Regioisomers of 1, 3-Dipolar Cycloadducts – A Computational Study

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ABSTRACT:

Theoretical investigation of regioisomers of 1,3-dipolar cycloadducts of pyridinium ylides using computational calculations to identify the stable regioisomer.

2. INTRODUCTION WITH REVIEW OF LITERATURE

1,3-Dipolar cycloaddition is a [3+2] cycloaddition reaction between a 1,3-dipole and a dipolarophile to form a five - membered ring.[1,2]
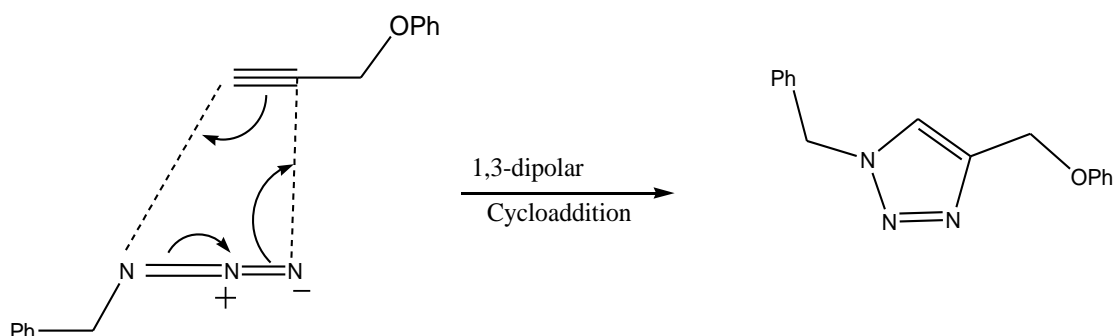
Scheme-1 1,3-dipolar cycloaddition between an organic azide and alkyne

Therefore 1,3- dipolar cycloaddition reaction is an important route to the regioselective and sterioselective synthesis of the five membered
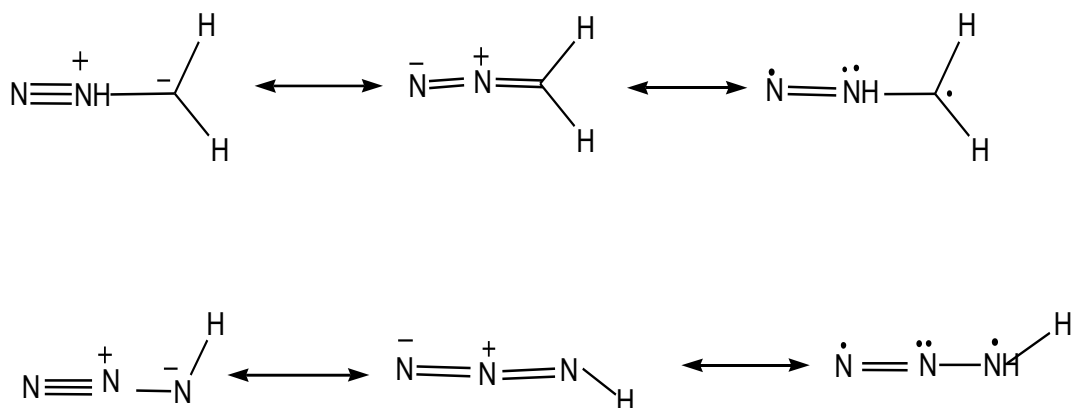
heterocyclic ring. Due to the regio and sterioselectivity of 1,3-dipolar cycloaddition reaction and mechanistic aspect, the 1,3-dipolar reaction are used as an important route for synthesis of five membered heterocycles and have interested both the academia and industry. 1,3-dipolar cycloaddition have an unusually large negative entropy of activation similar to that of the Diels-Alder reaction, suggesting that the transition state is highly ordered, which is a signature of concerted pericyclic reaction.

The 1,3-dipole reacts with the dipolarophile in a concerted and symmetry-allowed π_{4S}-π_{2S} fashion through a thermal six-electron Huckel aromatic transition state.

1,3-Dipole:

A 1,3-dipole is an organic molecule that can be represented as either an allyl-type or a propargyl / allenyl - type zwitter ionic octet / sextet structures. Both types of 1,3-dipoles share four electrons in the π-system over three atoms. The allyl-type is bent whereas the propargyl / allenyl-type is linear in geometry. Resonance structures can be drawn to delocalize both negative and positive charges onto *any* terminus of 1,3-dipole.

