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Estimating Regio and Stereoselectivity in [4+2] Cycloadditions of Vinyl-Substituted Cyclic Dienes with Maleic Anhydride[†]

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Density functional theory calculations are performed to examine the regio and stereoselective preferences in [4+2] cycloaddition reactions of vinyl cyclopentadiene (**1** and **2**) and vinyl heterocyclic (**1-N**, **1-O**, **1-S**, **2-N**, **2-O** and **2-S**) systems with maleic anhydride. Stepwise and concerted pathways of model systems **1** and **2** as dienes with ethylene as dienophile reveal that the reactions proceed through asynchronous and concerted pathway. 3-Vinyl systems (**2**) are predicted to be more reactive compared to 2-vinyl systems (**1**). The regio and stereoselective preferences are evaluated based on activation energies, reaction energies, density functional based descriptors and atoms in molecules analysis. In all cases, extra-annular cycloadducts are more feasible compared to intra-annular cycloadducts. Stereoselectivity depends on the favorable secondary orbital interactions. Solvents such as water, tetrahydrofuran, acetone, and dimethyl sulphoxide are employed to understand the effects of solvents on the cycloadduct formation. The computational results thus obtained are compared with the earlier experimental observations that are available.

Introduction

Various Diels−Alder methodologies have been implemented for a long time for synthesizing natural products, and novel heterocyclic and polycyclic heterocyclic systems that are of biological and pharmaceutical interest.[1] One among these methodologies involves the use of alkenyl-substituted heteroaromatic systems, which in general proceed through either extra-annular additions or intra-annular additions.[2−6] In the former, the exocyclic double bond of the heterocyclic system participates in the reaction, while in the latter the heterocyclic ring itself is involved. Previous experimental results, in most cases, showed extra-annular additions to be more feasible compared to intra-annular additions and the reason is attributed to π-excessive nature of the ring and heteroatoms present in the ring.[6] Reports have shown that 3-vinyl pyrrole with substituted acetylenes,[5a] and 2-vinyl thiophene[5b] and 2-vinyl furan[5d] with maleic anhydride (MA) yield extra-annular adduct alone. The reactions of 2-vinyl furan[5c] and 3-vinyl furan[5e] with dimethyl acetylene dicarboxylate (DMAD) result in the formation of both extra-annular and intra-annular adducts. Further 3-vinyl furan with *N*-phenyl maleimide results in the formation of both the regioisomers.[5c] In this reaction, both exo as well as endo adducts were reported. MA has been a choice for most of the chemists for carrying out such type of Diels−Alder reactions.

The facial, endo/exo, selectivity of Diels−Alder reactions attracted the attention of experimentalists and theoreticians for many years.[7,8] While the endo approach is favored in general, due to the presence of secondary orbital interactions its preference is not unambiguous in all cases. Atoms in molecules (AIM) analysis can be of help to gain insight[9a] into the bonding nature and was shown to be quite successful in pericyclic reactions.[9b,c] Computational prediction for the preference of concerted and stepwise mechanisms has been a topic of interest for chemists.[10] Understanding the causative factors for the observed regioselectivity is challenging and computational chemistry approaches provide valuable clues in this direction. Recently conceptual density functional theory (DFT) descriptors have proved to be quite useful in predicting the regioselectivity.[11−14] The relative reactivity difference of intra- and extra-annular additions seem to be interesting in its own respect, and to our knowledge no computational studies are available on this topic. Our group has been working on the different aspects of Diels−Alder reactions.[11c,14f,g,15a,b,16] In this study we undertake the task of systematically evaluating the reactivity of various dienes with maleic anhydride as dienophile. The reaction pathways for **1** and **2** as dienes and ethylene as dienophile are evaluated first (Scheme 1). This will be followed by reactions of **1**, **1-N**, **1-O**, **1-S**, **2**, **2-N**, **2-O** and **2-S** with MA (Scheme 2). Many of these reactions are studied experimentally.

The present study addresses the following aspects. (1) Which pathway do the reactants follow whether concerted or stepwise? (2) Which among the two dienes is reactive, the 2-vinyl system or the 3-vinyl system? (3) What is the propensity of the formation of regio and stereoisomers? (4) Do solvents play a role in deciding the regio or stereoselectivity preferences in such cycloaddition reactions? Efforts are made to estimate the reactivity and regioselectivity for the present set of compounds by computing DFT based descriptors namely Fukui function indices (f_k^+ and f_k^-), electronic chemical potential (μ), chemical hardness (η), global (S), and local softness (s_k^+ and s_k^-), global (ω) and local (ω_k) electrophilicity indices, multiphilic descriptor ($\Delta\omega_k$) and, global and local maximum amount of electrons ($\Delta N_{\max}$). AIM analysis is done to delineate the exo and endo selectivity of the dienophile and also to identify the reason for the stereoselectivity. Solvents such as water, acetone, tetrahydrofuran (THF), and dimethyl sulphoxide (DMSO) are considered and the effect of these solvents on the regio and stereoselectivity is analyzed.

Computational Details. Geometry optimizations and frequency calculations are carried out on the reactants, transition

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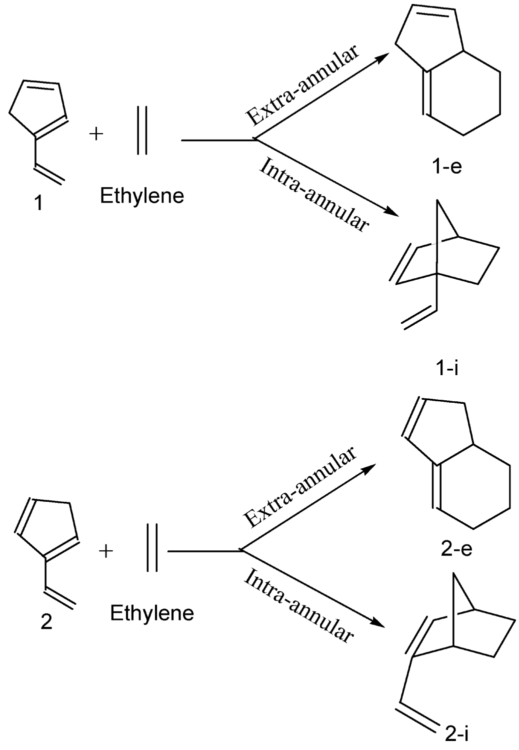
SCHEME 1: Schematic Representation for the Reaction between the Parent Systems, 1 and 2, and Ethylene



states (TSs) and products using B3LYP/6-31G* level of theory. Earlier studies reveal that B3LYP is a reliable method for Diels−Alder reactions.[15] The frequency calculations have been carried out to obtain physico chemical data and also to unambiguously characterize minima and TSs. B3LYP/6-311+G** calculations are carried out on B3LYP/6-31G* optimized geometries. uB3LYP method is used to calculate the stepwise TSs for the reactions between vinyl cyclopentadiene and ethylene. DFT-based descriptors are calculated using NPA charges. Solvent calculations are done at B3LYP/6-31G* level using PCM model. All the calculations are carried out using G03 program package.[17] AIM analysis is done for the TSs using AIM 2000 package.[18a,b]

