Abstract. The stereoselectivity of reaction of methyl acrylate, methyl methacrylate and methyl trans-crotonate with cyclopentadiene was studied with \textit{ab initio} RHF/6-31G* and B3LYP/6-31G* levels of theory. The stereoselectivities predicted for methyl acrylate and methyl methacrylate with cyclopentadiene in the gas phase were found to be in good agreement with experimental results. The preference of endo selectivity in solvents was more pronounced for methyl acrylate, however, the preference for the exo-addition for methyl methacrylate was predicted to be reduced in solvents. The solvent calculations predicted the endo- preference for methyl trans-crotonate in agreement with the experimental observations. The lower endo selectivity for methyl trans-crotonate with cyclopentadiene seems to be governed by the degree of asynchronicity of endo- and exo-transition states in water. B3LYP/6-31G* calculated activation enthalpy was found to be in good agreement with the observed activation enthalpy for methyl acrylate and cyclopentadiene, however, this method does not predict the stereoselectivities correctly in all cases. The hydrogen bonding between water and polarized transition states seems to be important for rate acceleration in water.

Keywords: DFT, Diels-Alder, stereoselectivity, solvent, global electrophilicity

INTRODUCTION

The Diels-Alder reaction is one of the most powerful carbon-carbon bond formation processes and continues to be an important subject for both computational\cite{1-7} and experimental studies.\cite{8,9} Solvent effects on the reactions have received much attention due to rate accelerations and selectivities that have been observed in different media.\cite{10-28} Recently, rate accelerations of traditionally Diels-Alder reactions have been studied computationally in aqueous media.\cite{1} The role of hydrophobic association of reactants and hydrogen bonding between the water molecules and the polarized transition states have been indicated. The stereoselectivity of Diels-Alder reactions have been examined experimentally in different solvents and the observed selectivities were rationalized via Alder rule of "maximum accumulation of unsaturation", dipole moment of transition states,\cite{17} hydrophobic and hydrogen bonding interactions\cite{16,30} and strong intermolecular attractive forces of alkyl groups overcoming secondary attractive forces of carbonyl or nitrile groups\cite{31} Domingo and co-workers have carried out studies to explain the stereoselectivity and role of water/organic solvents in Diels-Alder reactions with different dienes and dienophiles\cite{32,33} and demonstrated the usefulness of global electrophilicity power, $\omega$, to show the polarity of transition states in Diels-Alder reactions.\cite{34} However, computational reports to evaluate the importance of some of these factors toward the stereoselectivity of Diels-Alder reactions with similar dienophiles are limited in the literature.

To explore the stereoselectivities observed for Diels-Alder reactions in gas, aqueous and non-aqueous solvents, cyclopentadiene and three dienophiles namely, methyl acrylate, methyl methacrylate and methyl trans-crotonate (Scheme 1) has been investigated using \textit{ab initio} RHF/6-31G* and hybrid-DFT B3LYP/6-31G* calculations. Solvent calculations were performed in water and methanol. The calculated results were compared with the available experimental stereoselectivities for these Diels-Alder reactions. This study has focused on the relative importance of solvent polarity and dipole moment on the stereoselectivities observed in these cases.\cite{1} Further, the global electrophilicity index used to examine the electrophilicity power of diene and dieno-
philes in these DA reactions. This analysis will help to determine the polar nature of the transition states studied here.

**COMPUTATIONAL METHODOLOGY**

All calculations were performed with Gaussian 03 program at RHF/6-31G* level and single point calculations with B3LYP/6-31G* using RHF/6-31G* optimized geometries. The choice of the method and basis set in the present study was based on similar Diels-Alder reactions reported in the literature.31,36 The stationary points were characterized by frequency calculations in order to verify that the transition structures had one, and only one, imaginary frequency. To verify that each saddle point connects two putative minima, intrinsic reaction coordinate (IRC) calculations of gas phase geometries were performed in the forward and backward directions, i.e., by following the eigenvectors associated to the unique negative eigen value of the Hessian matrix, using the González and Schlegel integration method.37,38 Full geometry optimization was performed in water and methanol with Conductor-like Polarizable Continuum Model (CPCM).39-41 This approach describes the solvent reaction field by means of apparent polarization charge distributed on the cavity surface, which are determined by imposing that the total electrostatic potential cancels out on the surface.40