 A more accurate method to describe the electronic distribution on a 1,3-dipole is to assign the major resonance contributor based on experimental or theoretical data, such as dipole moment measurements or computations. For example, diazomethane bears the largest negative character at the *terminal* nitrogen atom, while hydrazoic acid bears the largest negative character at the *internal* nitrogen atom (shown in following fig.).
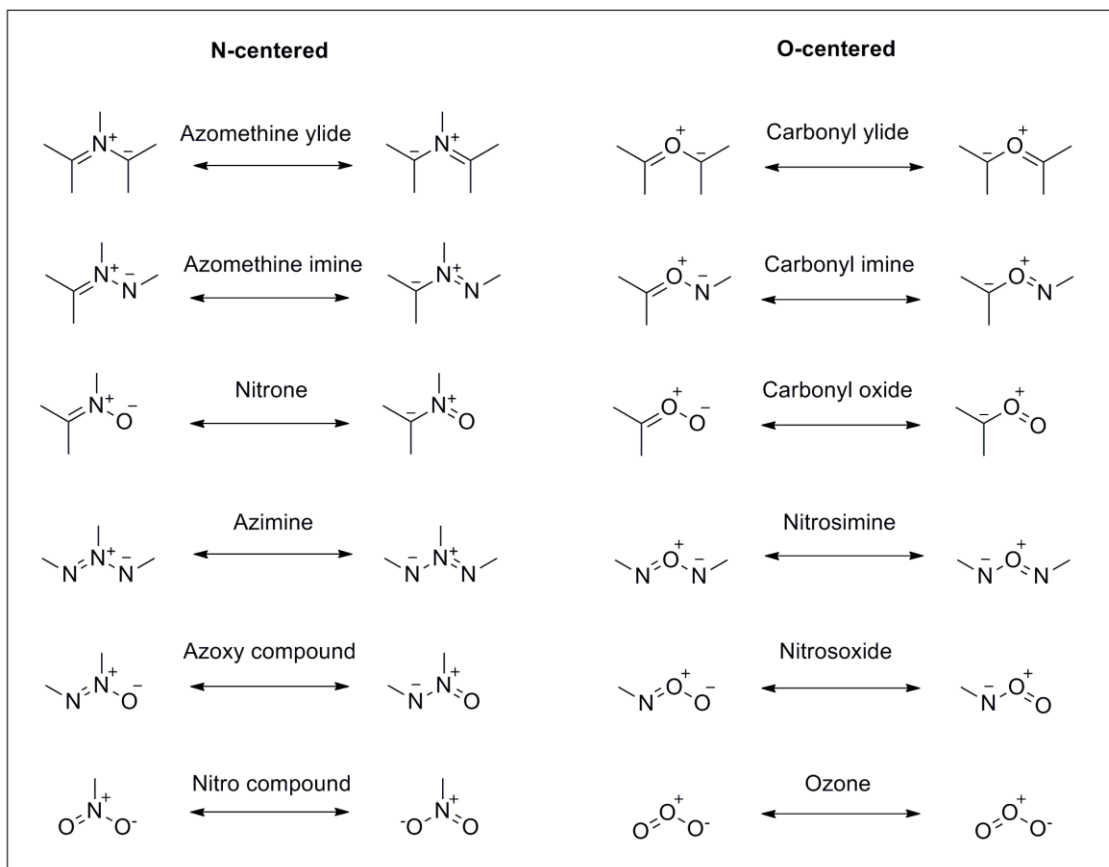
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Fig-1 Calculated Major resonatic structures of diazomethane and hydrazoic acid
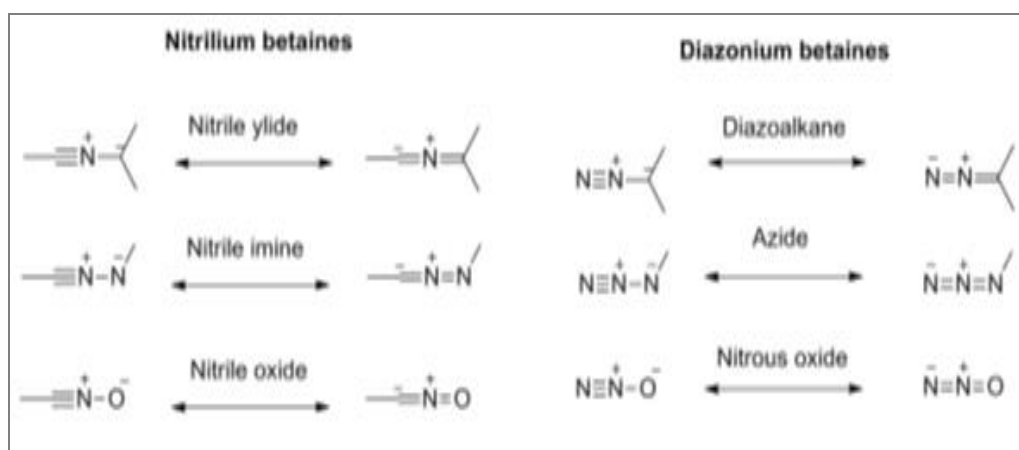
Classification of 1,3-dipole:

On the basis of the heteroatoms present in the dipole, they can be classified in following types –

