a rotation around the newly formed σ bond of the polar intermediate of the reaction. Because almost all azomethine ylide 1,3-DC reactions are concerted [29][30], it could be concluded that, in this unusual case, existence of some electron withdrawing functional groups on the dipole and an electron donor group (an amine) on the dipolarophile, would cause this to be a stepwise case.

Although a recent research by *Jasiński* [31] reported that in the 1,3-DC reaction of a nitrile oxide and a highly electron-poor dipolarophile (nitroacetylene), the reaction mechanism was not stepwise despite the expected zwitterionic intermediate. There are examples for this discussion in the literature reviews on the 1,3-DC reactions involving nitrile oxides which are postulated to have a zwitterionic mechanism; however, those claims have not been confirmed so far [32].

Also, the reaction between a highly electron negative dinitro alkene (*gem*-dinitroethene (DNE)) and a nitrone with high potentially resonance-stabilizing structure ((*Z*)-C,N-diphenyl nitrone) led to the formation of a 1,3-DC reactions [33]. In this particular case, however, the reaction mechanism was concerted in gas phase, although it was stepwise with toluene serving as a solvent. There have also been some examples of stepwise nitrone 1,3-DC reaction between *N*-methylnitrone and fluorinated ethylenes with toluene as the solvent [34]. In another report, it was found that steric congestion could not change the reaction mechanism from concerted to stepwise, at least in the 1,3-dipolar cycloaddition between a nitride ylide and an olefin in an ambient condition [35]. According to present results, factors, such as the nature of 1,3-dipole [36] dipolarophile [37], placement of the radical stabilizing functional group on the reactants [38], existence of electron donor or withdrawing groups on the dipole [39] or dipolarophile [40], presence of a simple solvent effect [41] having the cluster of solvent molecules with probable intermediate [42], and the presence of ionic liquids [43], may be considered as important alternatives with the capability of changing the mechanism of an ordinary 1,3-DC reactions from concerted into stepwise, or *vice versa*.

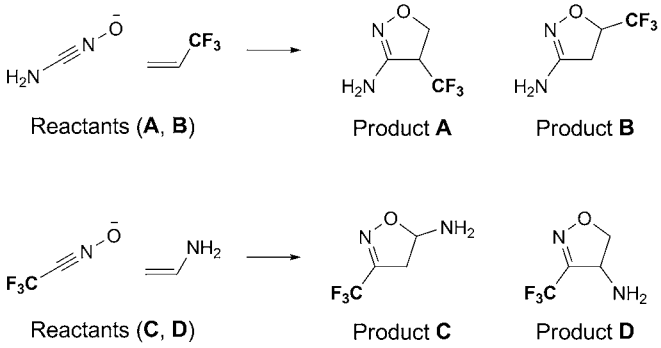
In addition, some studies have reported unusual cases of 1,3-DC reactions containing 1,3-dipole [44] or dipolarophile ionic form [45], diradical (theoretically by *Houk*, and experimentally by *Mlostoń*) [46 – 48] or radical cation species [49], light assisted [50], H-atom- [51] or metal-catalyzed [52], and C=X (X: heteroatom) dipolarophile [52][53] which were served as examples of leading the reaction mechanism into probable stepwise route.

In addition, recently, an example of a 1,3-DC reaction between methyl nitrile oxide as the 1,3-dipole, with a highly electron-rich alkene (tetraamino ethylene) was reported which clearly proceeds via a stepwise mechanism [54]. Also, in another research, it was found that during the 1,3-dipolar reaction of tetraaminoethylene as a highly electron-rich dipolarophile and trifluoromethyl azide as an electron-poor dipole, both stepwise and concerted pathways coordinate in a parallel situation [55]. In some of the papers on this subject, it has been claimed that the existence of electron withdrawing groups (EWG) or electron donor groups (EDG) on dipole or dipolarophile could result in the emergence of large energy gap between the dipole HOMO and dipolarophile LUMO (or vice versa) as well as the development of a stable zwitterionic intermediate in the course of the reaction pathway. Furthermore, it switches the concerted reaction mechanism to stepwise [33].

