Cycloaddition of Methyl Acrylate with Substituted Pyridinium-3-olates and Pyrazinium-3-olates: 1,3-Dipolar Cycloaddition versus Diels-Alder

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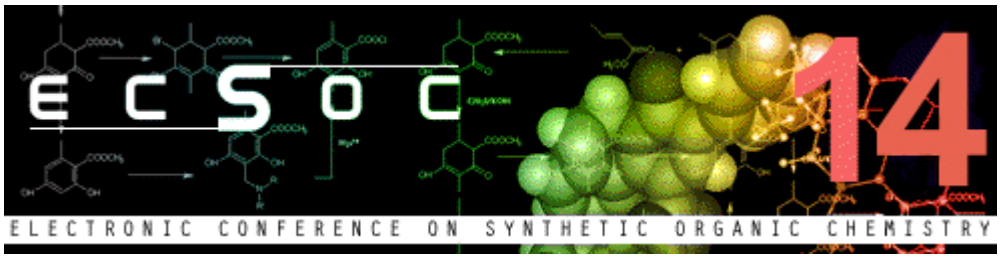
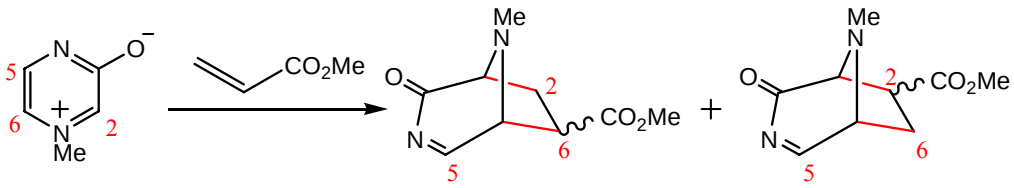


"This presentation is part of the MPhil/PhD research work of Miss Lydia Rhyman (lydrhy@hotmail.com). Her research is based on the theoretical study of cycloaddition reactions of pyridinium-3-olates and pyrazinium-3-olates. This study allows elucidation of the reaction mechanisms including different stereo- and regiochemical pathways and to predict the thermodynamic and kinetic parameters of the reactions."

Abstract

The 1,3-dipolar cycloaddition (1,3-DC) and Diels-Alder (DA) reactions of substituted pyridinium-3-olates and pyrazinium-3-olates with methyl acrylate are studied using DFT method at the B3LYP/6-31G(d) level of theory. The molecular mechanism of the possible stereo- and regiochemical pathways is characterized both in the condensed and solvent phases. It is found that 1,3-DC is the favourable pathway for the reaction of pyridinium-3-olates with methyl acrylate and the thermodynamically more stable 6-substituted 8-azabicyclo[3.2.1]oct-3-en-2-ones are formed preferentially. This research is further extended to substituted pyrazinium-3-olates. Reactions of unsubstituted pyrazinium-3-olate and 1-methyl pyrazinium-3-olate with both ethene and methyl acrylate show a preference for the DA cycloaddition reaction. However, the addition of methyl acrylate to substituted pyrazinium-3-olates results in competitive mechanistic pathways and the preferred cycloaddition pathway is dependent on the location of the methyl group on the pyrazinium ring. The presence of a methyl substituent on C5 of the pyrazinium-3-olate favours the 1,3-DC over the DA reaction as the 2,6 positions are not sterically crowded. However, when methyl groups are present at the C2 and C6 positions, cycloaddition occurs via a Diels-Alder route which is free from encumbrance and hence bond formation at the C5 position is more enhanced.

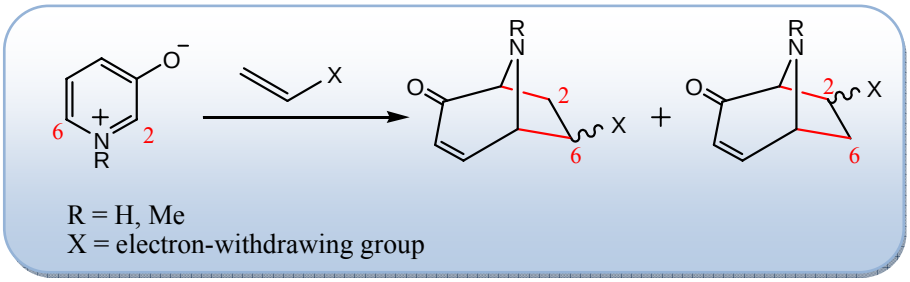


1.0 Introduction

- 1,3-Dipolar cycloaddition (1,3-DC) and Diels-Alder (DA) reactions are effective routes for the synthesis of carbocyclic and heterocyclic structures which are the backbones of many complex natural products.

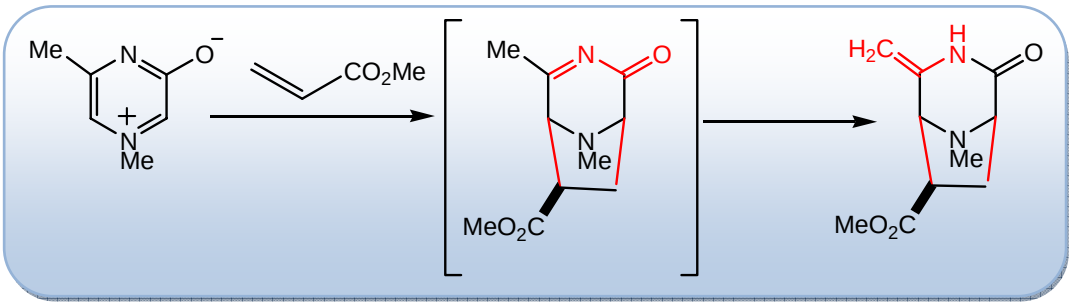
- Nitrogen-containing heterocycles occur widely in nature, in isolation and as structural subunits in many families of alkaloids with laboratory, industrial and pharmacological applications.[1-3] Of particular interest are the substituted pyridinium-3-olates and substituted pyrazinium-3-olates.