In CPCM approaches, the solute interacts with the solvent represented by a dielectric continuum model. The solute molecule is embedded into a cavity surrounded by a dielectric continuum of dielectric coefficient ε. The cavity surface is partitioned into small domains called tesserae. Each tessera is characterized by the position of its center, its area and the electrostatic vector normal to the surface passing through its centre. The CPCM solvation model also provides the nonelectrostatic contribution to the solute free energy.40,42

The global electrophilicity index, ω, was calculated for cyclopentadiene and all three dienophiles using the expression, ω = (μ²/2η).43,44 The electronic chemical potential μ and the chemical hardness η were evaluated in terms of one electron energies of the frontier molecular orbitals (FMO) HOMO and LUMO, ɑ_H and ɑ_L, using the expression, μ = (ɑ_H + ɑ_L)/2 and η = (ɑ_H − ɑ_L), respectively, at the ground state (GS) of the molecules using B3LYP/6-31G*//RHF/6-31G* level of theory.

**RESULTS AND DISCUSSION**

The transition state geometries of cyclopentadiene with methyl acrylate, methyl methacrylate and methyl trans-crotonate were located at RHF/6-31G* level of theory (Scheme 2 and Figure 1). These geometries were further located in water (ε = 78.4) and methanol (ε = 32.6). We have discussed the difference in geometries and energies in vacuum and in solvents and their influence on the observed endo/exo stereoselectivities. Methyl trans-crotonate can exist in s-cis and s-trans-forms. The s-cis conformation was used in most of the studies due to stereoselective preferences.45 We have also examined the s-cis conformation in our study for comparison in the gas and solvent phase. The predicted geometries for the transition states correspond to a concerted although asynchronous in agreement with the earlier reports.46 The newly forming bond carries the −CO2Me group is larger than the other C···C forming bond in all the computed transition state geometries (Figure 1). The asynchronicity was found to be larger for methyl methacrylate than methyl acrylate and methyl trans-crotonate. Further, the computed intrinsic reaction coordinates (IRCs) starting from the TSs demonstrated that such points connect nicely the reactants and cycladduct products. These points are located in a smooth drop in energy after the barrier height, explaining the unfeasibility of finding any molecular complex or intermediates as a stationary point. IRC calculated results revealed that these cycloadditions follow a concerted mechanism.

The transition state geometries in water also show that the newly forming C···C bonds are asynchronous in nature (Figure 1). However, the bonds carrying the −CO2Me groups are longer in water than the gas phase calculated geometries. Similar observation was also made for methanol calculations (Figure 1). The change of TS location in solutions, as compared to the gas phase suggests that the reaction path in solution cannot be deduced from the reaction path in a vacuum by simply adding the solvation energy and that a full geometry (and electronic) relaxation of the solvated TS structures is required. The calculated RHF/6-31G* energies suggest that the endo-transition state for methyl acrylate is 0.5 kcal mol⁻¹ stable than the corresponding exo-transition state in the gas phase (Table 1). This result was found to be in good agreement with the observed results.17 The preferential formation of endo- transition state support the rule of “maximum accumulation of unsaturation.”29 Moving from methyl acrylate to methyl methacrylate, the transition state calculations show that
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The exo-TS is stable by 0.7 kcal mol\(^{-1}\) compared to endo-TS (Table 1). The calculated exo-selectivity was found to be in agreement with experimental observations.\(^{17}\) To explain the failure of Alder’s rule of the stereoselectivity for methyl methacrylate, Furukawa attempted to rationalize the stereoselectivity on the basis of the strong intermolecular attractive forces of methyl groups.\(^{30}\) To examine this hypothesis, we have performed the charge analysis to verify the attractive force with the methyl group of the dienophile and diene in the transition state geometries of methyl methacrylate and cyclopentadiene. The Mulliken charge analysis suggests that the charge distribution was similar in both exo- and endo-transition structures (Figure 2) and any unusual attractive interaction was not observed for the exo-transition state geometry. However, it is to note that the Mulliken population analysis is significantly dependent on the choice of basis set.\(^{47,48}\) The Natural population analyses (NPA),\(^{49}\) however, is less sensitive with the choice of basis set, and hence we have also computed natural charges for those exo- and endo-transition structures (Figure 2). The NPA charge distributions were found to be similar to that of the calculated Mulliken charges. The inadequacies of the Alder rule were also revealed in the case of methyl trans-crotonate. The experimental results show that the ratios of products is close to the statistical 1:1 distribution in all solvents.\(^{17}\) Recently, the product ratios determined in different solvents show that the endo-addition is preferred over the exo-addition and supports the Alder rule.\(^{13,29}\) The calculated results with RHF/6-31G* level show that exo-TS is favored over endo-TS for methyl trans-crotonate (Table 1). The gas phase predicted exo-