To answer this question, I developed a reaction scheme (*Scheme 1*) to show how a functionalized nitrile oxide reacts with an alkene in a sample. To do so, I started by assuming the EWG on the dipole (nitrile oxide) and the EDG on the alkene in seeking the concerted pathways transition states as well as the possible intermediates that could be produced during the stepwise model of the reaction mechanism.

In another attempt, I supposed that assuming the electron withdrawing group on the dipole (nitrile oxide) and the electron donor group on the alkene in seeking the concerted pathway transition states as well as the possible intermediates that could be emerged in the process of stepwise reaction model, followed by designing the free-energy surface for both parallel reactions through using the results of *Gibbs* energy surfaces of all species.

Scheme 1. The possible regioisomers for 1,3-DC reaction of two different reaction entries: reactants (**A** – **B**) and reactants (**C** – **D**).



Computational Details

There have been several geometries which were presented and developed for each species in order to be used as input files, followed by being optimized in order to give the most possible states. Furthermore, more stable and metals table states were found as the transition states as well as intermediates.

The *Gaussian* 03 chemical quantum package [56] was used for performing all necessary calculations. In addition, the density functional theory procedure in B3LYP/6-311++ G(*d*,*p*) theoretical level was used for optimizing the structures [57 – 59]. The transition-state structures (TSs) were found by employing the synchronous transit-guided quasi-*Newton* (STQN) procedure [60][61]. The frequencies of each structure were extracted for calculating the thermodynamic energy in each state.

The intrinsic reaction coordinates (IRC) calculations verified the transition states [62][63]. In order to find the electrical charge of each atom in reactants, intermediate and transition states, the natural bond orbital (NBO) analysis was employed [64][65]. The related partial bond order was then defined through *Pauling* relation [66]. The synchronicity relation [67][68] was used to calculate the synchronicity [69][70] of the selected pathways.

The following formula was used in calculating global electron density transfer (GEDT) [71];

$$\mathrm{GEDT} = -/\Sigma qA/$$

where *qA* is the net *Mulliken* charge and the sum covered the entire atoms of dipolarophile species.

Results and Discussion

Two different reactants, namely reactants **A** – **B** and reactants **C** – **D** with different atomic numbers were designed in *Scheme 1*. In first stage, the reactants **A** – **B** geometrical system, representing trifluoromethyl vinyl and amino nitrile oxide system was drawn up, and optimized further to yield the most reliable geometry, followed by constructing product (**A**) and product (**B**) through changing the structures of reactants **A** – **B**.

The calculations led to the finding that the transition states for the concerted routes that links reactants **A** – **B** to the final products (**A**) and (**B**) as the regioisomers (see *Fig. 1*); however, any further attempts in locating an intermediate or transition states for the stepwise model failed. Thus, in case of **A** – **B** (trifluoromethyl vinyl and amino nitrile oxide) reaction system, it was only the concerted routes (TS (**Con-A**) and TS (**Con-B**)) that were possible rather than stepwise pathways.

In the second stage, reactants **C** – **D** with different atomic number than those of reactants **A** – **B** were designed. The transition states for the concreted routes, TS (**Con-C**) and TS (**Con-D**) were found after detecting the structures of products (**C**) and (**D**). However, in the stepwise pathways, an intermediate (Int (**C-1**)) was located only between the reactants **C** – **D** and product (**C**). Subsequently, the transition state TS (**C-1**) that links reactants **C** – **D** to this intermediate as well as transition state TS (**C-2**) linking the intermediate to product (**C**) were found and optimized after detecting and optimizing the intermediate (**C-1**) (*Fig. 1*).