- Katritzky *et al.*[4,5] have studied the 1,3-DC reactions of 1-substituted pyridinium-3-olates with a variety of dipolarophiles whereby the predominant mode of reaction is across the 2,6-positions (Scheme 1).



Scheme 1. 1,3-DC of 1-substituted pyridinium-3-olates with dipolarophiles.

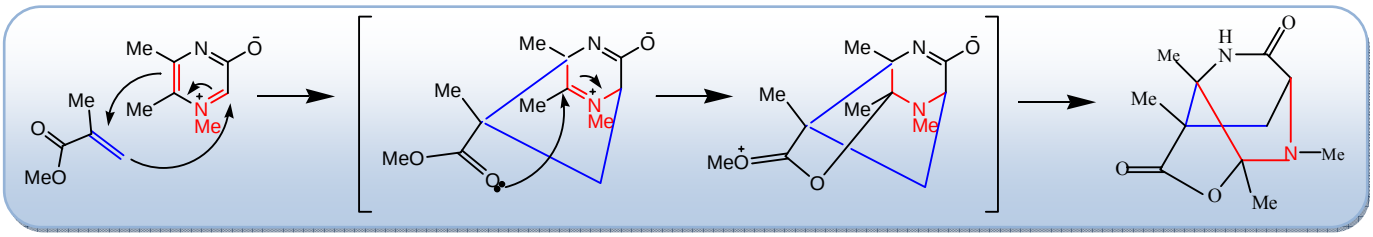
- Based on the pioneering studies and a series on benchmark papers by Katritzky *et al.*[4-8] on 1-substituted pyridinium-3-olates, Joule and coworkers[9-13] have investigated the cycloaddition of substituted pyrazinium-3-olates with dipolarophiles such as methyl acrylate, methyl methacrylate, acrylonitrile and methyl propiolate.



Scheme 2. 1,3-DC of 1,5-dimethyl pyrazinium-3-olates with methyl acrylate.

- Joule and coworkers[11-13] extended their studies by assessing the influence of introducing alkyl substituent on the future ring-junction of the 1,3-dipole. The steric effect of the alkyl group was clearly observed as the cycloadducts undergo extensive rearrangement.

- Recently, Joomun *et al.*[14] have shown that these reactions may proceed through a different mode of initial addition. They inferred that the diazabicyclo[3.2.1]octanes were produced by an initial DA addition followed by rearrangement rather than the 1,3-DC reaction (Scheme 3).



Scheme 3. Cycloaddition reaction of a hindered pyrazinium-3-olate with methyl methacrylate.

- These observations call into question the 1,3-DC of the 1-substituted pyridinium-3-olates studied by Katritzky *et al.*, which may also proceed *via* the DA cycloaddition followed by rearrangement and set the objectives of this present research.