![Figure 1. RHF/6-31G* calculated geometrical parameters (Å) of TS for various systems in gas phase, aqueous phase ( ) and in methanol ( [] ) [Gray = Carbon, Red = Oxygen and White = Hydrogen].](image)

**Table 1.** RHF/6-31G* calculated relative electronic energies (kcal mol\(^{-1}\)) between endo and exo TS in the gas phase, water and methanol\(^{(a)}\)

<table>
<thead>
<tr>
<th>Medium</th>
<th>Cyclopentadiene + Methyl acrylate</th>
<th>Cyclopentadiene + Methyl methacrylate</th>
<th>Cyclopentadiene + s-cis-Methyl trans-crotonate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>endo</td>
<td>exo</td>
<td>endo</td>
</tr>
<tr>
<td>Gas phase</td>
<td>0.0</td>
<td>0.43</td>
<td>0.75</td>
</tr>
<tr>
<td></td>
<td>(0.0)</td>
<td>(0.49)</td>
<td>(0.69)</td>
</tr>
<tr>
<td></td>
<td>[2.28]</td>
<td>[2.00]</td>
<td>[1.98]</td>
</tr>
<tr>
<td>Water</td>
<td>0.0</td>
<td>1.32</td>
<td>0.18</td>
</tr>
<tr>
<td></td>
<td>(0.0)</td>
<td>(1.30)</td>
<td>(0.25)</td>
</tr>
<tr>
<td></td>
<td>[3.62]</td>
<td>[3.46]</td>
<td>[3.15]</td>
</tr>
<tr>
<td>Methanol</td>
<td>0.0</td>
<td>1.10</td>
<td>0.18</td>
</tr>
<tr>
<td></td>
<td>(0.0)</td>
<td>(1.07)</td>
<td>(0.28)</td>
</tr>
<tr>
<td></td>
<td>[3.53]</td>
<td>[3.39]</td>
<td>[3.10]</td>
</tr>
</tbody>
</table>

\(^{(a)}\) Relative free energies (kcal mol\(^{-1}\)) calculated at 298 K are in ( ) and dipole moments (debye) in [ ].
preference for methyl trans-crotonate with cyclopenta-
diene was not in agreement with experimentally ob-
served results.13,17

The effect of solvents on the transition state ener-
gies was also examined at RHF/6-31G* level of theory. The calculated results show that the endo preference seen in the gas phase for methyl acrylate is more pro-
nounced in water. The electrostatic effect of the solvent favors the endo with respect to exo isomers, in agree-
ment with the experimentally observed results i.e., in-
crease of the endo/exo selectivity as a function of sol-
vent polarity for the reaction of cyclopentadiene with methyl acrylate.30 The less polar solvent, methanol also shows the pronounced endo preference compared to the calculated gas phase results, however, the transition state energy difference is smaller than water (Table 1). Experimentally, the endo/exo stereoselectivity was not ob-
served in pure water, however, the organic solvent-
aqueous mixture showed the enhanced selectivity for endo-addition with higher percentage of water.30 The effect of solvent polarity was also observed on stereose-
lectivities in other Diels-Alder reactions.51 The degree of asyncronicity of C1···C2 vs. C3···C4 bond forma-
tions in the exo- and endo- transition states for methyl acrylate with cyclopentadiene is similar in both water and methanol solvents (Scheme 2 and Figure 1). There-
fore, the influence of hydrophobic interaction towards the association of transition states in water does not seem to be important in this case.16,17 The enhance-
ment in the endo-selectivity presumably arises between the electrostatic effect of the water and polarized transition states more compared to methanol.

