Regio and stereoselectivity in ionic cycloadditions†

VENKATACHALAM TAMILMANI, DURAIRAJAN SENTHILNATHAN and
PONNAMBALAM VENUVANALINGAM*
School of Chemistry, Bharathidasan University, Tiruchirappalli 620 024
e-mail: venuvanalingam@yahoo.com

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Abstract. Acridizinium cation (ACR) and 2,3-dimethylisoquinolinium ion (DMIQ) undergo \([2 + 4^+\)] addition with dienophiles methyl vinyl ether (MVE) and propylene (PY) and the addition takes place across the diene unit containing the cationic centre and the dienophile acts as the electron donor. These reactions have two regiochemical paths and in each of them two possible stereo adducts could be formed. DFT calculations performed at B3LYP/6-31G(d) level have shown that the reactions pass through concerted mechanism and the TSs are highly asynchronous. Methoxy group in the dienophile can take up \textit{cis} or \textit{trans} orientation with respect to the double bond and in that \textit{trans} orientation of the methoxy group is preferred. Calculations further show that \textit{syn} \textit{2} adduct is kinetically and thermodynamically more favoured in both the reactions in excellent agreement with the experimental observations. ACR is found to be more reactive than DMIQ as a diene and as a dienophile MVE is found to be more reactive than PY. Computed bond orders establish that the \textit{syn} \textit{2} transition states are the most ‘reactant’ like. Though the reactions have both electrostatic control and frontier orbital control the former dominates in the initial stages of the reaction.

Keywords. Stereoselectivity; ionic cycloaddition; density functional theory; acridizinium ion; methyl vinyl ether; 2,3-dimethylisoquinolininium ion.

1. Introduction

In polar or ionic cycloadditions both or either of the addends is ionic, and they can be either a cation or anion but anionic cycloadditions are very rare. When both the addends are neutral partners, the reaction generally prefers concerted mechanism and introduction of electronegative atoms like, oxygen, nitrogen in the reaction site induces asynchronicity in the transition states. In dipolar or ionic cycloadditions mechanistic cross over from concerted to step-wise path has been observed.\(^1\) The effect of heteroatom substitution in ionic addends could have a different effect and have not been investigated before, specifically in terms of mechanism and this has been the main motivation for this work. In ionic cycloadditions, in addition to frontier orbital control, electrostatic control could have a significant influence and affect the course of the reaction. Further cationic addends have a low-lying LUMO and anionic addends have a high-lying HOMO and this enhances the reactivity of these addends towards addition. This reaction principle has been used in the synthesis of many carbocycles, heterocycles, less reactive \(\pi\) systems and heteromultiple bonds.\(^2\) ACR and DMIQ have been specifically chosen here as they have been reported to undergo 1,4 as cycloadditions with some dienophiles.\(^3,10\) Bradsher and co-workers have shown that ACR undergoes \([2 + 4^+\)] DA reaction with MVE and PY to give stereoselective isomer which is \textit{syn} to the phenylene ring\(^8,10\) with the methoxy/methyl substituent maximally displaced from ring nitrogen. Further, they have investigated the reaction of DMIQ with CP\(^5\) and MVE\(^4,7\) for the understanding of high regio and stereoselectivity. In the ionic cycloaddition of ACR, stereoselectivity,\(^5\) \textit{peri} strain\(^6\) and electrostatic repulsion\(^7\) play an important role. We have modelled DMIQ–CP reaction and analysed the role of electrostatic control on this reaction.\(^11\) In the case of DMIQ reaction with MVE, 97% of stereoselective adduct has the methoxyl group directed over the phenylene moiety (\textit{syn} \textit{2}). These interesting observations have also stimulated us to explore mechanism of the ACR/DMIQ reactions with MVE/ PY, inves-

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\(^*\)For correspondence
Scheme 1. Possible reaction pathways for the \([2 + 4^+]\) reaction between PY, MVE and ACRs. Trans and cis orientations of MVE is given in the inset.

Figure 1. Free energy profile for the \([2 + 4^+]\) reaction of ACR with MVE (a) cis orientation, (b) trans orientation.

tigate further the factors that influence the reaction pathway and its regio and stereoselectivity.