Methodology. Within finite difference approximation, chemical hardness[14c] is related to the energy gap between occupied and unoccupied molecular orbitals and is defined as

$$\eta = (\varepsilon_{\mathrm{LUMO}} - \varepsilon_{\mathrm{HOMO}})/2 \qquad (1)$$

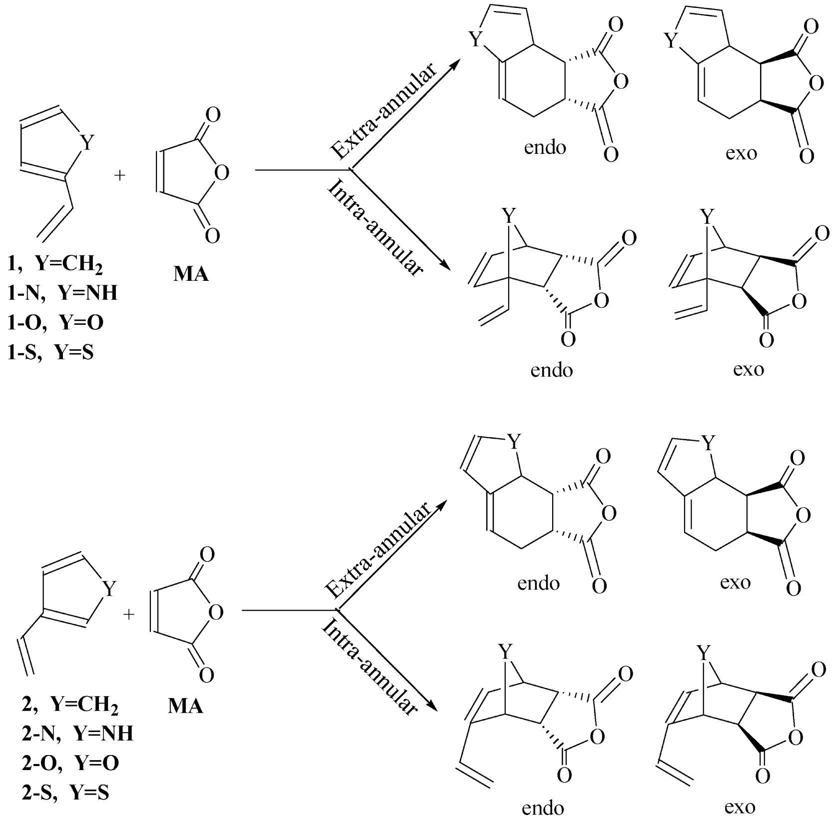
Fukui function, $f(r)$ is defined as the change of the electron density $\rho(r)$ at each point r corresponding to change in total number of electrons or as the sensitivity of the chemical potential of the system to an external perturbation at a particular point r

$$f(r) = \left(\frac{\partial\rho(r)}{\partial \mathrm{N}}\right)_{\nu(r)} = \left(\frac{\delta\mu}{\delta\nu(r)}\right)_N \qquad (2)$$

Yang and Mortier have proposed an approach to calculate Fukui function indices at an atom k based on electronic population by applying finite difference approximation[14a]

$$f_{\mathrm{k}}^{+} = q_{\mathrm{k}}(N_0 + 1) - q_{\mathrm{k}}(N_0) \quad \text{(for nucleophilic attack)} \qquad (3)$$

SCHEME 2: Schematic Representation for the Reactions between Various Dienes (1, 1-N, 1-O, 1-S, 2, 2-N, 2-O, and 2-S) and MA



$$f_k^- = q_k(N_0) - q_k(N_0 - 1) \quad \text{(for electrophilic attack)} \tag{4}$$

$$f_k^{\cdot} = q_k(N_0 + 1) - q_k(N_0 - 1) \quad \text{(for free radical attack)} \tag{5}$$

where $q_k(N_0)$, $q_k(N_0 - 1)$ and $q_k(N_0 + 1)$ denote the electronic population on atom k for N_0, $N_0 - 1$ and $N_0 + 1$ electronic systems, respectively.

Yang and Parr[14b] in 1985 introduced local softness $s(r)$ to predict the reactivity

$$s(r) = f(r)S \tag{6}$$

where S is the global softness that is inversely related to global hardness (η) and is defined as $S = (1/2\eta)$.

$$S = 1/(\varepsilon_{\text{LUMO}} - \varepsilon_{\text{HOMO}}) \tag{7}$$

Electronic chemical potential (μ) describes the changes in electronic energy with respect to the total number of electrons. In general it can be defined as

$$\mu = (\varepsilon_{\text{HOMO}} + \varepsilon_{\text{LUMO}})/2 \tag{8}$$

Electrophilicity index (ω)[12f] in normal terms is defined as the electrophilic power of a ligand or the capability of an agent to accept electrons. It can also be defined as a measure of lowering the energy due to the maximum flow of electrons. The global electrophilicity index is given by

$$\omega = \mu^2/2\eta \tag{9}$$

The local electrophilicity index (ω_k), which gives the maximum electrophilicity power in molecule developed at a particular site, is given by

$$\omega_k^{+} = \omega f_k^{+} \quad \text{(for nucleophilic attack)} \tag{10}$$

$$\omega_k^{-} = \omega f_k^{-} \quad \text{(for electrophilic attack)} \tag{11}$$

$$\omega_k^{\cdot} = \omega f_k^{\cdot} \quad \text{(for free radical attack)} \tag{12}$$

According to the recent studies by Toro-Labbé et al.,[13a,b] a dual descriptor, ($\Delta f(r)$), which is defined as the derivative of