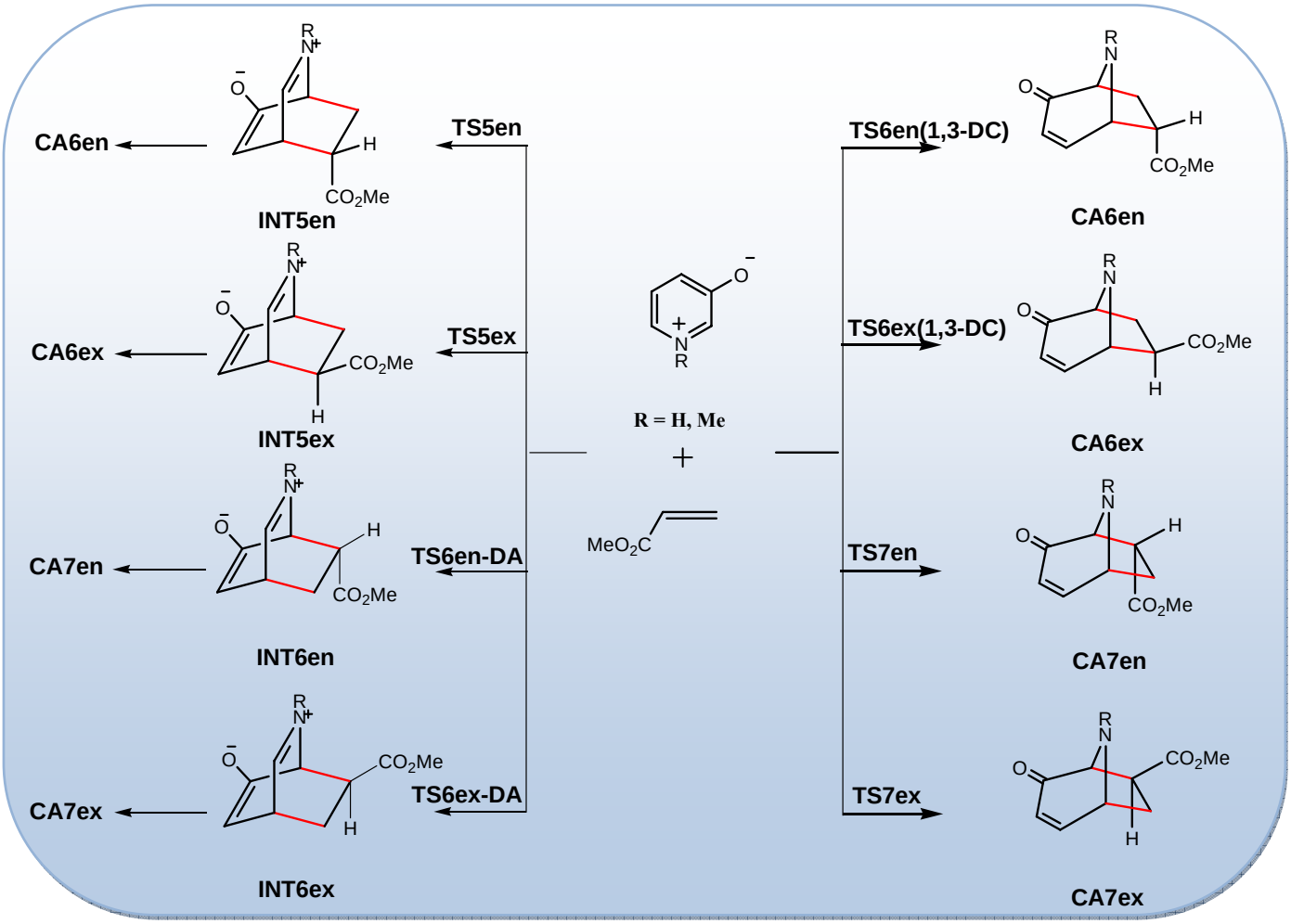
1.1 Objectives

- To study the 1,3-DC and DA reactions of substituted pyridinium-3-olates and pyrazinium-3-olates with methyl acrylate using theoretical methods.
- To elucidate the reaction mechanisms and to discuss the kinetics and thermodynamic parameters in both gas and solvent phases.
- To analyse the regio- and stereoselectivity of the cycloaddition reactions.
- To investigate the effect of the position of the methyl group on the pyrazinium-3-olates.

2.0 Results and Discussion

2.1 Reaction of 1-substituted pyridinium-3-olates with methyl acrylate

In continuation to our previous DFT study[15] on 1,3-DC of 1-substituted pyridinium-3-olates with methyl acrylate, we have now examined the DA reaction of 1*H*-pyridinium-3-olate (**R = H**) and 1-methyl pyridinium-3-olate (**R = Me**) with the same electron-deficient alkene (Scheme 4). The relative energies of the DA reactions of the dipoles with methyl acrylate are listed in Table 1.



Scheme 4. Reaction pathways for the 1,3-DC and DA reactions of pyridinium-3-olates with methyl acrylate.

Table 1: Activation energies (ΔE, in kJ mol^{-1}) computed at 298.15 K and 1 atm in gas phase and THF involved in the 1,3-DC and DA reactions of 1-substituted pyridinium-3-olates with methyl acrylate.

1,3-DC			**DA**		
	Gas phase	THF		Gas phase	THF
TS6en-H(1,3-DC)	83.2	74.9	**TS5en-H**	126.0	115.2
TS6ex-H(1,3-DC)	60.0	67.7	**TS5ex-H**	109.6	109.1
TS7en-H	91.0	86.1	**TS6en-H(DA)**	142.2	140.6
TS7ex-H	70.1	77.2	**TS6ex-H(DA)**	123.7	130.3
TS6en-Me(1,3-DC)	82.9	68.8	**TS5en-Me**	117.4	108.4
TS6ex-Me(1,3-DC)	70.5	66.5	**TS5ex-Me**	99.0	115.3
TS7en-Me	90.6	81.7	**TS6en-Me(DA)**	138.0	137.3
TS7ex-Me	80.4	75.5	**TS6ex-Me(DA)**	125.9	131.0

1,3-DC of 1-substituted pyridinium-3-olates

- The gas phase energy differences between 6-*exo* and 7-*exo* (10.1 kJ mol^{-1}) and between 6-*endo* and 7-*endo* (7.8 kJ mol^{-1}) are too small to account for the regioselectivity reported in the literature, where 6-substituted 8-azabicyclo[3.2.1]oct-3-en-2-ones are preferred.

- The pathways leading to the formation leading to 6-esters are found to be more favourable than those leading to 7-esters.

1,3-DC versus DA reactions

- The activation energies of the DA reaction pathways are significantly higher than for the 1,3-DC reaction. Thus, the 1,3-DC reaction is kinetically favoured in a range of 28.5 to 53.6 kJ mol^{-1} in the gas phase and 39.6 to 55.6 kJ mol^{-1} in THF.

- The 1,3-DC reactions are exothermic processes[15] and the **CA6ex** is slightly more stable than the **CA6en**. Thus, from kinetic and thermodynamic points of view, the results suggest that the pathways leading to the **CA6ex** is preferred.

- The experimental observations that mixtures of four products are normally obtained, but with the 6-esters predominating and 6-*exo* and 6-*endo* formed in similar amounts, are supported by

the computations, where only a small energy difference between the *endo* and *exo* CAs is observed.