2. Computational details

Density functional theory (DFT) calculations have been performed using B3LYP method with 6-31G(d) basis set. The optimizations were carried out using the Berny\textsuperscript{12} analytical gradient optimization method. Stationary points have been located and characterized by computing the vibrational frequencies for reactants, products and transition states. In all cases, reactants and products had all real frequencies and the transition states had a single imaginary frequency.
Figure 2. Optimized transition state geometries for the [2 + 4+] reaction between MVE (trans orientation) and ACR along with degree of asynchronicity (α), quantum of charge transfer (q_{ct}) and dipole moment (μ).

Transition states have been further confirmed by animating the imaginary frequency in MOLDEN. The intrinsic reaction coordinate (IRC) paths were traced to check the energy profiles connecting each transition structure to the two associated minima of the proposed mechanism by using the second-order González–Schlegel integration method.\textsuperscript{13,14} Free energy and enthalpy calculations have been done using thermochemical calculations. All computations have been carried out using Gaussian 03, Revision B.01 and C.01.\textsuperscript{15} Bond orders have been calculated from the Wiberg\textsuperscript{16} indices using NBO analysis and from
them bond formation index $BF_i$ and bond cleavage index $BC_i$ have been calculated as described by Manoharan and Venuvanalingam.  

## 3. Results and discussion

### 3.1 Acridizinium ion as a diene

The detailed mechanistic scheme for the [2 + 4] addition of MVE with ACR is given in scheme 1 and free energy profile is presented in figure 1. The optimized geometries are depicted in figure 2. Computed thermodynamic data and FOE gap values (eV) are presented in table 1. Bond order analysis data for the reaction of ACR with MVE and PY are given in table 2. ACR has three diene units and therefore, in principle, the cycloaddition can undergo across any of these units but C6–N5–C11–C12 unit forms the LUMO and therefore the reaction undergoes prefer-
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Figure 3. Structures of the species which lie at ‘half way’ between the TS and product: Pathways for the [2 + 4] DA reactions.

Figure 4. Free energy profile for the [2 + 4'] reaction between (a) PY-ACR and (b) PY-DMIQ.

3.1a Reaction between acridizinium ion and methyl vinyl ether: Computed FOE gap values (table 1) show that this is an inverse electron demand type reaction and this is due to the fact that the diene is a cation and has a very low-lying LUMO and the calculated $q_e$ (figure 2) values indicate the transfer of charge from dienophile to diene. Scheme 1 shows that four pathways are open for this reaction and they are described as syn 1, anti 1, syn 2 and anti 2 depending on methoxy group orientation with respect to the phenylene ring and its disposition towards C6 atoms. Regio 1 path will have two stereo adducts syn 1 and anti 1 and regio 2 path will have two stereo adducts syn 2 and anti 2. Further, the...
paths alone could be located and all the transition 
tive additions have been attempted but concerted 
as shown in (inset) scheme 1. Then, there are eight 
anti
syn
1
TS
31
anti
2
TS
32
syn
1
TS
37
anti
1
TS
36
syn
2
TS
24
anti
2
TS
24
PY–ACR reaction 

<table>
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<th>BF&lt;sub&gt;i&lt;/sub&gt;</th>
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| MVE–ACR reaction 
| Cis orientation 
| syn 1 TS | 43.18 | 57.82 |
| anti 1 TS | 40.65 | 52.18 |
| syn 2 TS | 5.62 | 11.28 |
| anti 2 TS | 4.62 | 11.16 |
| Trans orientation 
| syn 1 TS | 42.55 | 59.32 |
| anti 1 TS | 41.17 | 52.32 |
| syn 2 TS | 6.41 | 10.36 |
| anti 2 TS | 46.36 | 11.26 |
| PY–ACR reaction 
| syn 1 TS | 31.57 | 31.30 |
| anti 1 TS | 31.59 | 31.91 |
| syn 2 TS | 19.60 | 21.03 |
| anti 2 TS | 19.95 | 21.53 |

methoxyl group in dienophile can take up two orient-
tions, cis or trans with respect to the double bond 
as shown in (inset) scheme 1. Then, there are eight 
stereo adducts possible for this reaction. Both con-
certed and step-wise paths for all these stereoas-
selective additions have been attempted but concerted 
paths alone could be located and all the transition 
structures are found to be asynchronous as reflected 
in the ω<sup>20</sup> values (figure 1) and this is in view of 
asymmetry in the structure of diene and dienophile. 
In all these eight possible paths C6–C13 bond is found 
to be shorter than C11–C14 in the concerted TS and 
this gives clear evidence that in the beginning phase 
of the reaction electrostatic control is dominant. C6
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Figure 5. Optimized transition state geometries for the [2 + 4'] reaction between PY and ACR along with degree of asynchronicity ($\alpha$), quantum of charge transfer ($q_{ct}$) and dipole moment ($\mu$).