As mentioned before, in reactants **A** – **B**, there are only concerted routes possible for the reaction. The relative *Gibbs* energy profile (*Fig. 2*) shows that transition states (**Con-A**) and (**Con-B**), with an energy surfaces of 15.78 kcal/mol and 16.72 kcal/mol, are in a close competition (the relative *Gibbs* energy surface of each species is given in *Table 1*).

As shown in *Fig. 2*, formation of TS (**Con-A**) (black line) which leads to the development of product (**A**) is slightly more favorable than TS (**Con-B**) (red line), which in turn leads to the emergence product (**B**). That is, yielding product (**A**) is kinetically favored compared to product (**B**), and in terms of thermodynamic preference, it is product (**B**) with a relative *Gibbs* free-energy surface of −33.44 kcal/mol, which proves to be more favored compared to product (**A**) with the relative *Gibbs* free energy of −31.69 kcal/mol. As mentioned before, I could not find any reliable intermediate between reactants **A** – **B** and product (**A**) or (**B**), which implies that perhaps

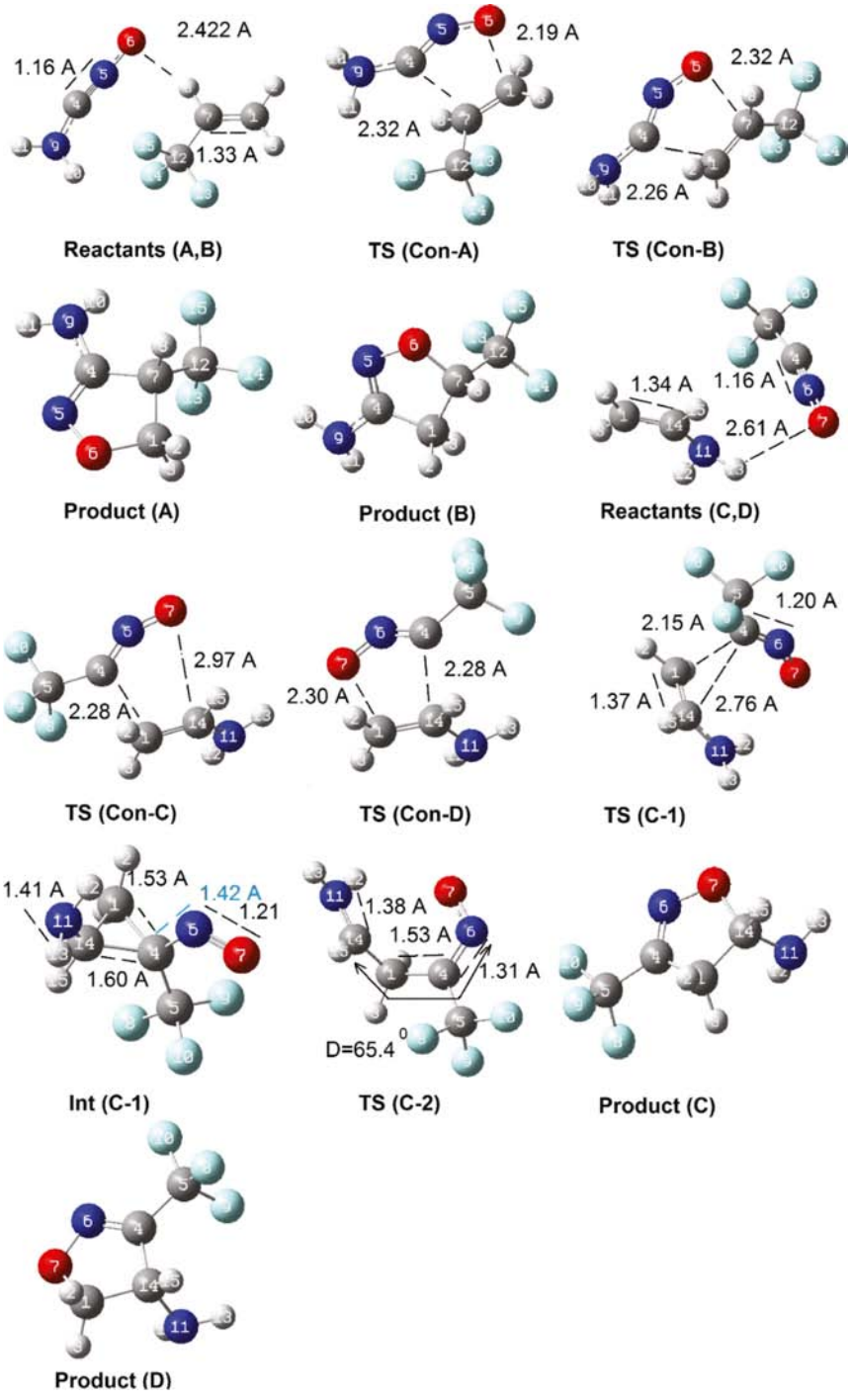


Fig. 1. The optimized structure for each possible species, emerged during the reaction coordinate, calculated at B3LYP/6-311++G(*d*,*p*) level.

this is not a true stepwise pathway. Therefore, when the EWG is placed on the alkene and the EDG is placed on the 1,3-dipole (nitrile oxide), the reaction mechanism will be concerted rather than stepwise (in the present reaction). Then, the EWG and EDG positions were altered between the alkene and nitrile oxide to see whether or not putting EWG on the nitrile oxide (1,3-dipole) and EDG on the alkene would lead the reaction mechanism to become stepwise.

As mentioned above, the only mechanism in the formation of product (**D**) is the concerted route TS (**D**) (Brown line in *Fig. 2*) with a *Gibbs* energy content of 25.34 kcal/mol that is significantly higher than both the concerted and stepwise pathways in leading to product (**C**).

Unlike route (**D**), there are two routes containing a stepwise and a concerted pathway between reactants and product I. The concerted transition state TS (**Con-C**) has