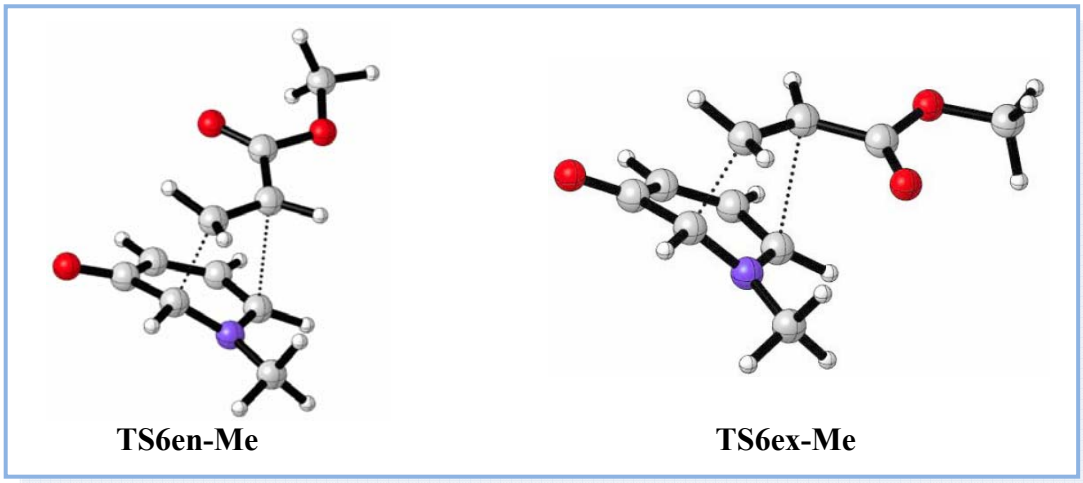


Figure 1. TSs leading to the 6-esters.

2.2 Parent system

The simplest model system examined was the cycloaddition reaction of unsubstituted pyrazinum-3-olate itself with ethene whereby this system is free of regio- and stereoselectivity issues, as shown in Figure 2.

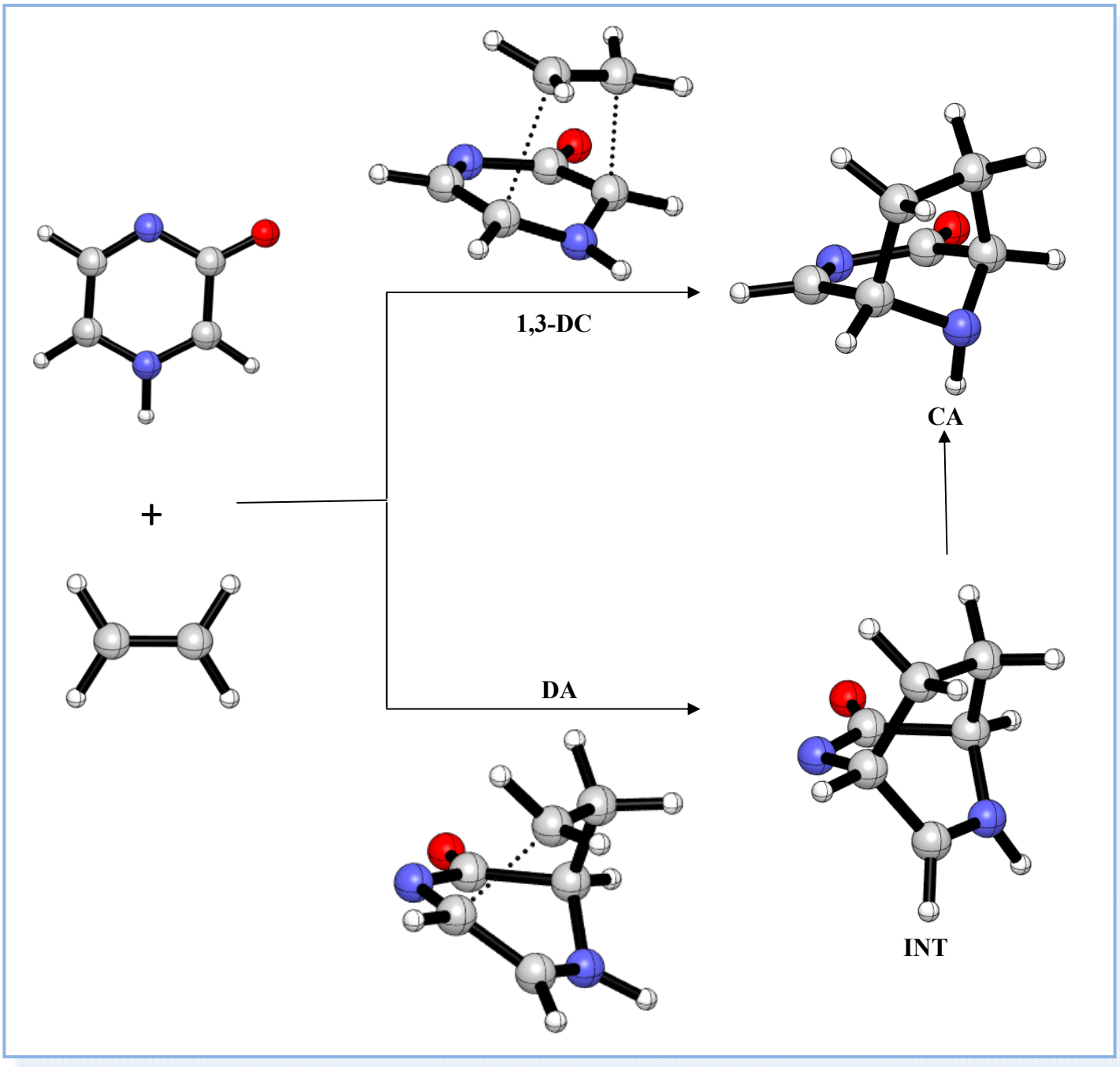


Figure 2. Proposed mechanism for the cycloaddition of 1*H*-pyrazinium-3-olate with ethene.