**Table-1** Classification of 1,3-dipole

Allyl type

N-centered		O-centered	
	Azomethine ylide		Carbonyl ylide
	Azomethine imine		Carbonyl imine
	Nitrone		Carbonyl oxide
	Azimine		Nitrosimine
	Azoxy compound		Nitrosoxide
	Nitro compound		Ozone

Allenyl type

Nitrilium betaines		Diazonium betaines	
	Nitrile ylide		Diazoalkane
	Nitrile imine		Azide
	Nitrile oxide		Nitrous oxide

Dipolarophile:

The most commonly used dipolarophiles are alkenes and alkynes. Heteroatom-containing dipolarophiles such as carbonyls and imines can also undergo 1,3-dipolar cycloaddition. Other examples of dipolarophiles include fullerenes and nanotubes, which can undergo 1,3-dipolar cycloaddition with azomethine ylide.
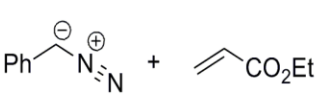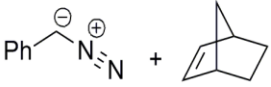
- More polarizable dipolarophiles are more reactive because diffuse electron clouds are better suited to initiate the flow of electrons.

- Dipolarophiles with high angular strain are more reactive due to increased energy of the ground state.

- Increased steric hindrance in the transition state as a result of unhindered reactants dramatically lowers the reaction rate.

- Hetero-dipolarophiles add more slowly, if at all, compared to C, C-dipolarophiles due to a lower gain in sigma bond energy to offset the loss of a pi bond during the transition state.

- Isomerism of the dipolarophile affects reaction rate due to steric effects. *Trans*-isomers are more reactive (*trans*-stilbene adds to diphenyl (nitrile imide) 27 times faster than *cis*-stilbene) because during the reaction, the 120° bond angle shrinks to 109°, bringing eclipsing *cis*-substituents towards each other for increased steric clash.
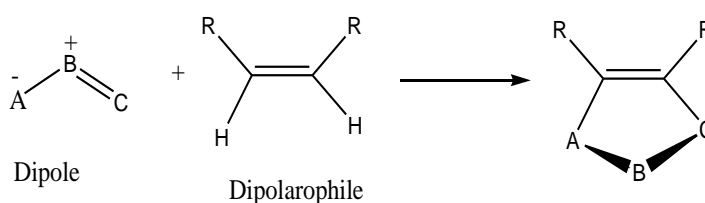
Scheme-2 1,3-dipolar cyclisation of alkene dipolarophile

1,3-Dipolar cycloaddition reactions show very little effect of solvent polarity, in line with the pericyclic mechanism (where polarity does not change much in going from the reactant to the transition state) because both, the reactant and its resonating structure are generally non polar. For example, the rate of reaction between phenyl diazomethane and ethyl acrylate or norbornene (see table below) changes only slightly, upon varying solvents from cyclohexane to methanol.

**Table-2** Solvent effect on rate of 1,3-dipolar reaction

Solvent	$Ph\!-\!\overset{\ominus}{CH}\!-\!\overset{\oplus}{N}\!\equiv\!N$ + CO_2Et	$Ph\!-\!\overset{\ominus}{CH}\!-\!\overset{\oplus}{N}\!\equiv\!N$ + (norbornene)
	relative k_1	relative k_2
cyclohexane (non-polar)	1	1
dioxane	1.48	0.82
DMF	3.16	1.06
methanol (polar)	5.34	0.98

MECHANISM:

Originally two proposals were presented to describe   the mechanism of the 1,3-cycloaddition reaction:

  i.   Concerted pericyclic mechanism (proposed by Huisgen)[3]
  ii. Step-wise diradical mechanism (proposed by Firestone)[4]

Though, there has been a debate on the mechanism of 1,3-dipolar reaction, the involvement of concerted mechanism (Scheme - 3) is now generally accepted.[5]
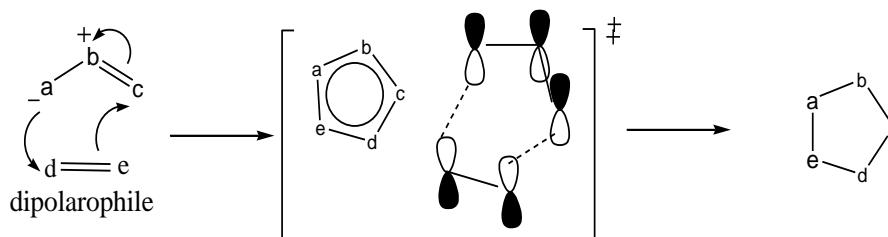
Scheme-3 Concerted mechanism and orbital interaction of 1,3-dipolar reaction

The mechanism of 1,3-dipolar cycloaddition reaction is considered to be concentered pericyclic cycloaddition, which was proposed by "Rolf – Huisgen."