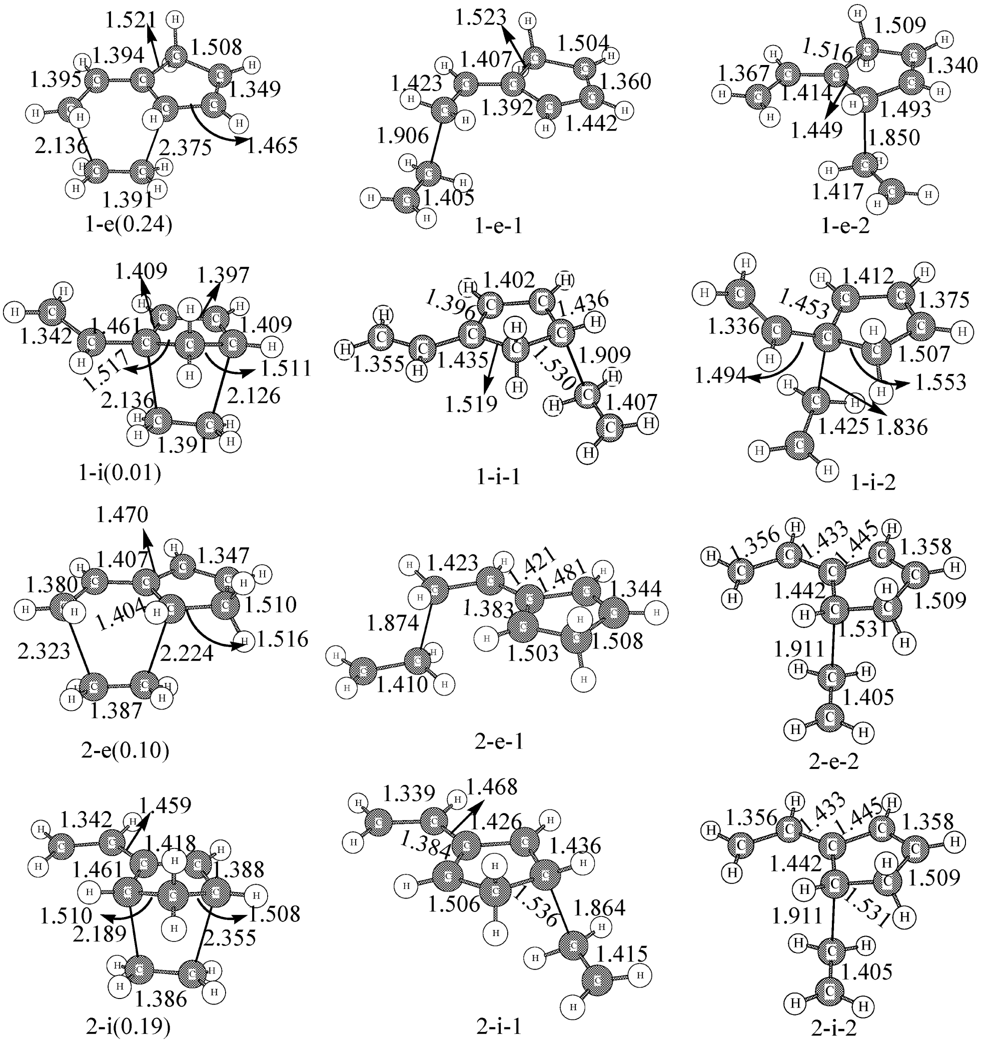


Figure 1. Optimized geometries for the concerted and stepwise TSs for the reactions between **1** and **2** with ethylene. Asynchronicity values are given in parentheses.

molecular hardness with respect to the external potential and which can be expressed as the difference between the nucleophilic and electrophilic Fukui functions, is given by

$$\Delta f(r) = [(f^{+}(r)) - (f^{-}(r))] \tag{13}$$

Another term known as the multiphilic descriptor using the unified philicity concept, which can characterize both the nucleophilic and electrophilic nature of a chemical species, is introduced recently.[13c] It is defined as the difference between the nucleophilic and electrophilic condensed philicity functions, and is given by

$$\Delta\omega_{k} = [\omega_{k}^{+} - \omega_{k}^{-}] = \omega[\Delta f_{k}] \tag{14}$$

If $\Delta\omega_k > 0$, then the site k favors a nucleophilic attack, whereas if $\Delta\omega_k < 0$, then the site k favors an electrophilic attack.

The maximum amount of electronic charge that an electrophile can accept is given by

$$\Delta N_{\max} = -(\mu/\eta) \tag{15}$$

The maximum amount of electronic charge condensed on to atoms is given by

$$\Delta N_{\max k} = \Delta N_{\max} f_{k}^{+} \tag{16}$$

Results and Discussion

The discussion is planned in the following manner. Initially concerted and stepwise mechanisms of vinyl cyclopentadiene and ethylene are explored in order to know the possible mechanism which will be followed by such [4+2] cycloaddition reactions. The reactions of various dienes and MA are discussed next. This includes the discussion on geometrical parameters, extra-annular versus intra-annular adduct formation and endo vs exo selectivity. Regioselectivity is explained based on DFT based descriptors and stereoselectivity is explained based on the molecular structures obtained using AIM analysis. The results obtained in the present study are correlated with the previous experimental studies. Finally solvent effects on regio and stereoselectivity for the present set of reaction series are discussed. Throughout the paper "-e-" represents extra-annular addition and "-i-" represents intra-annular addition of the diene.

A principal point of concern in most cycloaddition reactions is that whether the reactions proceed through a concerted mechanism or a stepwise mechanism. To understand the nature of reaction pathway in the current series of diene−dienophile complexes, model reactions of **1** and **2** with ethylene are subjected to systematic computational explorations which delineate the relative presence of concerted and stepwise paths (Scheme 1). This procedure gives an insight as to how such reactions proceed- whether via concerted pathway or via