The effect of solvent seems to be more pro-
nounced on the endo/exo selectivity of methyl metha-
crylate. The computed gas phase transition state energy difference is reduced in water and methanol solvents. The exo-addition is preferred over endo-addition by 0.2 kcal mol⁻¹ (Table 1). This is in agreement with the previously observed result for methyl acrylate that the endo-addition gets stabilized more in solvents compared to exo-addition. Consequently, the transition state ener-
gy difference is smaller in solvents than the gas phase calculated results. The experimentally observed en-
do/exo ratio in methanol for methyl methacrylate with cyclopentadiene was 40:60.17 In one of the recent stu-
dies, the endo/exo ratio reported in water was 29:71.13

These experimental results suggest that the transition state energy difference should be larger in water com-
pared to methanol and that was not observed with CPCM solvation model. It is to note that the ratios were determined in different experimental conditions. There-
fore, the quantification of computed results seems to be not possible. Comparing the transition state geometries obtained in water and methanol, it appears that the hy-
drophobic interaction towards the association of transi-
tion state geometries is less important (Figure 1). The degree of asyncronicity of newly formed bonds in the transition states is similar in both endo- and exo- case. Moving to methyl trans-crotonate, the transition state calculations predicts endo preference in water and methanol, which is in agreement with the experimental observations (Table 1).13 The exo-selectivity predicted in the gas phase for methyl trans-crotonate with cyclo-
pentadiene and the change to endo-preference in the solvents further verifies that solvents stabilize the endo-transition state more compared to exo-transition state. Comparing the endo/exo selectivities observed in water and methanol, it appears that the endo preference is less in water compared to organic solvents.13 The calculated results show that the energy difference be-
tween the endo- and exo- transition states is higher by 0.1 kcal mol⁻¹ in methanol than water, which qualita-
tively supports the observed selectivities (Table 1). Recently, the lower endo-selectivity in water than or-
ganic solvents was explained with the hydrophobic packing of the methyl group in the transition states.13 The methyl group is more hydrophobic than the carbox-
yleate group, so the hydrophobic packing of the methyl group in the transition state would lead to more endo
endo- (exo-transition state) corresponding to more exo-methyl (endo-transition state). However, our calculated endo-
and exo- transition state geometries suggest that the associa-
tion of diene and dienophile do not support the tight association of the former transition state than the later in water (Figure 1). The degree of asynchronicity obtained is more in the exo-transition state of methyl trans-crotonate with cyclopentadiene than the corre-
sponding endo-transition state in water. However, in methanol the asyncronicities are similar for both the transition states. This analysis suggests that the asyn-
chronicity of the reaction is favored by the interactions with solvent. The exo-TS for methyl trans-crotonate with cyclopentadiene seem to be stabilized more in water than methanol compared to their corresponding endo-transition states and hence the endo/exo selectivity would expected to be lower in water than methanol.13

To gain further insights concerning the polar na-
ture of the transition states of these DA reactions, global
electrophilicity index\textsuperscript{43} was examined within the context of the conceptual density functional theory.\textsuperscript{52} In Table 2, the electronic chemical potential, \( \mu \), chemical hardness, \( \eta \), and the global electrophilicity, \( \omega \), are shown. The large electrophilicity difference, \( \Delta \omega \), between cyclopentadiene and the dienophiles used in this study indicates that these DA reactions would be polar in nature. To examine the reliability of the method used to calculate the global electrophilicity, we have also chosen 1,3-butadiene and ethylene as a reference for a non-polar DA reaction.\textsuperscript{34} The electrophilicity difference for non-polar DA reaction between 1,3-butadiene and ethylene showed comparable \( \omega \) values at the same level of theory (Table 2). The electronic chemical potential, \( \mu \), of the dienophiles are less than cyclopentadiene, indicating that the charge transfer will take place from cyclopentadiene to the dienophiles, whereas, the electronic chemical potential, \( \mu \), values are comparable for 1,3-butadiene and ethylene (Table 2). Therefore, neither of them tend to provide charge to the other, in agreement with a non-polar pattern.