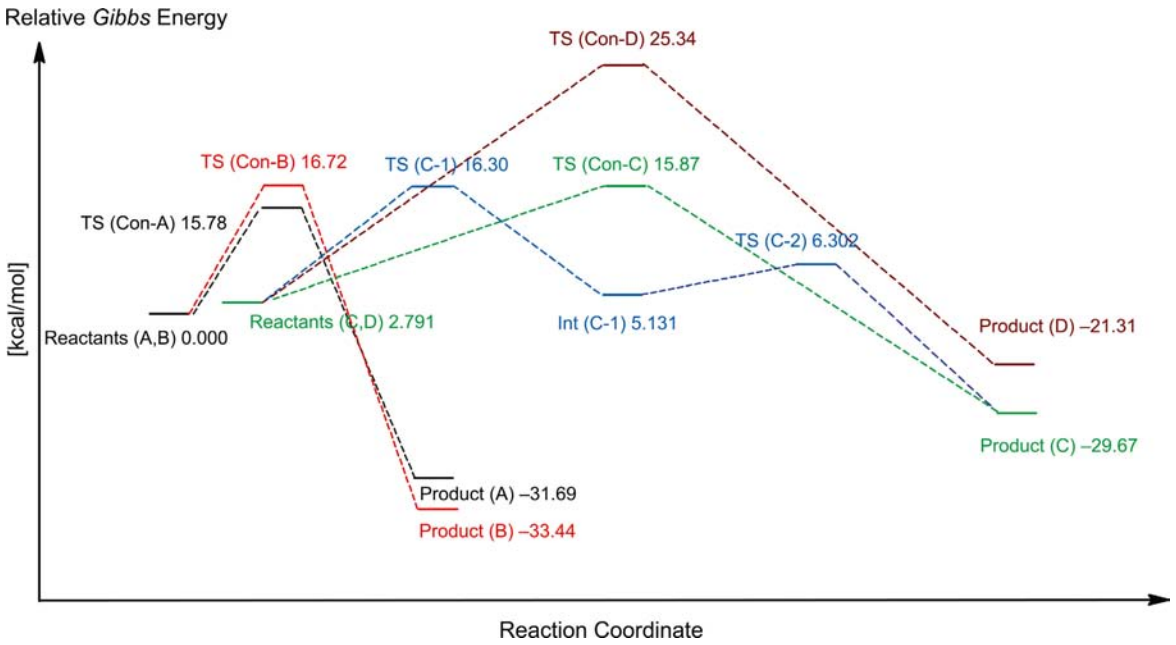


Fig. 2. The relative *Gibbs* free-energy surfaces of each species, for all of the possible reaction channels, calculated at B3LYP/6-311++G(*d*,p) level.

Table 1. The *Gibbs* free energy for each probable species calculated at B3LYP/6-311++G(*d*,*p*) level

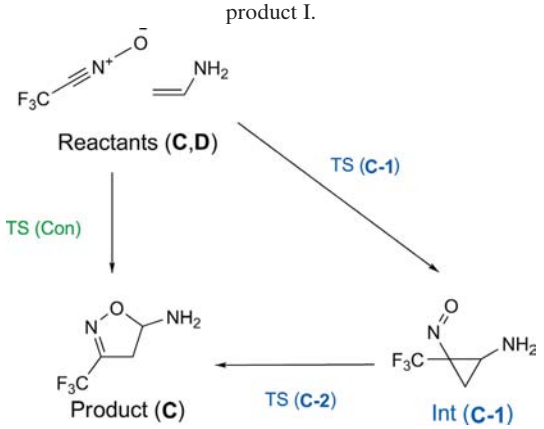
Species (**A** – **B**)	*Gibbs* Free Energy (*Hartree*)	Relative *Gibbs* Free Energy [kcal/mol]	Species (**C** – **D**)	*Gibbs* Free Energy (*Hartree*)	Relative *Gibbs* Free Energy [kcal/mol]
Reactants (**A** – **B**)	−639.716072	0.000	Reactants (**C** – **D**)	−639.711624	2.791
TS (**Con-A**)	−639.690913	15.78	TS (**Con-C**)	−639.690779	15.87
TS (**Con-B**)	−639.689424	16.72	TS (**Con-D**)	−639.675677	25.34
TS (**A-1**)	–	–	TS (**C-1**)	−639.690092	16.30
Int (**A-1**)	–	–	Int (**C-1**)	−639.707894	5.131
TS (**A-2**)	–	–	TS (**C-2**)	−639.706028	6.302
TS (**B-1**)	–	–	TS (**D-1**)	–	–
Int (**B-1**)	–	–	Int (**D-1**)	–	–
TS (**B-2**)	–	–	TS (**D-2**)	–	–
Product **A**	−639.766581	−31.69	Product **C**	−639.763363	−29.67
Product **B**	−639.769374	−33.44	Product **D**	−639.750033	−21.31

an energy content of 15.78 kcal/mol (green line) which is in close competition with the rate determining transition state of the stepwise pathway TS (**C-1**) with 16.30 kcal/mol *Gibbs* energy surface (blue line). It shows that there is a chance of developing stepwise mechanism when regiosiomer product **C** is being yielded. As it is clear, the stereospecificity of the reaction is lost when the mechanism of 1,3-DC reaction becomes stepwise. After losing energy, TS (**C-1**) transforms into intermediate (**C-1**) (5.131 kcal/mol) which has a three-member ring in its structure. The process continues as Int (**C-1**) receives energy and reaches to acyclic transition state TS (**C-2**) (6.302 kcal/mol) which contains an activation energy much lower than TS (**C-1**). *Scheme 2*, shows the schematic pathway of the stepwise model. Finally TS (**C-2**) loses energy and turns into product I (−29.67 kcal/mol).