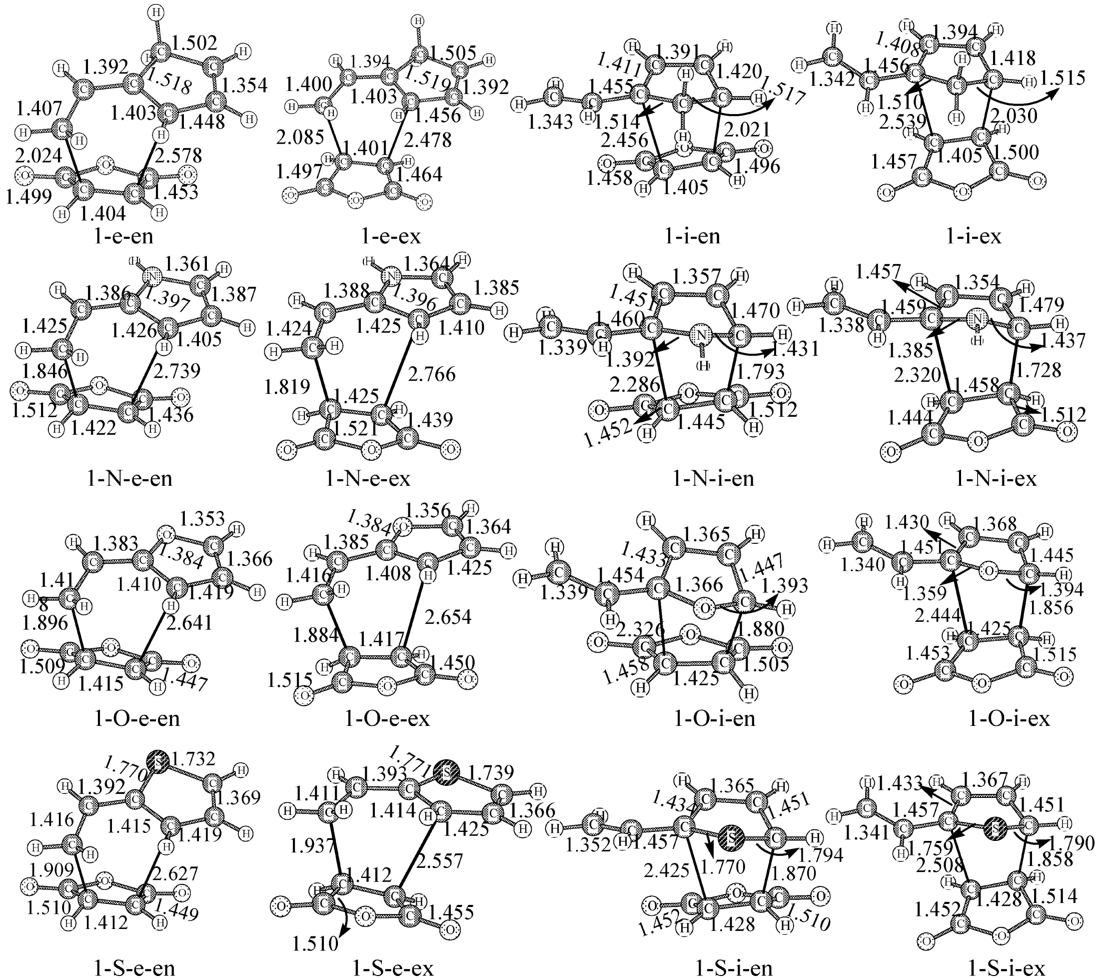
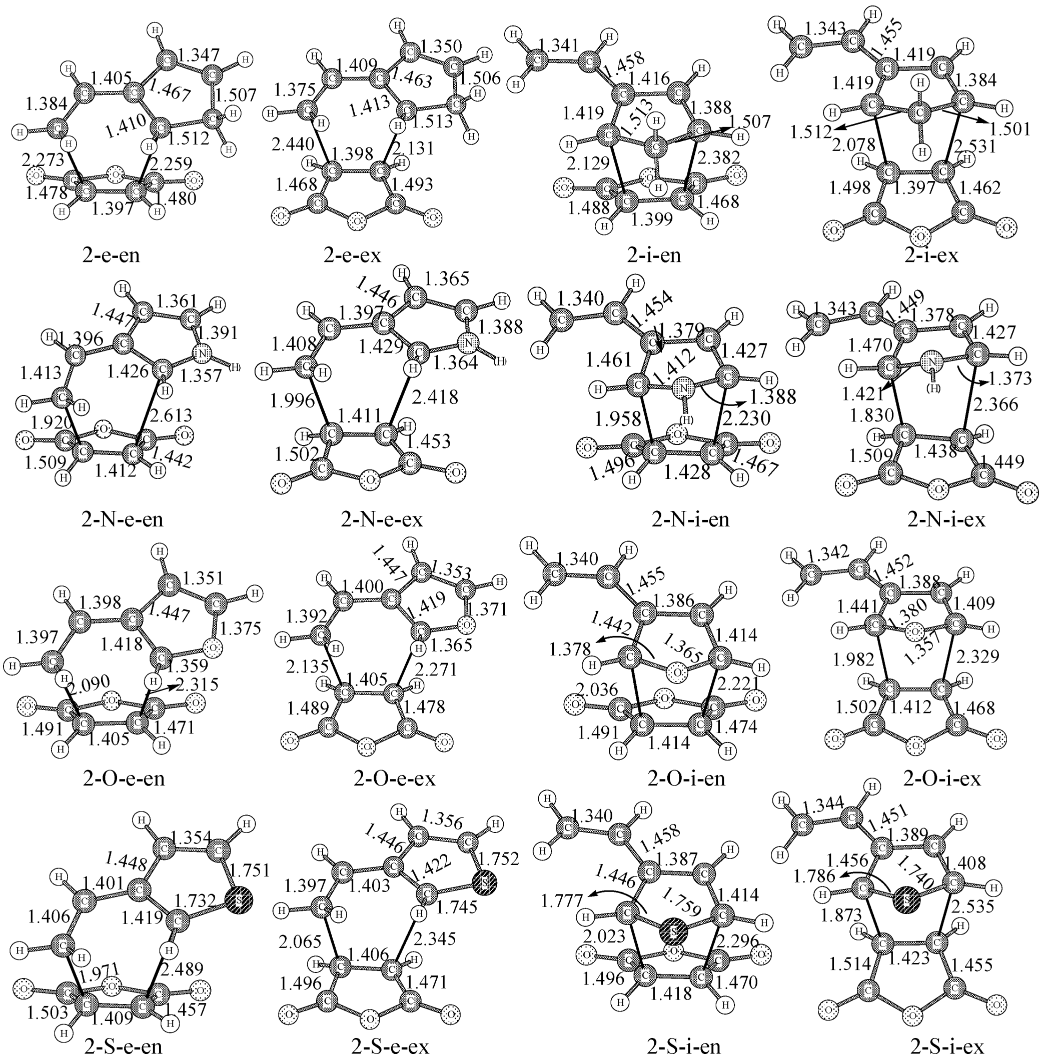


Figure 2. Optimized geometries of the TSs involving 2-vinyl systems at B3LYP/6-31G(d) level.


2-e-en 2-e-ex 2-i-en 2-i-ex

2-N-e-en 2-N-e-ex 2-N-i-en 2-N-i-ex

2-O-e-en 2-O-e-ex 2-O-i-en 2-O-i-ex

2-S-e-en 2-S-e-ex 2-S-i-en 2-S-i-ex

Figure 3. Optimized geometries of the TSs involving 3-vinyl systems at B3LYP/6-31G(d) level.

TABLE 1: Activation and Reaction Energies for the Concerted and Stepwise Mechanism of 1 and 2 with Ethylene at B3LYP/6-31G(d) Level[a]

	$\Delta E^{\ddagger}$			
product	concerted	stepwise[b]		ΔE_r
1-e	20.8 (23.8)	1	27.4 (32.5)	−37.3 (−30.5)
		2	34.8 (40.7)	
1-i	21.2 (24.0)	1	30.5 (35.9)	−18.7 (−13.0)
		2	39.7 (46.4)	
2-e	18.7 (21.6)	1	29.5 (35.2)	−43.9 (−36.6)
		2	26.9 (31.5)	
2-i	18.2 (21.1)	1	34.1 (40.2)	−28.3 (−21.5)
		2	26.9 (31.5)	

[b] The numbering 1 and 2 for the activation energies of the TSs for the stepwise pathway corresponds to the terminal carbon (1) and inner carbon (2) that are involved in the forming bonds. [a] Values in parentheses correspond to B3LYP/6-311+G(d,p)//B3LYP/6-31G(d) level.

stepwise pathway. The geometries for both stepwise and concerted TSs are depicted in Figure 1. Asynchronicity values for the concerted TSs are given in parentheses. Asynchronicity is taken as the difference in the lengths of forming bonds.