Huisgen Cycloaddition - regioselectivity of 1,3-dipolar cycloadducts :

The Huisgen Cycloaddition is the reaction of a dipolarophile with a 1,3-dipolar compound that leads to 5- membered heterocycles.[6,7]

Examples of dipolarophiles are alkenes and alkynes and molecules that possess related heteroatom functional groups (such as carbonyls and nitriles). 1,3-Dipolar compounds contain one or more heteroatoms and can be described as having at least one Mesomeric structure that represents a charged dipole.
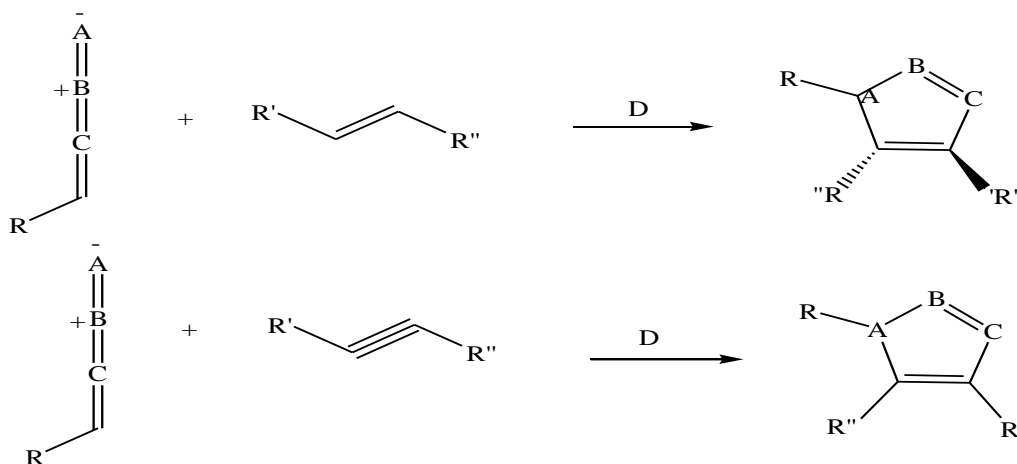
Scheme-4 Reaction of dipolarophile with charged 1,3-dipole

Regioselectivity in 1,3-dipolar cycloadducts:

A regioselective reaction is one in which one direction of bond making or breaking occurs preferentially over other possible direction. Such as, the 1,3-dipolar reaction of pyridinium N-ylide with unsymmetrical dipolarophile may take place via two different approaching orientation of diolarophile to ylide.
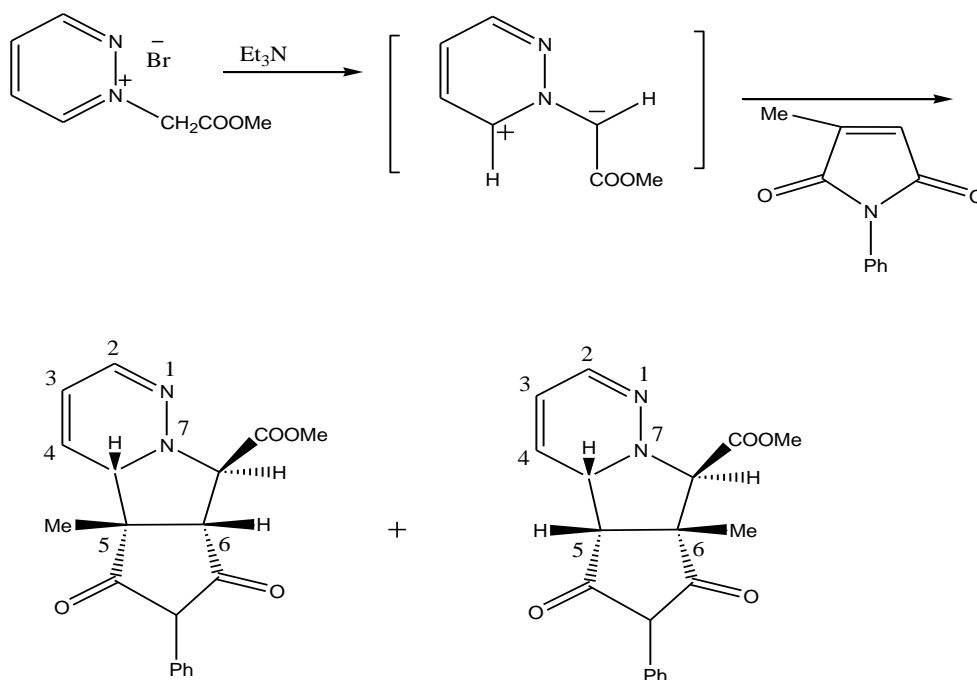
Scheme-5 Regioselectivity in cycloaddition of pyridazinium N-ylide

The regioselectivity in the cycloaddition of pyridazinium N-ylides is determined by the nature of substituents attached to the ylidic carbanion. Thus, when the substituent is Ar, then the reaction is completely regioselective. Whereas, with COOMe substituent a mixture of regioisomers is obtained. From

the stereochemistry of the compound, it is possible to conclude that in the cycloaddition reaction of the pyridinium ylides participate only in the anti-forms.