According to the results, when the EWG is on the nitrile oxide (dipole) and the EDG is on the alkene (dipolarophile), the reaction mechanism for favorable product (product **C**) could be stepwise; however, when the EDG is on the nitrile oxide (dipole) and the EWG is on the alkene (dipolarophile), the reaction mechanism is clearly concerted for both regioisomers. Therefore, the significant energy difference between HOMO of dipole and LUMO of dipolarophile (or vice versa), may not be the only alternative that could lead to changing the nature of 1,3-DC reaction mechanism from concerted into stepwise. In this point, a comparison will be made between concreted and stepwise routes in the mechanism of yielding the product I.

The concerted mechanism for route C (green line in *Fig. 2*) begins by the formation of C(14)–O(7) and

Scheme 2. The stepwise model of the reaction route, leading to product I.



C(1)–C(4) σ bonds, and the C(1)–C(14) and C(4)–N(6) π bonds cleavage. The bond length for C(14)–O(7) and C(1)–C(4) σ bonds are 2.19 and 2.32 Å, respectively, with 1.37 and 1.20 Å for C(1)–C(14) and C(4)–N(6) π bonds in the transition-state (**Con-C**) structure. The *Pauling* relation [66] was used to determine the related partial bond orders of 0.084, 0.074, 0.895, and 0.861 values for **C**(14)–O(7), C(1)–C(4), C(1)–C(14), and C(4)–N(6), respectively. The partial bond order calculations indicated that C(1)–C(4) and C(14)–O(7) had 7.40% and 8.40% proximity amount to the transition state, whereas 10.5% and 13.9% of the π bond in C(1)–C(14) and C(4)–N(6) bonds, respectively, appeared to be broken. The synchronicity value of the concerted reaction route that leads to the development of product I was calculated by using the previously described synchronicity relation [67][68].

The values of 0.157, 1.52, 1.98, 0.333, and 0.158 were calculated for $\partial B_{(C1–C14)}$, $\partial B_{(C1–C4)}$, $\partial B_{(C1–O7)}$, $\partial B_{(C4–N6)}$, and $\partial B_{(N6–O7)}$, respectively. In addition, the value of 0.829 was calculated for the ∂B_{av}. The synchronicity for the selected pathway was also low (S_y = 0.416). It showed that the synchronicity value for this path is considerably low, and therefore, the possibility of a stepwise channel for this reaction route was increased.

In the stepwise pathway (blue line), the nonbonding electron pair of N(11) stimulates the electron charge of C(4)–C(14) π bond to attack to C(4) atom. Therefore, the N(11)–C(14) bond length decreases from 1.39 Å in reactants (**C** – **D**) to 1.34 Å in TS (**C-1**) structure (*Fig. 1*). Subsequently, the length of C(4)–C(14) π bond increases from 1.34 Å in reactants (**C** – **D**) to 1.37 Å in TS (**C-1**) structure. The terminal C-atom, C(4) receives more electron density and increases its electron charge from 0.102 in reactants (**C** – **D**) to 0.089 in TS (**C-1**) (*Table 2*). The electronic charge of C(4) attacks C(1) of nitrile oxide and increases it charge distribution from −0.502 in reactants (**C** – **D**) to −0.540 in TS (**C-1**). In continuation, one of the C(1)–N(6) π bonds breaks and the bond length increases from 1.16 Å in reactants (**C** – **D**) to 1.20 Å in TS (**C-1**). During the attack, the C(4)–C(1) new σ bond is formed (2.15 Å in TS (**C-1**)). After losing energy, TS (**C-1**) transforms to an asymmetric three-member cycle intermediate (Int (**C-1**)). In spite of having same atoms and same bonds which are used in the triangle, a considerable difference is found between the bond lengths of the ring in the extent that the bond of C(1)–C(4) and C(4)–C(14) shows to 1.53 and 1.60 Å long, respectively. It shows that the ring is relatively unstable and will be likely to open as an acyclic species. Receiving energy, the nonbonding electron pair of the N(11) causes the ring of intermediate (**C-1**) to open from side of C(4)–C(14) bond and lead to the emergence of the acyclic transition state TS (**C-2**).