Figure 1 illustrates that concerted transition structures are asynchronous in nature ranging from 0.01−0.24 Å for **1-i** and **1-e** respectively. When concerted reaction pathway of 2-vinyl cyclopentadiene, **1**, as diene is considered, intra-annular TS, **1-i**, is virtually synchronous while the corresponding extra-annular TS, **1-e**, is highly asynchronous. In the case of reactions of 3-vinyl cyclopentadiene, **2**, as diene, variations in the asynchronicity are very small ranging from 0.10 for **2-e** to 0.17 for **2-i**.

Activation energies ($\Delta E^{\ddagger}$) and reaction energies (ΔE_r) for the systems at B3LYP/6-31G* and B3LYP/6-311+G**// B3LYP/6-31G* levels are illustrated in Table 1. The numbering “1” and “2” for the stepwise TSs is given according to the center that participates in the reaction, 1 for the terminal carbon and 2 for the inner carbon. From the table, one can infer that the concerted pathway is more feasible compared to the alternative stepwise pathway. Further considering the stepwise pathway 1 is more feasible compared to 2 when **1** is the diene, while 2 is more feasible compared to 1 when **2** is the diene. It can be observed from the geometries in Figure 1 that the electrons are more localized when the inner carbon (2) of **1** is considered while the electrons are more delocalized when outer carbon (1) is considered. In contrast, the electrons are more localized when the outer carbon (1) of **2** is considered while the electrons are more delocalized when the inner carbon (2) is considered. This further indicates that the delocalization plays a major role in stability of TSs. These results indicate the preference of 1 over 2 and 2 over 1 for **1** and **2**, respectively. From the above results it can be concluded that such reactions proceed through asynchronous concerted TS.

It can also be inferred that the reaction energies favor the formation of extra-annular product. However the difference in the activation energies between the extra-annular and intra-annular additions is of the order 0.4−0.5 kcal/mol. Also the reactivity of **2** is found to be more compared to **1** when both activation and reaction energies are considered.

On the basis of the results obtained from the above study, the reactions of vinyl cyclic and heterocyclic systems (**1**, **1-N**, **1-O**, **1-S**, **2**, **2-N**, **2-O** and **2-S**) with MA (Scheme 2) have been examined. From the above analysis, one would expect that such reactions would proceed through asynchronous concerted pathway and therefore in the present case only concerted pathways are explored for all the systems. Different combinations of dienes and dienophile that lead to a total of 40 distinct reaction channels have been considered (Scheme 2). The suffixes "-en" and "-ex" represent endo and exo orientations of the dienophile respectively. For example, **1-e-en** is the combination of extra-annular part of vinyl cyclopentadiene and endo orientation of MA. In the case of "N"-substituted systems, two different isomers, syn (hydrogen attached to N facing toward the dienophile) and anti (hydrogen attached to N facing away from the dienophile), are considered. Out of the two possibilities, only syn TSs could be located and all our attempts to locate the anti TS were futile. Such observations have been made earlier, which may be attributed to the competition among both syn and anti pathways along the same reaction coordinate.[14g] However the corresponding products could be obtained except for **1-N-e-en** and **1-N-e-ex**. As the trends obtained at B3LYP/6-31G* and B3LYP/6-311+G**//B3LYP/6-31G* levels are similar, albeit the latter values being higher, further discussion is carried out by considering B3LYP/6-31G* values unless otherwise specified. The geometries of the TSs involving 2-vinyl and 3-vinyl dienes are depicted in Figures 2 and 3, respectively. The activation energies, reaction energies, and asynchronicity values are provided in Table 2.

Equilibrium Geometries. A cursory look at the Table 2 suggests that all the reactions despite being concerted show a highly varied asynchronicity ranging from 0.01 (for **2-e-en**) to 0.95 (for **1-N-e-ex**). In general, the asynchronicity is observed to be high for endo TSs in case of extra-annular additions, except for **1-O-e** and **2-e**, and exo TSs in the case of intra-annular additions. The reactions involving **1**, **1-N**, **1-O**, and **1-S** bear shorter terminal forming bonds compared to the inner bonds. Similar trends are observed in case of reactions involving **2**, **2-N**, **2-O**, and **2-S** except for the reactions where intra-annular additions of heterocyclic systems are involved. Such differential distal parameters between the forming bonds may arise due to the electronic or steric parameters of the bond forming centers.

Energetics. The foregoing sections discuss the extra-annular versus intra-annular selectivity and exo versus endo selectivity of the reactions. The gas phase energetics of the reactions at B3LYP/6-311+G**//B3LYP/6-31G* level from the Table 2 suggest that the reactions are exothermic in all cases except for **1-N-i**, **1-O-i**, **1-S-i**, and **2-N-i**. Also extra-annular additions seem to be more feasible compared to the intra-annular additions. This might be due to the strain that develops due to the formation of norbornene ring and thus the product stability may be an important factor for the feasibility of these reactions.[14f] Among all the reactions considered, lower activation energies are observed in case of reactions where vinyl cyclopentadiene acts as a diene. Introducing a heteroatom into the cyclic system increases the activation energy barrier. Considering the activation and reaction energy values for 2-vinyl and 3-vinyl systems, 3-vinyl systems are found to be more reactive compared to 2-vinyl systems.