- The calculated activation energies for the 1,3-DC are 66.1 and 77.3 kJ mol^{-1} while for the DA reaction, activation energies of 56.7 and 53.8 kJ mol^{-1} in the gas phase and THF, respectively are observed.

- On comparing the activation barriers, it can be concluded that the DA reaction is energetically the more favourable cycloaddition reaction of 1*H*-pyrazinium-3-olate with ethene. In addition, both the 1,3-DC and DA reactions are exothermic processes.

- The two C-C bonds forming in the transition state are not formed to the same extent for the 1,3-DC. The forming bonds at C6 and C2 of the unsubstituted pyrazinium-3-olate are 2.421 and 2.123 Å in the gas phase and 2.458 and 2.049 Å in THF. Similarly, bond formation between the carbon of ethene and C5 of 1*H*-pyridinium-3-olate is more advanced. Hence, the 1,3-DC and DA reactions take place *via* asynchronous TSs.

2.3 Effect of N-methyl substituent on cycloaddition processes

- The gas phase activation energies associated with the 1,3-DC and DA reactions are 65.9 and 58.9 kJ mol^{-1}, indicating a preference for the DA pathway.

- Inclusion of THF solvent is in line with the gas phase results whereby the DA is kinetically favourable by 19.4 kJ mol^{-1}. Hence it can be concluded that substitution of a hydrogen atom by the methyl group on the nitrogen of pyrazinium-3-olate does not alter the mode of initial addition to ethene.

- Figure 3 shows the TS of the 1,3-DC and DA reactions including the bond lengths of the forming bonds. Note that the *N*-methyl substituent does not have any effect on the synchronicity of the forming bonds.

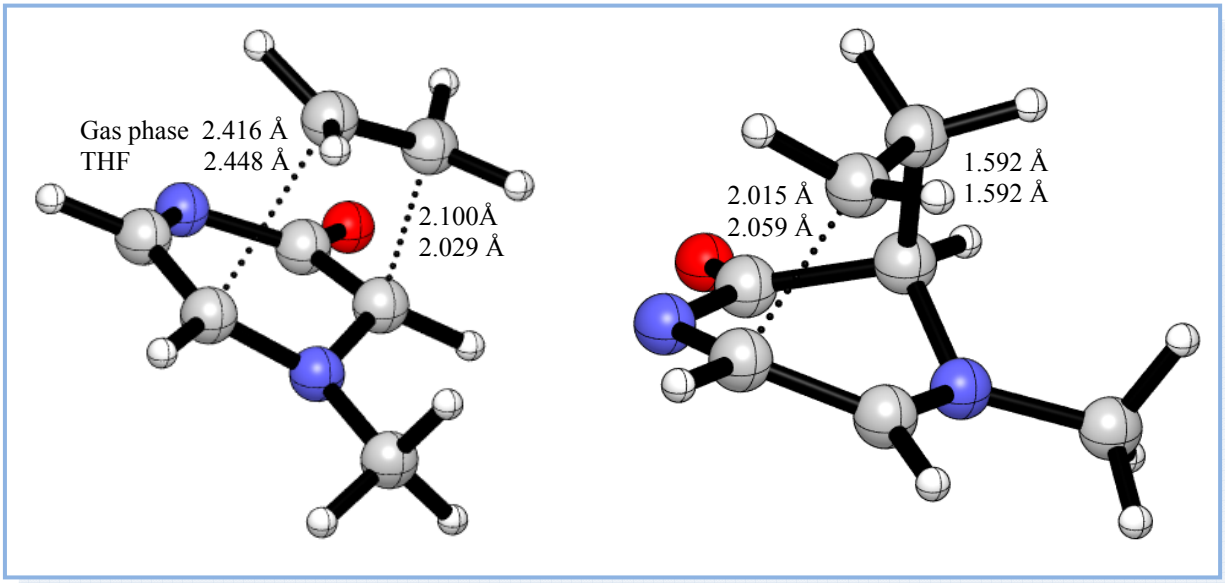
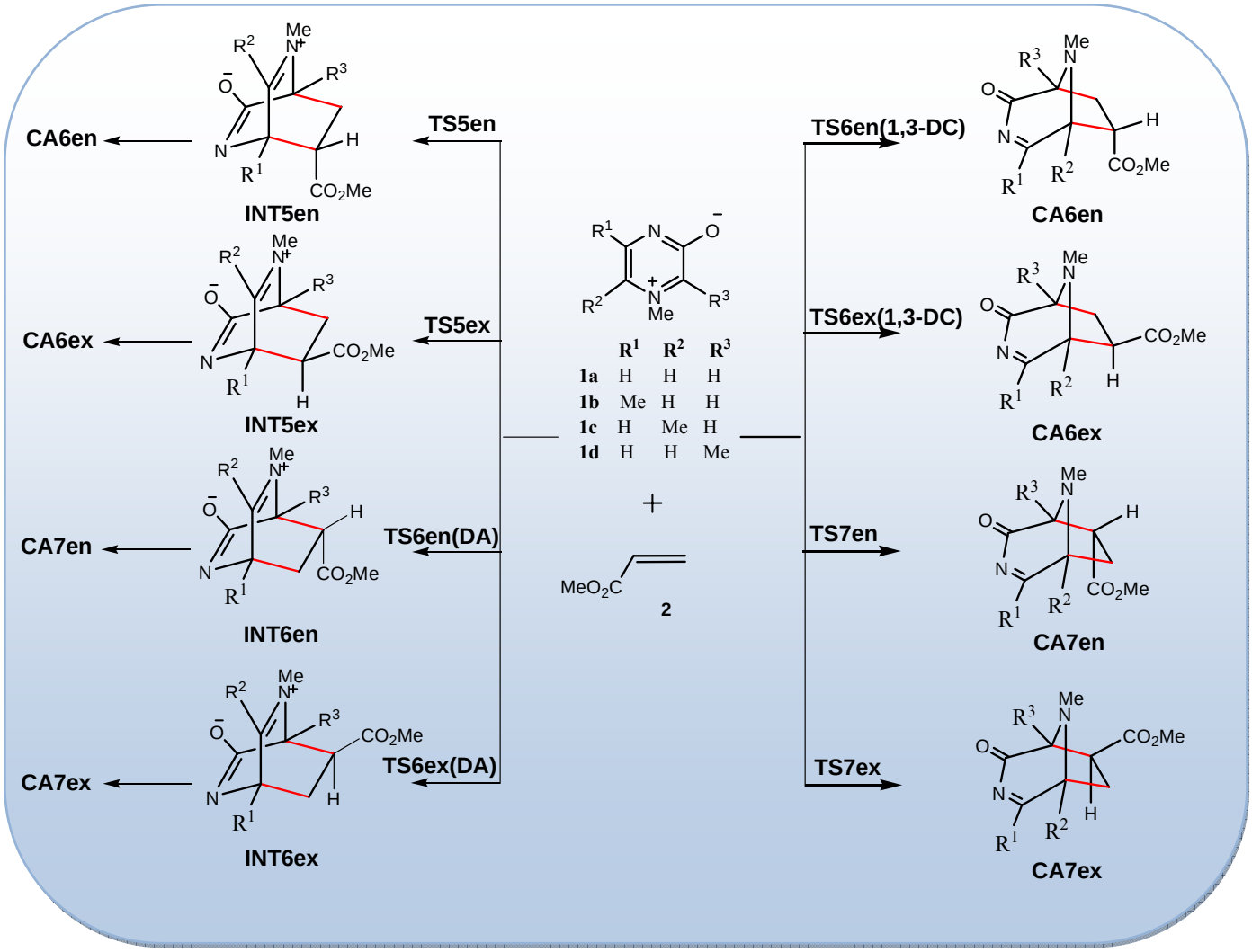


