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PM3 study of the stereochemistry of heterodienophile cycloadditions to pyrrole: endo lone pair effect

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Abstract

A semiempirical PM3 theoretical study of heterodienophile addition to pyrrole, a heterocyclic aromatic diene is presented. The results are compared with the ethylene addition to pyrrole. Three approaches were used to determine the reactivity of the dienophiles: frontier orbital energy correlation, comparison of the calculated activation barriers, and comparison of the structural features of the transition state structures, all generated by PM3 calculations. On the basis of the frontier molecular orbital theory it was concluded that the reaction is LUMO dienophile controlled and that all studied heterodienophiles are more reactive than ethylene. Because pyrrole has a higher HOMO energy than cyclopentadiene, it was concluded that pyrrole is more reactive than cyclopentadiene as the diene in Diels–Alder reactions with normal electron demand. On the other hand, reaction energy barriers predict that almost all heterodienophiles except oxygen are less reactive than ethylene. Discrepancies in the frontier orbital and activation energy predictions are discussed in the light of repulsion interactions between the heteroatom endo lone pair and the π -system of pyrrole. In this way the stereoselectivity of the heterodienophile cycloadditions to pyrrole, as well as the geometries of the transition structures, can be explained.

1. Introduction

Hetero-Diels–Alder reactions are often a key step in the stereoselective syntheses of natural products [1] and a source of new functionalities in the molecule [2]. Many five membered aromatic heterocycles normally react with heterodienophiles [1] producing desirable reaction intermediates. It has been generally accepted that heterodienophile addition to butadiene derivatives

follows a concerted, asynchronous mechanism, although a stepwise zwitterionic mechanism is also possible with polar dienophiles and catalyzed processes [3]. The all-carbon Diels–Alder reactions have been studied extensively [4], but there are only a few experimental [5] and theoretical [3,6] examples of heterodienophile additions to butadiene derivatives and, to the best of our knowledge, there are no theoretical calculations of the transition state structures for heterodienophile addition to five membered heteroaromatics. As part of a wider general theoretical investigation of hetero Diels–Alder reactions [7], here we will present our PM3 semiempirical study of heterodienophile additions to pyrrole.

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2. Methodology

All calculations were performed on a DEC 7620 computer. CHEM-3D PLUS on a Macintosh IIfx was used as a graphical interface for drawing and visualizing all structures and for preparing input files for MOPAC 6.0 [8]. The search for the transition states and their verification [9] was performed as described previously [10]. Vibrational and thermodynamic analyses were performed on all optimized structures.

3. Results and discussion

The geometries of the reactants and corresponding transition states were optimized by PM3 [11] of the MOPAC computational package [8]. We have considered only the concerted pathways for the dienophile addition to pyrrole although the non-concerted reaction pathways might also be contemplated. A stepwise mechanism for these hetero Diels–Alder reactions might be possible, but we have abandoned that possibility because it usually involves reactants with substituents that can stabilize ionic or radical species formed along the reaction pathway. Such substituents are absent for the studied compounds.

We have evaluated the reactivity of the heterodienophiles in three different ways: by correlating the energies of the reactants' frontier orbitals, by comparison of the activation barriers of the

addition reaction as well as the geometrical features of the transition state structures.

3.1. Frontier orbital approach

According to the frontier orbital theory [12] the rate of a reaction is determined largely by the degree of the HOMO–LUMO interactions of the reactants. Better orbital overlap will be obtained by two frontier orbitals that have similar energies, or in other words, if the energy gap between the frontier orbitals of the reactants is smaller. The PM3 calculated energies of frontier orbital and their energy gaps are presented in Table 1.

Better orbital overlap should be obtained between the HOMO orbital of pyrrole and the LUMO orbital of the heterodienophile than in the other combination, because the energy gaps are smaller (Table 1). Accordingly, the reaction is LUMO dienophile controlled, and the most reactive heterodienophile will be the one that has energetically the lowest LUMO orbital. The heterodienophiles in Table 1 are listed in order of increasing acceptor ability as predicted by PM3 calculations. In comparison with cyclopentadiene, pyrrole should have higher reactivity towards the heterodienophiles because it has a higher HOMO energy, making the HOMO–LUMO gap smaller. Thus it is predicted that the least reactive dienophile in the series should be formaldimine, while the most reactive should be oxygen. It is interesting that frontier orbital theory predicts that all the studied heterodienophiles should be more reactive than ethylene, although the experimental evidence does not seem to support this. There are many published results of substituted ethylene additions to pyrrole, but to the best of our knowledge there are none for heterodienophile additions. One possible explanation for the absence of reports for this reaction is that in the heterodienophile addition to pyrrole, a fast degradation of the Diels–Alder adduct might occur, giving rise to polymeric materials, which synthetic chemists tend to encounter in reactions with pyrroles.