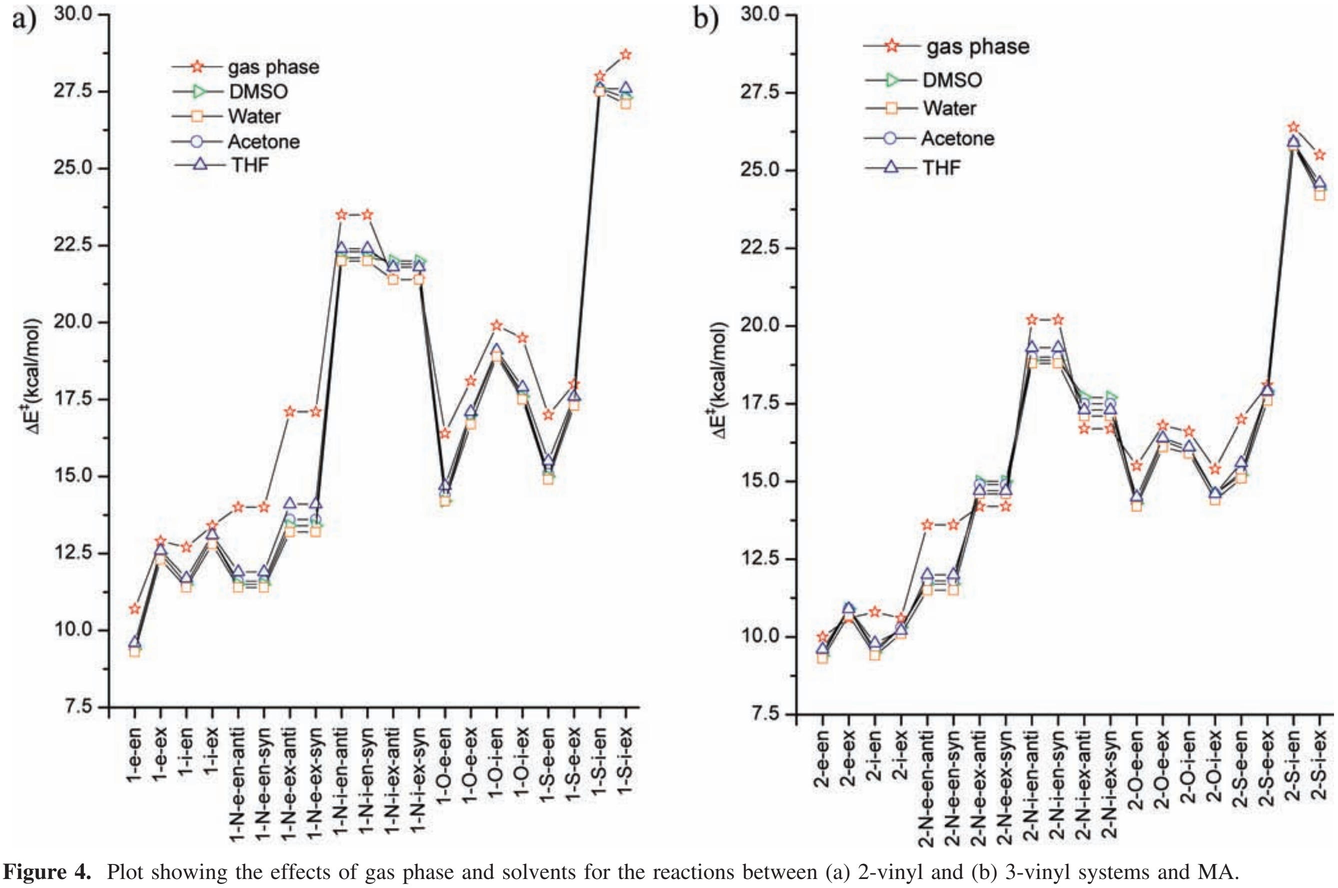


Figure 4. Plot showing the effects of gas phase and solvents for the reactions between (a) 2-vinyl and (b) 3-vinyl systems and MA.

TABLE 2: Activation and Reaction Energies (kcal/mol), Normal (E_n) and Inverse (E_i) Electron Demands (eVs) and Asynchronicity (Asyn) Calculated at B3LYP/6-31G(d) Level[a]

Sl No	name	$\Delta E^{\ddagger}$	ΔE_r	asyn
1	**1-e-en**	10.7(13.3)	−33.0(−27.5)	0.55
2	**1-e-ex**	12.9(15.3)	−33.2(−28.0)	0.39
3	**1-i-en**	12.7(15.2)	−15.1(−3.7)	0.44
4	**1-i-ex**	13.4(16.1)	−16.0(−11.2)	0.51
5	**1-N-e-en**-anti			
6	**1-N-e-en**-syn	14.0(16.6)	−16.3(−10.8)	0.95
7	**1-N-e-ex**-anti			
8	**1-N-e-ex**-syn	17.1(19.6)	−16.2(−11.2)	0.95
9	**1-N-i-en**-anti		9.5(13.8)	-
10	**1-N-i-en**-syn	23.5(26.5)	12.4(16.7)	0.49
11	**1-N-i-ex**-anti		6.9(12.0)	
12	**1-N-i-ex**-syn	21.4(24.5)	11.3(15.8)	0.59
13	**1-O-e-en**	16.4(19.1)	−18.7(−13.5)	0.75
14	**1-O-e-ex**	18.1(20.5)	−18.8(−14.0)	0.77
15	**1-O-i-en**	19.9(22.1)	3.1(6.3)	0.45
16	**1-O-i-ex**	19.5(21.9)	1.1(4.8)	0.59
17	**1-S-e-en**	17.0(19.4)	−19.4(−13.9)	0.72
18	**1-S-e-ex**	18.0(20.5)	−20.0(−14.7)	0.62
19	**1-S-i-en**	28.0(30.1)	3.8(7.5)	0.56
20	**1-S-i-ex**	28.7(30.8)	2.5(6.7)	0.65
21	**2-e-en**	10.0(13.1)	−39.8(−33.7)	0.01
22	**2-e-ex**	10.6(13.3)	−39.7(−34.1)	0.31
23	**2-i-en**	10.8(13.5)	−24.7(−19.5)	0.25
24	**2-i-ex**	10.6(13.1)	−26.2(−21.0)	0.45
25	**2-N-e-en**-anti		−18.6(−13.0)	
26	**2-N-e-en**-syn	13.6(16.3)	−20.4(−14.1)	0.69
27	**2-N-e-ex**-anti		−20.8(−15.6)	
28	**2-N-e-ex**-syn	14.2(16.9)	−19.7(−14.2)	0.42
29	**2-N-i-en**-anti		0.7(6.1)	
30	**2-N-i-en**-syn	20.2(23.9)	2.4(7.9)	0.27
31	**2-N-i-ex**-anti		−2.7(2.8)	
32	**2-N-i-ex**-syn	16.7(19.9)	0.6(5.7)	0.54
33	**2-O-e-en**	15.5(18.5)	−25.2(−19.8)	0.23
34	**2-O-e-ex**	16.8(19.5)	−25.1(−20.4)	0.14
35	**2-O-i-en**	16.6(19.3)	−7.2(−3.0)	0.19
36	**2-O-i-ex**	15.4(17.8)	−10.2(−6.1)	0.35
37	**2-S-e-en**	17.0(19.5)	−22.4(−16.8)	0.52
38	**2-S-e-ex**	18.1(20.5)	−24.1(−18.7)	0.28
39	**2-S-i-en**	26.4(28.7)	−4.8(−0.5)	0.27
40	**2-S-i-ex**	25.5(27.5)	−6.3(−2.1)	0.66

[a] Values in parentheses are at B3LYP/6-311+G(d,p)//B3LYP/6-31G(d) level.