Different reaction path modes of 1,3-dipole can be explained by use of the following FMO approach.

Frontier Molecular Orbital Theory:

The 1,3-dipole reacts with the dipolarophile in a concerted, and symmetry allowed $\pi_{4s} + \pi_{2s}$ through a thermal six-electron Huckel aromatic transition state.

1,3-Dipolar cycloaddition reaction obey the Dewar-Zimmerman rules and the Woodward–Hoffmann rules. In the Dewar-Zimmerman treatment, the reaction proceeds through a 5-center, zero node, 6-electron Huckel transition state. Whereas, In the Woodward-Hoffmann treatment, frontier molecular orbital of the 1,3-dipole and the dipolarophile interact in $\pi_{4s} + \pi_{2s}$ manner for an allowed reaction.

On the basis of the interaction of frontier molecular orbital and energy gap between the HOMO and LUMO of both reactants (dipole and dipolarophile), 1,3-dipolar reaction is classified in three types.[8-11] The dominant path way is the one which possesses the smallest HOMO-LUMO energy gap.

Type I - blue path
Type II - mix of both blue and red paths
Type III - red path
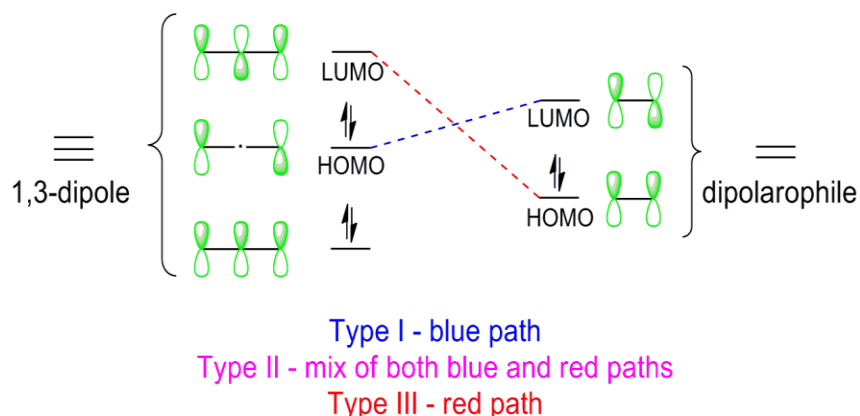
Fig-2 The three types of FMO approaches

Type I

The dipole has a high-lying HOMO which overlaps with LUMO of the dipolarophile. A dipole of this class is referred to as a HOMO-controlled dipole or a nucleophilic dipole, which includes azomethine ylide, carbonyl ylide, nitrile ylide, azomethine imine, carbonyl imine and diazo alkane. These dipoles add to electrophilic alkenes readily. Electron-withdrawing groups (EWG) on the dipolarophile would accelerate the reaction by lowering the LUMO, while electron-donating groups (EDG) would decelerate the reaction by raising the HOMO.

Type II

HOMO of the dipole can pair with LUMO of the dipolarophile; alternatively, HOMO of the dipolarophile can pair with LUMO of the dipole. This two-way interaction arises because the energy gap in either direction is similar. A dipole of this class is referred to as a HOMO-LUMO controlled dipole or an ambiphilic dipole, which includes nitrile imide, nitrone, carbonyl oxide, nitrile oxide, and azide.

Type III

The dipole has a low-lying LUMO which overlaps with HOMO of the dipolarophile (indicated by red dashed lines in the diagram). A dipole of this class is referred to as a LUMO-controlled dipole or an electrophilic dipole, which includes nitrous oxide and ozone.

3. EXPERIMENTAL DETAILS (COMPUTATIONAL METHODS)

Computational Chemistry is generally the applicative part of chemical, mathematical and computing ability to solve the important chemical problems. Computational chemistry is very important and easy way to investigate compounds that are too difficult to find or too expensive. It uses computers to   generate   important and useful   information such as properties of molecules or different chemical behavior.[12]

It also helps chemists make predictions before running the actual experiments so that they can be better prepared for making observations. The basic Schrodinger equation is used for most of the computational chemistry scientist by the use of computational chemistry we can calculate:

- ➢ Geometry optimizations.
- ➢ Electronic structure determinations.
- ➢ Thermodynamic calculations: heat of reaction, energy of activation.
- ➢ Rate constant for chemical reactions.
- ➢ Potential energy surface.
- ➢ Electron and charge distributions.

➢   Transition structures.

➢   Frequency calculations.