is more electropositive and interacts strongly with the negative end of the dienophile and forms the bond quickly over the other forming bond C11–C14. The latter bond develops at a slower pace and this leads to asynchronous TSs. The computed free energies of activation data presented in table 1 show that the trans orientation is more favoured compared to cis orientation by approximately 5 kcal/mol. So, further discussions are restricted to trans adducts.

The free energy of activation for the anti 1, syn 1, anti 2 and syn 2 reactions are found to be 29.8, 29.9, 23.6 and 19.0 kcal/mol respectively and this clearly indicates that syn 2 adduct is the most favoured one from kinetic considerations. Computed enthalpy of activation of syn 2 is 10.6 kcal/mol and on comparison with all the adducts entropy loss is found to be less in syn 2. This is in good agreement with the report of Bradsher and co-workers.8 IRC calculations are found to connect the reactant and the corresponding products. When newly forming bonds mature at different rates asynchronous structure forms but this has to be carefully distinguished from TSs leading to step-wise intermediates. This can be done by moving the TS ‘forward’ along intrinsic reaction coordinate (IRC). If the weaker bond starts growing in the forward direction the TS is concerted asynchronous and if the second bond does not mature it is a step-wise TS. This can be verified by examining the bond length of newly forming bonds in halfway structures. By ‘halfway’ structures it is meant that species that lie on the reaction path originating from TS and ending at the product. There is a gradual increase in the formation of C11–C14 bond on moving the reaction system from the TS towards the products and this confirms that the TSs are concerted. TSs and the corresponding structure of the species which lie at ‘half way’ between the TS and the product are shown in figure 3(a). The possibility of step-wise mechanism is thus ruled out. Bond order analysis shows the bond formation and cleaving indices and their average. BFC$_{Ave}$ gives the average percentage of all main bond forming and cleaving processes at various species. Lower BFC$_{Ave}$ value, that are less than 50, indicate ‘early’ or ‘reactant’ like or ‘loose’ nature of the TS and higher values indicate ‘late’ or ‘product’ like or ‘tight’ nature of the TS. This is the
usual measure to position the TS on the reaction path and locate them precisely. BFC_{ave} (table 2) reveals that the TSs are ‘reactant’ like and show that syn 2 TS is the most reactant-like. The regio and stereoselective formation of syn 2 isomer is also further supported by the stereoselective rule\(^7\) that says that the system tends to choose an orientation so as to have a maximum dipole moment\(^21\) and syn 2 TS has the highest dipole moment among all TSs and therefore is preferred.

3.1b Reaction between acridinium ion and propylene: ACR undergoes [2 + 4\(^+\)] reaction with PY and there are two regiochemical paths (regio 1 and regio 2) possible and in each of them two stereoselective adducts (syn 1 and anti 1 and syn 2 and anti 2) could be formed. Calculated FOE gap (table 1) and \(q_{ct}\) (figure 5) values show that the reaction is inverse electron demand type. The LUMO of ACR is C6–N5–C11–C12 \(\pi^*\) and therefore addition takes place across this unit. Computed free energy of activation and reaction (table 1) points out that the syn 2 is kinetically and thermodynamically the most favoured. Optimized asynchronous TSs shown in figure 5 and \(\alpha\) values reveal that formation of C14–C6 bond is much faster than the C13–C11 and the most electron deficient carbon atom is C6 and the first attack takes place involve this carbon atom. The entropy loss is less for the syn 2 isomer than the other isomer. In addition to that, dipole moment values suggest that the syn 2 TS has maximum separation of charges and is the most stable and preferred one.\(^21\) This is in
Figure 6. Optimized transition state geometries for the $[2 + 4\, +]$ reaction between MVE (trans orientation) and DMIQ along with degree of asynchronicity ($\alpha$), quantum of charge transfer ($q_{ct}$) and dipole moment ($\mu$).