Extra-Annular versus Intra-Annular Adducts. The present section discusses the regioselectivity based on activation energies and DFT based descriptors. Attempt has been made to draw a correlation among various parameters. DFT-based descriptors have been extensively used in the recent years in explaining the regioselectivity in many cases. Hence for the present study various descriptors namely Fukui function indices[14a] (f_k^+ and f_k^-), electronic chemical potential (μ), chemical hardness[14c] (μ), global (S) and local softness[14b] (s_k^+ and s_k^-), global (ω) and local (ω_k) electrophilicity indices,[12f] multiphilic descriptor ($\Delta\omega_k$),[13c] and global and local $\Delta N_{\max}$ are considered for evaluating the regioselectivity for the present set of compounds. A systematic evaluation of all global and local DFT based descriptors are done for the systems considered in the study. The values of the DFT based descriptors along with the normal and inverse electron demands are given in Table 3.

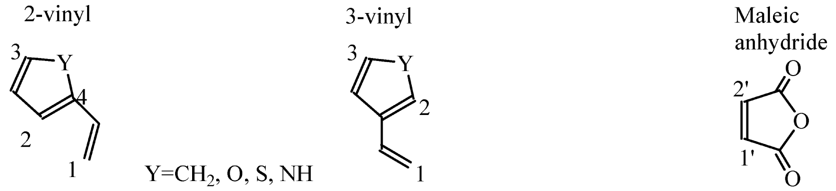
The global parameters μ, ω, and $\Delta N_{\max}$ suggest that the dienes act as nucleophiles while the dienophile acts as an electrophile and that the flow of electrons is from diene to the dienophile. These values are in agreement with the $\Delta E_{\text{HOMO-LUMO}}$ values that suggest that all the reactions proceed through normal electron demand (E_n), that is, HOMO of the diene reacts with LUMO of the dienophile. The smaller values of chemical hardness (0.17−0.20) and the larger values of softness (5.02−5.90) indicate that the reactions are soft−soft interactions further indicating that the forming bonds are covalent in nature.

Since the diene is acting as nucleophile and dienophile as electrophile, local Fukui function indices, f_k^-, and local softness values, s_k^-, of the diene are considered. From Table 3, it can be observed that f_k^- and s_k^- values for the center 1 range from 0.39−0.50 and 2.31−3.01, respectively, which are high compared to the values for the center 3 for which the f_k^- and s_k^- values range from 0.15−0.48 and 0.78−2.75, respectively. Also the values are high for the center 2 compared to that of 4. These results suggest the feasibility of extra-annular adducts over intra-annular adducts in all the cases. Further considering the multiphilic descriptor ($\Delta\omega_k$) values, except for the center 4 of **1-S**, all the sites of the dienes bear a negative $\Delta\omega_k$ value which indicates that the sites favor electrophilic attack. The $\Delta\omega_k$ values for all the dienes are high for the center 1 compared to center 3 within a range of 0.05−1.24. The range is high for sulfur substituted compounds while low for nitrogen substituted compounds.

The difference in the activation energy values for the regioisomers of **1** and **2** is 1.9 and 0.0 kcal/mol respectively and the range of ω_k^+ values are of the order 0.26 and 0.17 respectively. Though the ω_k^+ value for **2** is higher the difference in the activation energy value is negligible. Thus it can be inferred that **1** forms extra-annular adduct and **2** forms both extra- as well as intra-annular adducts. To our knowledge there are no experimental reports where **1** and **2** are dienes. For **1-N** and **2-N**, the difference in the activation energy values is 7.9 and 3.6 kcal/mol, respectively, and the ω_k^+ values are of the order 0.06 and 0.26, respectively. The smaller difference in the ω_k^+ value of **1-N** may be attributed to the delocalization of electrons. However, in this class of compounds the loss of aromaticity in the products brings in huge variation in the product stability during the formation of intra-annular adduct. From these results one can conclude that the extra-annular adduct should alone be observed. These results are in accordance with the experimental results observed for **1-N** and **2-N**.[5a] In the case of **1-O** and **2-O** the difference in the activation energy values is 2.8 and 0.7 kcal/mol, respectively, and the ω_k^+ values are of the order 0.27 and 0.32, respectively, which in turn show considerably higher value for center 1 compared to center 3. The differences in the activation energies and the local electrophilicity indices are large for **1-O** which indicates that **1-O** prefers extra-annular adduct alone. Smaller difference in the activation energies for **2-O** suggests that **2-O** prefers both extra-annular and intra-annular adducts. These results are in accordance with the earlier experimental results of **1-O**[5d] and **2-O**.[5c] For **1-S** and **2-S**, the difference in the activation energy values is 10.7 and 8.0 kcal/mol, respectively, and the ω_k^+ values are of the order 0.56 for both the isomers, which is huge and shows considerably higher value for center 1 compared to center 3. Thus, the extra-annular adducts should be exclusively formed. The experimental observations also show similar trends.[5b] From the local electrophilicity indices and the activation energies, it can be inferred that while **2**, **2-O** form both the regioisomers, **1**, **1-O**, **1-N**, **2-N**, **1-S**, and **2-S** exclusively form extra-annular adduct. Thus, DFT-based descriptors appear to predict regioselectivity in all cases except in those cases where the selectivity based on the activation energies is virtually nonexistent.

Endo versus Exo Selectivity. Recently AIM analysis has gained momentum and is very much helpful in explaining the bonding properties in molecules. This concept has been

TABLE 3: Normal (E_n) and Inverse (E_i) Electron Demands (evs), Electronic Chemical Potential (μ), Chemical Hardness (η), Fukui Function Indices (f_k), Local (ω_k), and Global (ω) Electrophilicity Index, Multiphilic Descriptor ($\Delta\omega_k$), Local (ΔN_{maxk}) and Global (ΔN_{max}) Electronic Charge Acceptance and Local (s_k) and Global (S) softness Values for the Reactants Using NPA Charges at B3LYP/6-31G(d) Level