To solve the chemistry problems computational quantum chemistry is used by the numerical computation of molecular electronic structure by - *Ab-initio*, semi-empirical or molecular mechanics techniques.[13,14]

I.   **Molecular mechanics :** uses classical   physics to explain the environment of atoms and molecular.[15]

II.   **Semi-empirical techniques:** uses an   approximation   digit from the experimental data.

III.   *Ab-initio:* is group of methods in which molecular structures can be calculated by using the Schrodinger equation.[16]

Methodology used in each category of above mentioned method:

I. Molecular mechanics:

This method uses classical mechanics to model molecular system.[17]
It can be used   to study micro molecules as well as macromolecules.

Molecular mechanics methods have the following properties:

• Each atom is simulated as a single particle.

• Each particle is assigned radius polarizability, and a constant charge.

• Bonded   interactions are treated as "SPRINGS" with an equilibrium distance   equal to the experimental or   calculated bond length .[18-20]

II.   Semi-empirical techniques:

It is based   on the "HARTREE-FOCK FORMALISM" and it also contain many approximation and final obtain some parameters   from

empirical data. These data are very important for studying large molecules in the computational chemistry.

In the frame work of the Hartree-Fock calculation, some information are completely omitted. In order to correct for this loss, Semi-empirical methods are parameterized, that is their results are fitted by a set of parameters, normally in such a way as to produce results that best agree with experimental data, but sometimes to agree with *Ab-initio* results. The use of empirical parameters appears to allow some inclusion of electron co-relation effect in to the methods.[21,22]

Semi-empirical calculations are much faster than their *Ab-initio* method. Because of the use of the zero differential overlap approximation.[23,24] Empirical research is a way of gaining knowledge by means of direct and indirect observation or experience. As with empirical methods, we can distinguish methods that are:

- Restricted to π-electrons. These methods are used for the calculation of electronically rich excited states of polyenes, for both cyclic and linear. These methods, such as the Pariser- Parr –Pople method (PPP), can provide good estimates of the π-electronic excited states, when parameterized well.[25,26]
- Restricted to all valence electrons. These methods can be grouped in to several groups:
- Methods like ZINDO and SINDO, whose primary aim is to calculate excited states and hence predict electronic spectra.[27,28]
- Methods whose primary aim is to predict the geometries of coordination compounds, such as AMI/Sparkle, available for lanthanide complexes.

- Method that are in the MOPAC, AMPAC, and SPARTAN computer programs originally from the group of Michael Dewar.[29] These are MINDO, MNDO,[30] AMI [31] PM3[32], RMI[33] PN6[34] and SAMI.

- Method such as CNDO/2, INDO, and NDDO that were introduced by John Pople.[35-37] The implementations aimed to fit, not experiment, but *Ab-intio* minimum basis set results. These methods are now rarely used   but the methodology is often the basis of later methods.

III. *Ab-initio* method:

This method directly derived from theoretical principles, with no Inclusion of experimental   data, are called *Ab- initio* method.[38,39] This does not imply that the   solution is an exact   one; they are all approximate   quantum mechanical calculations.[40] It   do not include any empirical or semi- empirical parameters in their equation. The simplest   type of *Ab-initio* electronic structure calculation is the Hartree-Fock, an extension of molecular orbital theory in which the correlated electron-electron   repulsion is not specifically taken but its average effect is included in the calculation.[41,42]

IV. Density functional method (DFT):

DFT methods are often considered to be *Ab-initio* method for determining the molecular electronic structure, even though many of the most common functional use parameters derived from empirical data or from more complex calculations. In DFT, the total energy is express in terms of the total one- electron density.[43-45] DFT is used in physics, chemistry, and materials   science for investigation the electronic structure of many- body system the particularly in atoms molecules, and condensed phases.[46,47] DFT   is a computational quantum mechanical modeling method. By the help of this   theory, the   property of many   electron system can be determined   by using functional group, which   in this

case are the spatially dependent electron density. Therefore, the name density functional theory arises from the use of functional of the electron density.[48-50] DFT is the most popular and versatile method.