Table 2. The NBO charges as distributed on Reactant (**C** – **D**), the intermediate and the selected transition States at the B3LYP/6-311++G(*d*,*p*) level of theory

	C(1)	C(4)	C(14)	N(6)	O(7)
Reactants (**C** – **D**)	−0.502	0.102	0.016	0.243	−0.357
TS (**C-1**)	−0.540	0.089	0.110	0.108	−0.441
Int (**C-1**)	−0.370	−0.074	0.031	0.066	−0.297
TS (**C-2**)	−0.503	−0.054	0.285	0.009	−0.552

The bond length of N(11)–C(14) reduces from 1.41 Å in the intermediate structure to 1.38 Å in the transition state (**C-2**), furthermore, the C(4)–C(14) σ bond perishes in the process. The second step of the five-member ring closing process goes through TS (**C-2**) and continues with the appearance of the final product I with a *Gibbs* energy content of −29.67 kcal/mol (*Figs 1* and *2*).

The results of *Table 3* show that GEDT amount increases during the reaction coordinate. According to the data, the calculated GEDT values for reactants, TS (**C-1**), Int (**C-1**), TS (**C-2**), and product are 0.000, −0.286, −0.345, −0.493, and −0.129, respectively. It indicates that the polar character is preferred compared to diradical nature for the species which emerge during route I. TS (**C-1**) is the first special species of the route I, and according to its GEDT amount (−0.286), it has a relatively polar character. For Int (**C-1**), the next species of the route, the polarity ratio increases due to its GEDT surface (−0345) and the maximum polarity appears for the second step transition state, TS (**C-2**), with a GEDT amount of −0.493. It seems both the low synchronicity value of TS (**C-Con**) (S_y = 0.416), and the relatively high GEDT surface of the stepwise pathway of the route I, are responsible to emerge a parallel stepwise route for path I.

Table 3. Global Electron Density Transfer (GEDT) of the selected species for the reaction of methyl nitrile oxide and tetraamino ethylene reaction at the B3LYP/6-311++G(*d*,*p*) level

Species[a])	Reactants	TS (**C-1**)	Int (**C-1**)	TS (**C-2**)	Product I
GEDT	0.000	−0.286	−0.345	−0.493	−0.129

[a]) The sum is taken over all of the atoms of dipolarophile.

Conclusion

For the reactants (**A** – **B**), as the amino (EDG) is on the dipole (nitrile oxide) and the triflouromethyl (EWG) is on the dipolarophile (alkene), both pathways leading to production of possible regioisomers (product **A** and **B**) occur through a single step concerted mechanism. However, for reactants (**C** – **D**), which triflouromethyl (EWG) is on the dipole and the amino (EDG) is on the dipolarophile, the pathway which leads to emergence of the kinetically and thermodynamically preferable product (product **C**) occurs through two parallel pathways (path (**Con-C**), shown by green line, and another two-step route, shown by blue line, that are in a highly close competition states). The concerted route proceeds across the concerted transition state, TS (**Con-C**) with an energy content of 15.78 kcal/mol, which is much closer to the rate determining step transition state of the stepwise route, TS (**C-1**) with an energy content of 16.30 kcal/mol.

These observations showed that when a researcher uses a nitrile oxide functionalized by an electron withdrawing group, such as triflouromethyl, and a dipolarophile (like alkene) functionalized by an electron donor group like amino, there will be a concern of the 1,3-DC reaction to become nonstereospecific. Lose of stereospecificity of 1,3-dipolar cycloaddition may lead to subsequent problems like emergence of poisonous enantiomer or diasteremomers during the synthesis of natural products.

The results of this work and some of the previous reports show, when 1,3-DC reaction of some of dipoles like nitrile oxide or 17-azomethine ylide is inverse electron demand (IED) dipolar reaction (HOMO of dipolarophile–LUMO of dipole), the possibility of the stepwise parallel pathway increases.

Conflict of Interests

The author declares that there is no conflict of interests.

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