The higher level DFT B3LYP/6-31G* calculated results predict the \textit{exo}-selectivity for methyl acrylate with cyclopentadiene in the gas phase. However, the selectivities predicted in water and methanol is \textit{endo}-preferred (Table 3). Methyl methacrylate with cyclopentadiene is \textit{exo}-selective in all cases as predicted in the RHF level of theory and in agreement with the observed selectivities.\textsuperscript{17} The trend of \textit{endo}/\textit{exo} selectivity for methyl trans-crotonate with cyclopentadiene predicted at B3LYP was found to be \textit{exo}-selective in all cases, which is opposite to the observed selectivity ratios. These results suggest that the hybrid-DFT B3LYP calculations do not predict the stereoselectivity correctly in all cases. To verify the B3LYP/6-31G* calculated single point results, the transition structures were optimized in the gas phase and water at this level of theory as well. The computed relative energies upon optimization at B3LYP/6-31G* level was found to be similar to that obtained with B3LYP/6-31G*/RHF/6-31G* single point calculations (Table 3).

The activation barrier calculated for methyl acrylate in gas phase, water and methanol with CPCM model was found to be higher at RHF/6-31G* level of theory (Table 4). It is known that the HF calculations overestimate the activation barriers for Diels-Alder reactions.\textsuperscript{36} The experimental activation enthalpy measured for methyl acrylate and cyclopentadiene in Toluene is 15.1 kcal mol\textsuperscript{-1}.\textsuperscript{31} The B3LYP/6-31G* calculated activation enthalpy for methyl acrylate and cyclopentadiene in methanol and water was predicted to be 15.2 kcal mol\textsuperscript{-1} in good agreement with the experimental result. Comparing the computed activation enthalpy in the gas and water, it appears that the barrier is marginally lower in water with CPCM solvation model (Table 4). Recently, the QM/MM study performed for Diels-Alder reactions suggest that the increase in the rate in water are primarily due to enhanced hydrogen bonding between the solvent and the polarized transition states. The contribution from enforced hydrophobic association is of minor importance.\textsuperscript{1} In our study, the calculations with CPCM solvation model lacks the hydrogen bonding interaction between the solvent and the transition states, and hence the reaction rate predicted to be marginally preferred in water. To examine further, the importance of hydrogen bonding in rate acceleration in water, we have used the semi-empirical AM1-SM5.4

<table>
<thead>
<tr>
<th>Molecule</th>
<th>Global properties</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>( \omega / \text{eV} )</td>
</tr>
<tr>
<td>Methyl acrylate</td>
<td>5.49</td>
</tr>
<tr>
<td>Methyl methacrylate</td>
<td>4.99</td>
</tr>
<tr>
<td>s-cis-Methyl trans-crotonate</td>
<td>4.89</td>
</tr>
<tr>
<td>Cyclopentadiene</td>
<td>3.12</td>
</tr>
<tr>
<td>Ethylene</td>
<td>0.71</td>
</tr>
<tr>
<td>Butadiene</td>
<td>0.95</td>
</tr>
</tbody>
</table>

Table 2. B3LYP/6-31G*/RHF/6-31G* calculated global properties for diene and dienophiles in gas phase

<table>
<thead>
<tr>
<th>Molecule</th>
<th>Global properties</th>
</tr>
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<tbody>
<tr>
<td></td>
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<td>0.71</td>
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<tr>
<td>Butadiene</td>
<td>0.95</td>
</tr>
</tbody>
</table>

Table 3. B3LYP/6-31G*/RHF/6-31G* calculated relative electronic energies (kcal mol\textsuperscript{-1}) between \textit{endo} and \textit{exo} TS in the gas phase, water and methanol\textsuperscript{(a)}