First of all the structure of regioisomers of pyridinium ylide obtainable by the reaction with acrylonitrile regioisomer-1 and regioisomer-2, (shown in Scheme 6) is drawn with the Gauss view software and input file is prepared. Calculation is done with Gaussian 98 software at different levels such as Semi-empirical, Ab-initio, etc. to get stable regioisomers. Two suitable regioisomers are taken as input to know which one is more stable. The Chemcraft software was used to show the result of quantum mechanical calculation.
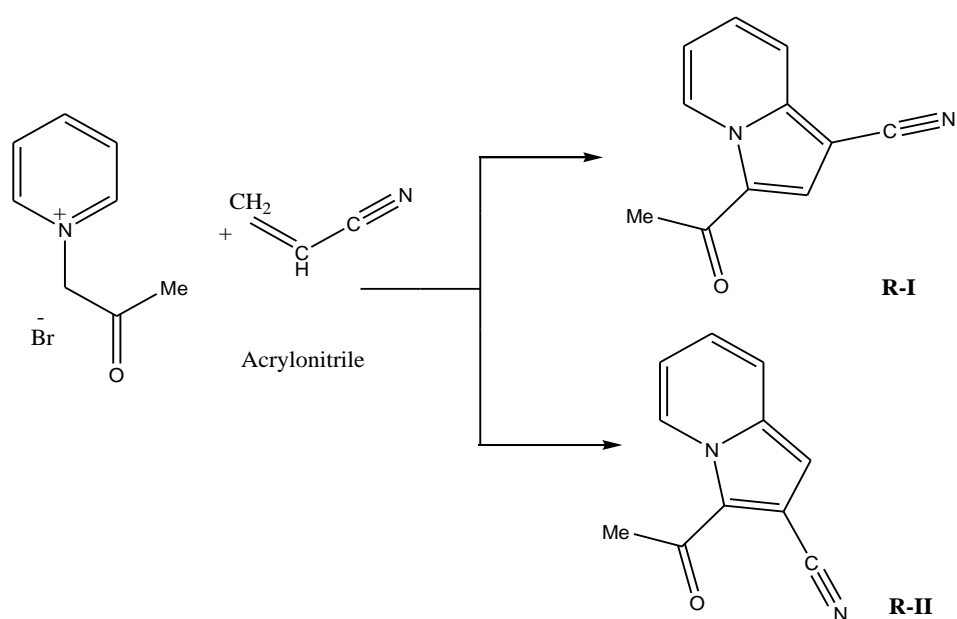
Scheme-6 1,3-dipolar reaction between pyridinium salt and acrylonitrile

4. RESULTS AND DISCUSSION

The calculation of optimized energy of the above two regioisomers were done by the changing the different calculation level to find out, which regioisomer is most stable. On the reaction of pyridinium ylide with acrylonitrile two

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product are possible, one having less energy i.e. more stable product but the other having higher total energy, less stable product.

Table-3 - Energy of regioisomers on optimization at HF level

Regioisomer	Optimization energy	Zero-point energy (Hartree)	Sum of electronic and zero-point energies (in a.u.)	(Relative energy) Kcal/mol
R-I	-598.5180124	.219054	-598.2989584	0
R-II	-598.5173278	.219030	-598.2982978	0.4141562

Energy of regioisomers on optimization at B3LYP level: **(Table-4)**

Regioisomer	Optimization energy	Zero-point energy (Hartree)	Sum of electronic and zero-point energies (in a.u.)	Relative energy (kcal/mol)
R-I	-606.4848422	0.187823	-606.297019 (more stable)	0
R-II	-606.48301	0.187792	-606.29522 (less stable)	0.934989

The regioisomer-1 is more stable regioisomer than regioisomer-2, as evident from energy calculation at different levels according above mentioned.

Optimized geometries at B3LYP level are presented in following figures:
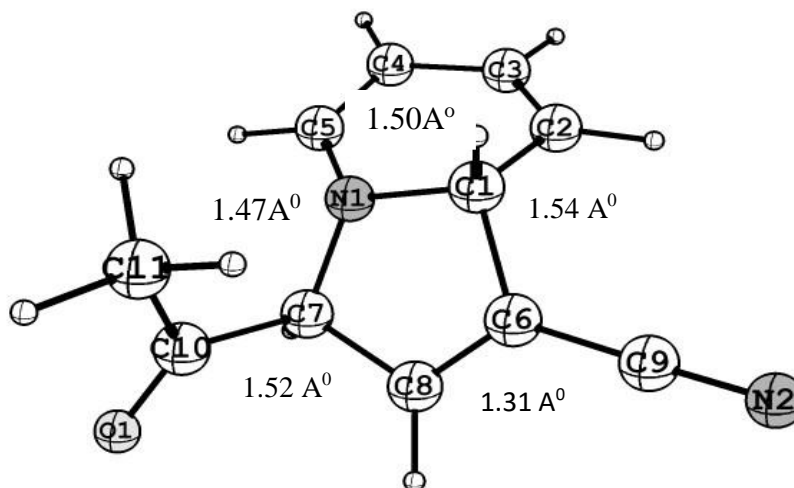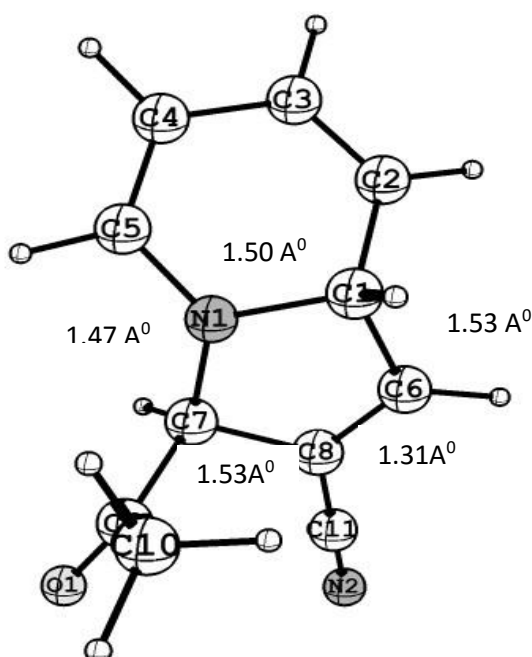
Fig-4   Regioisomer-I