Figure 3: TSs arising from 1,3-DC and DA reactions.

2.4 Model system

The model system examined consists of the reaction of the as-yet unreported cycloaddition reaction of 1-methylpyrazinum-3-olate (**1a**) with methyl acrylate whereby the pyrazinium ring is free from steric hindrance. The two potential mechanisms for these cycloaddition reactions, the 1,3-DC and DA reaction pathways leading to the cycloadducts, are studied according to Scheme 5.



Scheme 5. Alternative pathways for the 1,3-DC and DA reactions of pyrazinium-3-olates with methyl acrylate.

Table 2 reports the relative energies for the reaction between **1a** with methyl acrylate taking into account the two possible reaction pathways.

Table 2: Energies (E, in au) and relative energies[a] (ΔE, in kJ mol^{-1}) computed at 298.15 K and 1 atm in gas phase and THF solvent involved in the 1,3-DC and DA reactions of **1a** with **2**.

	Gas phase		THF			Gas phase		THF	
	E	ΔE	E	ΔE		E	ΔE	E	ΔE
1a	-378.7235	-	-378.7461	-		-378.7235	-	-378.7461	-
2	-306.3746	-	-306.3805	-		-306.3746	-	-306.3805	-
TS6en(1,3-DC)	-685.0766	56.5	-685.1021	64.4	**TS5en**	-685.0755	59.3	-685.1052	56.3
TS6ex(1,3-DC)	-685.0846	35.5	-685.1052	56.3	**TS5ex**	-685.0831	39.4	-685.1081	48.6
TS7en	-685.0744	62.3	-685.0978	75.6	**TS6en(DA)**	-685.0682	78.6	-685.0962	79.8
TS7ex	-685.0800	47.5	-685.1007	68.1	**TS6ex(DA)**	-685.0730	65.9	-685.0983	74.4
CA6en	-685.1217	-61.9	-685.1375	-28.6	**INT5en**	-685.0945	9.6	-685.1259	1.9
CA6ex	-685.1214	-61.2	-685.1377	-29.2	**INT5ex**	-685.0975	1.5	-685.1279	-3.2
CA7en	-685.1220	-62.8	-685.1376	-28.8	**INT6en**	-685.0927	14.1	-685.1231	9.2
CA7ex	-685.1222	-63.3	-685.1383	-30.8	**INT6ex**	-685.0973	2.1	-685.1268	-0.4

a) Relative to **1a** + **2**.

- The gas phase energy differences between the 1,3-DC and DA reactions, in the range 2.8 to 18.4 kJ mol^{-1} and these differences are too small to account for the preferred reaction pathway.

- Solvent effect has been taken into account to assess the energy barriers whereby higher activation energies are observed in THF for all the cycloaddition processes due to the reactants being slightly more stabilized than the TSs.

- Analysis of the 1,3-DC and DA reactions indicate that the activation energies of the DA reactions are significantly lower than the 1,3-DC by 8.1 and 7.7 kJ mol^{-1} for 6-*endo* and 6-*exo* and hence, kinetically more favourable.

- For the 7-*esters*, the activation energies for the 1,3-DC reaction are slightly lower compared to the DA by 4.2 and 6.3 kJ mol^{-1} for the 7-*endo* and 7-*exo* pathways, respectively.

- The overall activation energies show that the preferred reaction mechanism is the DA cycloaddition leading to the 5-ester intermediates, which is kinetically more favourable than the 1,3-DC. Furthermore, this reaction pathway favours the same regiochemical sense as that observed in the studies of Katritizky and Joule, and the previously described theoretical[15] outcome of the cycloaddition reactions of pyridinium-3-olates with methyl acrylate.