3.2. Activation energy barriers

Better evaluation of the reaction can be obtained

Table 1
PM3 calculated HOMO and LUMO energies (eV) for the reactants in the Diels–Alder reaction with pyrrole

Reactant	$E(\text{HOMO})$	$E(\text{LUMO})$	$\Delta E(\text{A})^a$	$\Delta E(\text{B})^a$
cyclopentadiene	-9.23217	0.32407		
pyrrole	-8.92826	1.11401		
ethylene	-10.64167	1.22833	11.75568	10.15659
formaldimine	-10.01296	0.99561	11.12697	9.92387
formaldehyde	-10.63006	0.82658	11.74407	9.75484
<i>cis</i> -diazene	-9.58499	0.53213	10.69900	9.46039
<i>trans</i> -diazene	-9.61602	0.49747	10.73003	9.42573
nitrosyl hydride	-9.84176	0.07099	10.95577	8.99925
oxygen	-10.73322	-0.98204	11.84723	7.94622

$$^a \Delta E(\text{A}) = E(\text{LUMO}_{\text{pyrrole}}) - E(\text{HOMO}_{\text{dienophile}});$$

$$\Delta E(\text{B}) = E(\text{LUMO}_{\text{dienophile}}) - E(\text{HOMO}_{\text{pyrrole}})$$

by calculating its activation barrier. The activation barriers predicted by PM3 for the heterodienophile addition to pyrrole are presented in Table 2. These results are quite different than the ones predicted by frontier orbital theory. Ethylene is not the least reactive dienophile anymore. This difference in the predicted reactivity is not surprising. When calculating the frontier orbital energies, two separated reactants are considered, and the detailed steric and electronic interactions that might occur in the transition state are not accounted for. Those interactions are of crucial importance for the stereoselectivity of the Diels–Alder cycloadditions. For this reason, the calculation of the activation energies is the most reliable method for predicting the reactivity of the reactants. According to the activation barriers, the most reactive dienophile in this series is oxygen, the same as was determined by frontier orbital theory, but now diazene should be a considerably unreactive dienophile. In all cases, where exo/endo isomers are possible, the one that has the N–H bond endo or the lone electron pair exo is energetically preferred. Because the heterodienophiles do not have substituents other than hydrogen, the steric contribution to the energy barriers of the reaction is negligible. Consequently, electronic interactions must be predominant.

Examples that illustrate the electronic interactions are the isomeric additions of diazenes to pyrrole. In all cases, the pyrrole N–H bond can point toward or away from the incoming heterodienophile. From a steric point of view, it should be

more favorable to be pointing away from, but electronically it would be preferred that it points toward the incoming dienophile because then the lone pair orbital of the pyrrole nitrogen will not interact with the orbitals of the dienophile. PM3 predicts that the isomer with the N–H bond of pyrrole pointing toward the incoming dienophile is 10–20 kcal mol⁻¹ more stable. Although there are minimal interactions of the heterodienophile lone pair orbitals with the π -orbitals of pyrrole in the *cis*-diazene transition state when the N–H bonds are endo, some repulsion interactions still exist and make the *endo* N–H addition less favorable than in the addition of ethylene. Frontier orbital theory predicts otherwise (Table 1) because, as was already pointed out, it does not account for the detailed electronic interactions between the reactants. The activation barrier for addition of *cis*-diazene with N–H bonds in the exo position should be higher than for the N–H endo isomer because the repulsion interactions between the lone pair orbitals of the dienophile and the pyrrole π -orbitals should be maximal. The value of the activation barrier for addition of *trans*-diazene to pyrrole is between the two barriers for the *cis*-diazene addition to pyrrole, because one N–H bond is exo and the other is endo, making the n - π repulsion interactions lower than in the exo H but higher than in the endo H *cis*-diazene addition. The activation barriers for the addition of other dienophiles to pyrrole can be similarly explained by a combination of the frontier orbital energy gap and n - π repulsion interactions between the reactants in the transition structures.

The question always present in computational chemistry is how reliable the results are. Of course, it is best to compare them with experimental values when they are available, or to do a comparison of reactivities in a series of reactions, or to compare the calculations with higher level calculations that have proved to be reliable. In our case, the experimental results for these reactions are not available. There are no literature data available on the heterodienophile addition to pyrrole, but there are some data for the addition of the same series of dienophiles to butadiene [3](a) and cyclopentadiene [7]. The results are very similar to the ones obtained with the RHF/6-31G*//

Table 2
Activation energies (kcal mol⁻¹) of hetero-dienophile addition to pyrrole calculated by PM3 (showing comparison to ethylene)