diene	E_n	E_i	μ	η	ω	ΔN_{max}	S	site	f_k^-	s_k^-	ω_k^-	ω_k^+	$\Delta\omega_k$	ΔN_{maxk}
1	2.13	7.23	−0.12	0.08	2.31	1.46	6.30	1	0.48	3.01	1.10	−0.61	−1.72	−0.39
								2	0.26	1.63	0.60	−0.34	−0.93	−0.21
								3	0.38	2.38	0.87	−0.40	−1.27	−0.25
								4	0.20	1.26	0.46	−0.14	−0.60	−0.09
1-N	1.95	7.92	−0.10	0.09	1.46	1.09	5.54	1	0.50	2.88	1.21	−0.69	−1.89	−0.41
								2	0.24	1.35	0.57	−0.35	−0.92	−0.21
								3	0.48	2.75	1.15	−0.68	−1.84	−0.40
								4	0.30	1.74	0.73	−0.43	−1.16	−0.25
1-O	2.40	7.46	−0.12	0.09	2.00	1.28	5.55	1	0.50	2.76	0.73	−0.48	−1.20	−0.36
								2	0.26	1.42	0.37	−0.23	−0.60	−0.17
								3	0.32	1.75	0.46	−0.05	−0.51	−0.04
								4	0.16	0.91	0.24	0.02	−0.22	0.01
1-S	2.57	7.14	−0.12	0.09	2.41	1.42	5.73	1	0.50	2.76	1.00	−0.62	−1.62	−0.40
								2	0.28	1.57	0.57	−0.32	−0.89	−0.20
								3	0.22	1.21	0.44	0.06	−0.38	0.04
								4	0.04	0.24	0.09	0.19	0.10	0.12
2	2.34	7.38	−0.12	0.08	2.24	1.39	5.90	1	0.39	2.32	0.88	−0.52	−1.40	−0.32
								2	0.46	2.70	1.03	−0.48	−1.51	−0.30
								3	0.32	1.88	0.71	−0.25	−0.97	−0.16
2-N	2.07	8.25	−0.09	0.10	1.24	0.96	5.07	1	0.49	2.63	1.09	−0.55	−1.65	−0.33
								2	0.43	2.34	0.97	−0.77	−1.74	−0.46
								3	0.37	2.01	0.83	−0.51	−1.34	−0.30
2-O	2.62	7.67	−0.12	0.10	1.85	1.18	5.10	1	0.49	2.48	0.61	−0.37	−0.98	−0.29
								2	0.31	1.56	0.38	−0.13	−0.51	−0.10
								3	0.24	1.20	0.29	0.01	−0.28	0.01
2-S	2.71	7.31	−0.12	0.09	2.24	1.33	5.38	1	0.45	2.31	0.84	−0.51	−1.35	−0.32
								2	0.27	1.36	0.49	−0.07	−0.56	−0.04
								3	0.15	0.78	0.28	0.16	−0.13	0.10

dienophile	μ	η	ω	ΔN_{max}	S
MA	−0.21	0.09	6.48	2.29	5.49

undertaken to explain exo/endo selectivity of the dienophile. From the Table 2, it can be inferred that while thermodynamic stabilities of the adducts suggest the formation of exo product compared to endo for both intra-annular and extra-annular additions, it is difficult to draw a conclusion from the activation energy barriers as the difference between the exo and endo products in certain cases is around 0.2−1.3 kcal/mol (Table 2).

The molecular structures of the TSs are depicted in Supporting Information, Figure S4. From the molecular structures, it can be inferred that all the TSs are pericyclic. Considering the extra-annular additions in general, the molecular structures of the endo TSs show secondary orbital interactions (SOI). Thus the existence of SOI might lead to the stability of endo TSs. The systems involving **2-e**, **1-S-e**, and **2-O-e** are devoid of SOI and hence from the activation energy values both exo and endo products should be stable. Previous experimental results where **2-O** is the diene suggest that in such reactions both the products are formed with endo adduct in major quantities.[3d,5c] In the case of intra-annular additions, the TSs **1-S-i**, **2-N-i**, **2-O-i** and **2-S-i** show the existence of SOI which might lead to the stability of endo TSs compared to exo TSs. In the case of **1-i** and **2-i**, the existence of SOI is observed in both endo and exo TSs indicating the stability of both the adducts. In case of **1-N-i** and **1-O-i**, no secondary interactions are observed and hence from the activation energy values it can be inferred that exo adduct should alone be stable in the former and both exo and endo adducts should be stable in the latter.

Solvent Effects. The effect of solvents on regio and stereoselectivity is analyzed by considering the reactions in the presence of water, DMSO, THF, and acetone. Solvent and gas phase reactivities of 2-vinyl and 3-vinyl systems are depicted in Figure 4a,b, respectively. In almost all the cases, solvents showed considerable influence on reactivity and product feasibility. Water is observed to be a better solvent among all the solvents considered.

Considering the reactivity of 2-vinyl systems extra-annular additions are found to be more feasible compared to intra-annular adducts. Also endo orientation is preferred. However there are differences in the trends in case of solvent phase reactivities of intra-annular additions except for **1-O**. The intra-annular additions of **1** lower the activation energy barrier drastically. In case of **1-N-i** the difference in the activation energy barriers between the two stereoisomers is decreased. Unlike the gas phase reactivities the activation energy barrier for intra-annular addition of **1-S** shows preference for exo adducts.

Similar to the reactions of 2-vinyl systems, 3-vinyl systems show preference for the extra-annular endo additions. However the gas phase reactivities and the solvent phase reactivities show different trends in almost all the cases. The solvent phase reactivities of **2-e-ex**, **2-N-e-ex**, and **2-N-i-ex** are higher compared to gas phase reactivities. The activation energy barrier of **2-i-en** and **2-N-e-en** is lowered drastically. In the case of **2**, stability of both **2-e-en** and **2-i-en** is observed. The hydrocarbon species (**2**) of 3-vinyl systems shows the feasibility of intra-annular endo adduct while its hetero substituted analogues (**1-N**, **1-O**, and **1-S**) show preference for intra-annular exo adducts.

From the above results it can be concluded that while no effect is observed in the regioselectivity, except for 3-vinyl cyclopentadiene, solvents govern the stereoselectivity of the reactions.

Conclusions

The present study evaluates the reactivity, regio, and stereoselectivity of [4+2] cycloadditions of vinyl cyclopentadiene with ethylene, and vinyl cyclopentadiene and vinyl heterocyclic systems with MA at B3LYP/6-31G(d) level of theory. Calculations on the model systems **1** and **2** revealed that the stepwise pathway is higher in energy compared to the concerted pathway. Therefore such reactions proceed through asynchronous and concerted mechanism. In general, 3-vinyl cyclic systems are found to be more reactive compared to 2-vinyl systems. Extra-annular/intra-annular additions of the dienes to the dienophile and exo/endo orientation of the dienophile are assessed and the results are validated with the experimental trends. The regioselectivity and site-selectivity is explained based on the DFT-based descriptors. AIM analysis suggests the formation of endo adduct and the reason is attributed to the secondary interactions. In the presence of solvents, no effect is observed in the regioselectivity except for 3-vinyl cyclopentadiene, whereas solvents effect the stereoselectivity of reactions.

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Supporting Information Available: This material is available free of charge via the Internet at http://pubs.acs.org.

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