- The activation energies for formation of 5-esters intermediates, in THF, indicate that the *exo* approach is favoured over the *endo* approach; **TS5ex** is lower in energy than **TS6en** by 7.5 kJ mol^{-1}. Likewise, for the formation of 6-esters *via* the 1,3-DC, the *exo* approach remains the more favourable pathway; **TS6ex** is lower in energy than **TS6en** by 8.1 kJ mol^{-1}.

- Additionally, the other reaction pathways leading to the 7-esters *via* both the 1,3-DC and DA reactions are also feasible and hence their corresponding cycloadducts might also be expected to be observed.

- It is interesting to note that the activation enthalpy, gathered in Table 3, for the *exo* approach is lower compared to the *endo* approach. As a consequence, the activation free energy for formation of the **CA6ex** and **CA7ex** are lower than that for the **CA6en** and **CA7en**.

Table 3: Relative enthalpies (ΔH, in kJ mol^{-1}), free energies (ΔG, in kJ mol^{-1}) and entropies (ΔS, in J mol^{-1}) computed at 298.15 K and 1 atm in THF for the TSs and CAs involved in the 1,3-DC and DA reactions.

	1,3-DC				**DA**		
	ΔH	ΔG	ΔS		ΔH	ΔG	ΔS
TS6en(1,3-DC)	64.4	116.7	-175.4	**TS5en**	54.2	112.1	-194.0
TS6ex(1,3-DC)	56.2	109.3	-178.3	**TS5ex**	46.4	104.9	-196.2
TS7en	75.5	128.5	-177.7	**TS6en(DA)**	77.6	135.4	-193.6
TS7ex	67.9	121.3	-179.2	**TS6ex(DA)**	72.3	129.6	-192.3
CA6en	-30.6	24.7	-185.7	**INT5en**	-0.5	58.1	-196.5
CA6ex	-33.6	30.2	-214.0	**INT5ex**	-5.5	51.5	-191.1
CA7en	-31.0	26.0	-191.0	**INT6en**	6.9	64.9	-194.4
CA7ex	-32.9	24.0	-190.8	**INT6ex**	-2.6	55.2	-193.9

- From kinetic and thermodynamic points of view, the results suggest that the pathways leading to the **CA6ex** is preferred and the expected experimental observations that mixtures of the two products are obtained and 6-*exo* and 6-*endo* should be formed with 6-*exo* as the major product.

2.5 Effect of adding methyl substituent on pyrazinium-3-olate

The acronym **1b**, **1c** and **1d** will be added to the TSs, INTs and CAs. The energetic of the various pathways of the cycloaddition reactions are listed in Table 4.

Table 4: Energies (E, in au) and relative energies[a] (ΔE, in kJ mol^{-1}) computed at 298.15 K and 1 atm in gas phase and THF solvent involved in the 1,3-DC and DA reactions of **1b,c,d** with **2**.

	1,3-DC				DA		
	1b	**1c**	**1d**		**1b**	**1c**	**1d**
Gas Phase							
TS6en(1,3-DC)	53.7	54.1	63.6	**TS5en**	66.9	46.3	67.7
TS6ex(1,3-DC)	33.3	28.6	42.7	**TS5ex**	43.2	21.5	48.0
TS7en	58.1	65.5	61.2	**TS6en(DA)**	82.8	67.7	92.9
TS7ex	43.6	50.7	42.8	**TS6ex(DA)**	70.0	54.0	76.0
THF							
TS6en(1,3-DC)	62.6	58.2	76.2	**TS5en**	73.3	43.7	69.7
TS6ex(1,3-DC)	54.8	45.3	67.1	**TS5ex**	51.9	29.8	61.8
TS7en	72.1	75.9	77.2	**TS6en(DA)**	85.4	67.7	94.8
TS7ex	63.7	69.1	65.3	**TS6ex(DA)**	78.7	61.4	88.7

a) Relative to **1n** + **2**.(n = b, c, d)

- The 1,3-DC activation barriers show that the regiochemical pathway leading to the 6-esters is more favourable than the channels leading to the 7-esters.

- The data from Table 5 indicates the preference for one set of regioisomers when considering the DA cycloaddition with the kinetically more favourable *exo* TSs with all the three substituted dipoles.

- The DA is kinetically favoured over the 1,3-DC reactions due to their lower energy barriers. Introduction of a methyl group at C5 of the pyrazinium-3-olate **(1b)** causes a decrease in the activation energies when compared to 1-methylpyrazinium-3-olate **(1a)**.

- Interestingly, it is worth pointing out that the DA addition of **1b** to methyl acrylate requires only 51.9 kJ mol^{-1} for the eventual formation of 6-*exo* product. Therefore, from a kinetic point of view, it can be concluded that the 6-*exo* path is preferred and is independent of the mode of the initial addition. These results agree with experimentally observed major product and the isolation of the 6-esters with the predominating 6-*exo* cycloadduct in the ratio 4:1.[10,16]

- Introduction of a methyl substituent at the future ring junction (C2 and C6), **1c** and **1d**, does not yield the same ordering of cycloadduct formation as with **1b**. These reactions are experimentally untried and the possible outcomes are predicted based on the model reaction (**1a**).

- The preferred reaction mechanism in these cases is the DA cycloaddition with the predominant formation of the 6-esters. However, the 1,3-DC is also feasible as the predicted activation energies are comparable. The 6-*exo* reaction channel remains the more favourable pathway leading to the **CA6ex**.