Figure 7. Free energy profile for the $[2 + 4\, +]$ reaction of DMIQ with MVE (a) cis orientation, (b) trans orientation.

agreement with the experimental report of Bradsher and coworkers.\(^8\) Calculations have been done for the ACR-Ethylene reaction to compare the reactivity trends and the dienophile reactivities follow the order MVE > ET > PY as revealed by free energy of activation and it could be understood from that the HOMO of these dienophiles are progressively stabilized in the same order. The trend obtained is well expected as these additions are HOMO dienophile controlled. Bond order analysis (table 2) shows that syn 2 TS is more reactant like.

3.2 2,3-Dimethylisoquinolinium ion as a diene

3.2a Reaction of 2,3-Dimethylisoquinolinium-methyl vinyl ether: DMIQ and MVE undergo inverse electron demand $[2 + 4\, +]$ addition through synchronous concerted mechanism and as explained earlier two regioselective modes are possible due to asymmetric nature of diene and dienophile, i.e. carbon bearing methoxyl group can react with either C1 or C4 atom of DMIQ and further in each of these additions the methoxy group can have syn or anti orientation rela-
Figure 8. Optimized transition state geometries for the \([2 + 4\)] reaction between PY and DMIQ along with degree of asynchronicity \((\alpha)\), quantum of charge transfer \((q_{ct})\) and dipole moment \((\mu)\).
the TSs and in particular the syn 2 TS is the most reactant like. The IRC calculations provide that the geometry of the species that lie at ‘halfway’ between the TS and the cycloadducts (figure 3). These geometries that are located in a smooth drop in energy, after the barrier height show that C6–C1 bond is formed very fast about 1.72 Å. On the other hand, C5–C4 bond is much delayed and the distance is 2.95 Å. Moving the reacting system from the transition state towards the product side shows a gradual increase in the formation of C5–C4 bond and this confirms that the TSs obtained are indeed concerted asynchronous TSs and not step-wise TSs.

3.2b Reaction of 2,3-dimethylisoquinolinium-propylene: DFT Calculations have been performed for the reaction between DMIQ and PY and as described in scheme 2 four adducts (syn 1, anti 1, syn 2 and anti 2) are possible. thermochemical activation parameters and FOE gap values are collected in table 3 and the free energy profile is drawn in figure 7. Optimized transition state geometries of the TSs are given figure 8. Bond order analysis data for the reaction of ACR with PY are given in table 4. Computed FOE gap values reveal that the reaction is an inverse electron demand type. The whole potential energy surfaces have been scanned both for concerted and step-wise pathways but step-wise pathway was not found. Similar to the DMIQ–MVE reaction, activation free energy for the formation of the syn 2 TS is lower than that of all the other TSs. In this case also a syn 2 approach is found to be favourable. The values of degree of asynchronicity $\alpha$ confirm the asynchronous nature of the TSs. The reaction energies values show that this reaction is exothermic. The IRC calculations are found to connect the reactant and the corresponding products which show that concerted TS is on the right reaction path. BFC$_{Ace}$ values given in table 4 indicate that the above transition states are early transitions states. The free energies of activation of syn 2 adducts in reactions with MVE and PY show that between ACR and DMIQ the former is more reactive than the latter.

4. Conclusions

Cationic dienes ACR and DMIQ undergo regio and stereoselective [2 + 4'] cycloadditions with methyl vinyl ether and propylene through concerted mechanism. Highly stabilized LUMO in both dienes are responsible for the inverse electron demand nature of the reaction as revealed by computed charges on the addends in the TS and FOE gap values. Asynchronous nature of the TSs confirm that it is a one step, two stage process involving the two forming bonds maturing at different rates. First formation of the bond between the most electron deficient carbon atom in the diene with the electron rich carbon in the dienophile reveals the dominance of electrostatic control in the initial phase of the reaction. The diene unit containing the N$^+$ in ACR and DMIQ form the LUMO and is highly reactive and this fixes the regioselectivity. Among the four possible stereoselective adducts syn 2 adduct is favoured in both ACR and DMIQ reaction and this is in agreement with the experimental observations. The regio and stereoselective formation of syn 2 isomer is also further supported by the stereo selective rule. The reactivity of the dienophiles employed here are in the order MVE > ET > PY and this is true with the progressive stabilization of HOMO in them. Between ACR and DMIQ the former is more electron deficient and is more reactive diene. Bond order analysis reveals that all the TSs are ‘reactant’ like. In these reactions though both electrostatic and frontier orbital control plays significant role, the former is dominant in the initial stage of the reaction.

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