Fig-5 Regioisomers-II

Calculated bond lengths and bond angles are given in tables 5-8 at different levels.

Bond length and bond-angle of regioisomers at HF level

Table-5 Calculated Bond length (Å) of two regioisomers

Bond length	R I	R II
$R(C_1\text{-}C_2)$	1.530	1.531
$R(C_2\text{-}C_3)$	1.314	1.314
$R(C_3\text{-}C_4)$	1.479	1.479
$R(C_4\text{-}C_5)$	1.319	1.319
$R(C_5\text{-}N_1)$	1.434	1.434
$R(N_1\text{-}C_7)$	1.496	1.496
$R(C_1\text{-}C_6)$	1.540	1.529
$R(C_6\text{-}C_8)$	1.314	1.314
$R(C_7\text{-}C_8)$	1.524	1.534
$R(C_1\text{-}H)$	1.100	1.101
$R(C_2\text{-}H)$	1.082	1.082
$R(C_3\text{-}H)$	1.082	1.083
$R(C_4\text{-}H)$	1.079	1.079
$R(C_5\text{-}H)$	1.086	1.086
$R(C_8\text{-}H)$	1.082	1.082

Table-6 Calculated Bond angle (in degrees) of regioisomers

Bond angle	R I	R II
C_1-N_1-C_5	30.3	117.8
N_1-C_5-C_4	123.8	26.7
C_5-C_4-C_3	31.9	119.9
C_4-C_3-C_2	120.8	120.8
C_3-C_2-C_1	121.7	121.7
N_1-C_1-C_2	114.2	114.2
N_1-C_1-C_6	38.0	38.9
C_1-C_6-C_8	111.8	111.7
C_6-C_8-C_7	111.7	111.9
C_8-C_7-N_1	103.4	102.8
C_7-N_1-C_1	110.3	110.3
C_{11}-C_{10}-O	31.9	24.7
C_7-$C_{10}C_{11}$	32.2	33.7

Bond length and bond-angle of regioisomers at B3YLP level

Table -7 Calculated Bond length (Å) of two regioisomers

Bond length	R I	R II
$R(N_1$-$C_1)$	1.502	1.504
$R(C_1$-$C_2)$	1.517	1.521

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$R(C_2-C_3)$	1.343	1.344
$R(C_3-C_4)$	1.457	1.457
$R(C_4-C_5)$	1.351	1.352
$R(C_5-N_1)$	1.393	1.391
$R(C_1-C_6)$	1.538	1.515
$R(C_6-C_8)$	1.339	1.340
$R(C_8-C_7)$	1.516	1.535
$R(C_7-N_1)$	1.474	1.474
$R(C_8-H_7)$	1.080	1.080
$R(C_3-H_1)$	1.084	1.081
$R(C_4-H_3)$	1.080	1.080
$R(C_5-H_4)$	1.085	1.085
$R(C_1-H_5)$	1.103	1.104
$R(C_2-H_2)$	1.084	1.084
$R(C_7-H_6)$	1.096	1.095

Table-8 Calculated bond angle (in degrees) of two regioisomers

Bond angle	R I	R II
N_1-C_1-C_2	111.3	110.8
C_1-C_2-C_3	120.2	119.7
C_2-C_3-C_4	121.5	121.6
C_3-C_4-C_5	118.7	118.7
C_4-C_5-N_1	122.0	121.8
C_5-N_1-C_1	119.9	119.8
N_1-C_1-C_6	101.0	101.5
C_1-C_6-C_8	111.7	112.1
C_6-C_8-C_7	111.7	111.6
C_8-C_7-N_1	102.6	101.7
C_7-N_1-C_1	112.3	112.6
C_8-C_7-H_6	111.2	110.9

5. CONCLUSION

   1,3-Dipolar cycloaddition of pyridinium N-ylide with alkene dipolarophile has

been investigated at different computational level. In all calculation, the energy

of Regioisomer-I is lower than Regioisomer-II.

According to energy calculation (table-3 and 4) the energy difference between

regioisomer-I and II comes out to be 0.00066 kcal/mol (at HF level) and 0.9349

kcal/mol (at B3LYP level), so it can be concluded that Regioisomer-I is more stable than Regioisomer-II.

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