- As noted for the reaction of **1b** with methyl acrylate, the major product should be the 6-*exo* product followed by the formation of the next significant 6-*endo* product. Moreover, when considering the reaction of **1d** with methyl acrylate, the expected product mixture might consist of the 7-*exo* cycloadduct also arising from the 1,3-DC.

- However, when methyl substituents are present at C2 and C6 of the pyrazinium ring, the DA cycloaddition process is favoured over the 1,3-DC as the C5 position is not sterically crowded and hence bond formation at this position is more enhanced.

- The thermodynamic parameters of the substituted pyrazinium-3-olates are gathered in Table 5 for both 1,3-DC and DA reaction pathways.

Table 5: Relative enthalpies (ΔH, in kJ mol^{-1}), free energies (ΔG, in kJ mol^{-1}) and entropies (ΔS, in J mol^{-1}) computed at 298.15 K and 1 atm in THF for the TSs and CAs involved in the 1,3-DC and DA reactions.

Reactants	**1b**			**1c**			**1d**		
	ΔH	**ΔG**	**ΔS**	**ΔH**	**ΔG**	**ΔS**	**ΔH**	**ΔG**	**ΔS**
				1,3-DC					
TS6en(1,3-DC)	60.2	121.0	-203.9	58.4	111.2	-177.3	73.3	135.6	-208.8
TS6ex1,3-DC)	52.4	113.3	-204.5	45.1	99.4	-182.1	64.0	127.4	-212.4
TS7en	69.7	130.3	-203.3	75.9	129.6	-180.0	75.0	134.3	-199.1
TS7ex	61.2	122.7	-206.3	68.9	123.6	-183.4	62.5	125.1	-209.7
CA6en	-42.3	23.4	-220.1	-31.4	25.9	-192.1	-23.1	40.5	-213.4
CA6ex	-44.8	20.4	-218.6	-30.6	26.9	-192.9	-19.8	45.3	-218.2
CA7en	-44.1	21.5	-219.8	-25.5	31.9	-192.5	-23.5	42.5	-221.2
CA7ex	-45.9	19.0	-217.8	-35.2	20.3	-185.9	-20.1	47.3	-226.2
				DA					
TS5en	67.6	138.2	-236.6	42.0	99.5	-192.9	64.8	132.7	-227.7
TS5ex	46.9	115.4	-229.6	27.7	86.8	-198.1	56.9	124.9	-228.3
TS6en(DA)	80.6	148.0	-226.1	65.7	123.9	-195.2	89.7	158.3	-230.0
TS6ex(DA)	74.1	140.5	-222.8	59.4	117.2	-193.7	83.7	151.8	-228.4
INT5en	15.7	85.2	-232.9	-17.7	37.7	-186.0	9.9	76.3	-222.6
INT5ex	3.6	70.5	-224.4	-23.2	31.8	-184.3	5.0	69.0	-214.8
INT6en	14.2	82.6	-229.4	-11.0	43.8	-183.7	22.2	89.9	-227.1
INT6ex	5.3	73.7	-229.4	-6.9	51.3	-195.4	11.5	78.9	-226.1

- The computed activation enthalpies and entropies are lower for the *exo* channel compared to the *endo* channel, resulting into lower activation free energies for the *exo* pathway than the *endo* pathway.

3.0 Methodology

- All computations were carried out with the Gaussian 03[17] program package.

- The full geometry optimizations of all structures and transition states were computed using density functional theory (DFT) by applying the three-parameter hybrid functional by Becke's[24] (B3) and the correlation functional by Lee-Yang-Parr's (LYP).

- The basis set 6-31G(d) was employed as it is a well-established method for the prediction of activation energies of cycloaddition reactions and to provide geometries and electronic properties in good correlation with literature.

- Solvent effects were taken into account with the polarizable continuum model (PCM) as developed by Tomasi's group in the framework of self-consistent reaction field (SCRF).

- The solvent used in this present research is tetrahydrofuran (THF) with temperature and pressure considered at 298.15 K and 1 atm.

- The stationary points located (reactants, transition states, intermediates and cycloadducts) were characterized by frequency computations in order to verify that minima and TSs have zero and one imaginary harmonic vibrational frequency, respectively.

- The reported electronic energies include zero-point energies (ZPE) corrections scaled by a factor of 0.96.

4.0 Conclusions and Future Work

DFT computation using B3LYP functional in conjunction with the 6-31G(d) basis set has been used to study the 1,3-DC and DA reactions of pyridinium-3-olate and substituted pyrazinium-3-olates with methyl acrylate. Solvent effects were also evaluated so as to mimic the experimental environment and it is found that results in solvent phase are in accord with literature experimental results where 6-substituted 8-azabicyclo[3.2.1]oct-3-en-2-one and 6-substituted diazabicyclo[3.2.1]oct-3-en-2-ones are preferred.

The results of the two reaction pathways are compared and discussed:

- For the cycloaddition reactions of pyridinium-3-olates with methyl acrylate, the 1,3-DC is the more favourable pathway and this is in line with experimental outcomes; the *exo* cycloadducts are kinetically and thermodynamically favoured over the *endo* ones. In addition, substitution of *N*-hydrogen by *N*-methyl on the 1,3-dipole does not affect the course of the reaction.
- It is found that reactions between methyl-substituted pyrazinium-3-olates with methyl acrylate are dependent on the location of the methyl group on the pyrazinium ring.

In continuation of this study, the substituent effect on the pyrazinium-3-olate will be further investigated by using methyl methacrylate as the electon-deficient alkene.

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