<table>
<thead>
<tr>
<th>Medium</th>
<th>endo ( \omega / \text{eV} )</th>
<th>( \mu / \text{a.u.} )</th>
<th>( \eta / \text{a.u.} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gas phase</td>
<td>0.43</td>
<td>1.19</td>
<td>1.07</td>
</tr>
<tr>
<td>Water</td>
<td>0.0</td>
<td>0.87</td>
<td>0.56</td>
</tr>
<tr>
<td>Methanol</td>
<td>0.0</td>
<td>0.85</td>
<td>0.47</td>
</tr>
</tbody>
</table>

\( \textsuperscript{(a)} \) B3LYP/6-31G* optimized relative electronic energies (kcal mol\textsuperscript{-1}) are in ( ).
The importance of electric dipole moment of transition state geometries was also discussed in terms of influence of solvent polarity and selectivity.\textsuperscript{17,56} We have examined the role of dipole moment towards the selectivity ratios for these dienophiles with cyclopentadiene. The calculated dipole moments with RHF/6-31G* and B3LYP/6-31G* suggest that the endo-transition states have higher dipole moments than their corresponding exo-transition states in the gas and solvent phase (Table 1). The stereoselectivity trend observed for methyl acrylate, methyl methacrylate and methyl \textit{trans}-crotonate cannot be explained on the basis of dipole moment results. There is apparently no connection between the dipole moments and ratios of \textit{exo}- and \textit{endo}-products for these Diels-Alder reactions.

**CONCLUSION**

In the present work, we have investigated the stereoselectivities of methyl acrylate, methyl methacrylate and methyl \textit{trans}-crotonate with cyclopentadiene in gas and solvent phase. The stereoselectivities predicted for methyl acrylate were found to be in good agreement with the observed results. The higher \textit{endo} selectivity in water compared to methanol was also borne out from this computational study. The degree of asynchronicity of transition states seems to be important in solvents to determine the observed stereoselectivity. Hydrogen bonding between the solvent and the polarized transition states is more important for rate enhancement in water than the hydrophobic association of diene and dienophile. The computed activation enthalpy with B3LYP/6-31G* level is in good agreement with the experimental activation enthalpies, however, this method does not predict the stereoselectivity correctly in all cases. The global electrophilicity index calculations showed the polar nature of the transition states for these DA reactions.

**Acknowledgements.** We thank DST, New Delhi, India and DAE (BRNS) for financial support. One of the Authors MKK is thankful to UGC, New Delhi, India for Junior research fellowship. We also thank the reviewers for their comments and suggestions that have helped us to improve the paper.

**REFERENCES**


SAŽETAK

Utjecaj otapala na stereoselektivnost metil akrilata, metil metakrilata i metil \textit{trans}-krotonata s ciklopentadijenom: računska studija

Manoj K. Kesharwani i Bishwajit Ganguly

Central Salt & Marine Chemicals Research Institute (CSIR), Bhavnagar, Gujarat, India

Proučavana je stereoselektivnost metil akrilata, metil metakrilata i metil \textit{trans}-krotonata s ciklopentadijenom primjenom \textit{ab initio} RHF/6-31G* i B3LYP/6-31G* nivoa teorije. Predviđena stereoselektivnost za metil akrilat i metil metakrilat s ciklopentadijenom u plinskoj fazi je u dobrom slaganju s eksperimentalnim rezultatima. Prioritetnost \textit{endo}-selectivnosti u otopini je izraženija za metil akrilat, dok je prioritetnost \textit{egzo}-adicije metil metakrilata u otopini smanjena. Računi u otopini predviđaju \textit{endo}-prioritetnost za metil \textit{trans}-krotonat u skladu s eksperimentalnim opažanjima. Smanjena \textit{endo}-selectivnost metil \textit{trans}-krotonata s ciklopentadijenom čini se da je utvrđena stupnjem asinhroniteta \textit{endo}- i \textit{egzo}-prijelaznih stanja u vodi. Aktivacijske entalpije izračunate na B3LYP/6-31G* razini teorije su u dobrom slaganju sa opaženim aktivacijskim entalpijama metil akrilata i ciklopentadiena, no ova metoda ne predviđa stereoselektivnost na ispravan način u svim slučajevima. Stvaranje vodikove veze između molekula vode i polariziranih prijelaznih stanja ima važnu ulogu za ubrzavanje reakcija u vodi.