Dienophile	TS	PM3	PM3 + ZPE
ethylene	1	35.3 (0.0)	36.5 (0.0)
formaldimine, endo H	2	37.4 (+2.1)	38.6 (+2.1)
formaldimine, exo H	3	41.0 (+5.7)	42.1 (+5.6)
formaldehyde	4	44.6 (+9.3)	46.0 (+9.5)
<i>cis</i> -diazene, endo H	5	39.7 (+4.4)	41.1 (+4.6)
<i>cis</i> -diazene, exo H	6	47.5 (12.2)	48.7 (12.2)
<i>trans</i> -diazene	7	45.5 (10.2)	46.9 (10.4)
nitrosyl hydride, endo H	8	38.9 (+3.6)	40.5 (+4.0)
nitrosyl hydride, exo H	9	43.2 (+7.9)	44.8 (+8.3)
oxygen	10	28.3 (-7.0)	28.7 (-7.8)

RHF/3-21G ab initio theoretical model [3](a). There are no available ab initio results for oxygen addition to butadiene. According to ab initio calculations, the highest activation barrier is for the exo N–H addition of *cis*-diazene to butadiene, while the lowest is for the endo N–H addition of nitrosyl hydride to butadiene [3](a).

3.3. Geometries of transition structures

The geometries of the transition structures result from a combination of frontier orbital energy correlation and $n-\pi$ orbitals repulsion interactions. The PM3 generated transition structures are presented in Fig. 1. The ethylene addition to pyrrole has a transition structure very similar to the one obtained with the same method for ethylene addition to cyclopentadiene, with shorter (0.035 Å) new forming CC bonds [7]. As expected, because both the diene and the dienophile have a plane of symmetry, the reaction is synchronous.

For the cycloaddition of formalimine, two diastereomeric transition structures **2** and **3** were located. The asynchronicity of the transition structure depends on the position of the nitrogen lone pair. In the case of an exo nitrogen lone pair in **2**, the new forming C–N bond is a little shorter (0.009 Å) compared to the other isomer **3**. That is a result of the higher $n-\pi$ repulsion interactions between formalimine and pyrrole in **3** than in **2**. The asynchronicity of transition states **2** and **3** is 0.245 Å and 0.257 Å, respectively. The effect of the repulsion interactions is illustrated by the dihedral angle between two new forming bonds (C_2XXC_5). In the case of transition state **2** where these interactions are minimal, the dihedral angle is -3.4° , but in the isomeric transition structure **3** it seems like the nitrogen is pushed away and the dihedral angle is 7.2° .

The transition structure for the addition of formaldehyde to pyrrole must be asynchronous because two different bonds, CC and CO, are being formed. The oxygen bond is shorter and the asynchronicity of the transition structure is relatively small (0.060 Å). The repulsion interactions between the lone pairs of oxygen and the π -system of pyrrole are reflected in the dihedral angle ($d = 2.2^\circ$).

cis-Diazene adds to pyrrole with the formation of two possible isomers through transition structures **5** and **6**. Both of them are synchronous because both the dienophile and the diene have a plane of symmetry. The repulsion interactions are clearly seen in transition structure **6** where the new forming C–N bond is 0.027 Å longer. The $n-\pi$ repulsion interactions are clearly demonstrated by the dihedral angle of the two new forming C–N bonds in transition structure **7** of *trans*-diazene addition to pyrrole. In this transition structure, one of the two lone pairs of *trans*-diazene is in the exo, while the other is in the endo position. The nitrogen atom with endo lone pair is pushed away from the structure making the dihedral angle 5.7° .

Both transition state structures that represent the cycloaddition of nitrosyl hydride to pyrazole are asynchronous. There are three electron pairs that can electronically interact with the π -orbitals of the pyrrole moiety in transition structures **8** and **9**. The asynchronicity is higher when the lone pair on nitrogen is in the exo position because the whole dienophile is pushed away. The asynchronicity of transition structure **8** with the exo nitrogen lone pair is 0.279 Å, and in transition structure **9** with an endo nitrogen lone pair it is 0.299 Å. Again the dihedral angle between the new forming C–O and C–N bonds demonstrates the effect of the $n-\pi$ repulsion interactions. In the case of the exo nitrogen lone pair (transition structure **8**), the dihedral angle is 6.8° , while in **9** with the endo nitrogen lone pair the dihedral angle of -5.5° .

The last reaction studied here is the addition of oxygen to pyrrole. Both frontier orbital theory and the calculated energy barriers predict it to be the most reactive dienophile studied here. The transition structure **10** supports this conclusion. The forming C–O bond is considerably shorter than in the case of nitrosyl hydride addition to pyrrole. The transition structure is synchronous and in many ways resembles the classical picture of a synchronous Diels–Alder transition structure.

4. Conclusion

Three different approaches to determining the reactivity of heterodienophiles in Diels–Alder

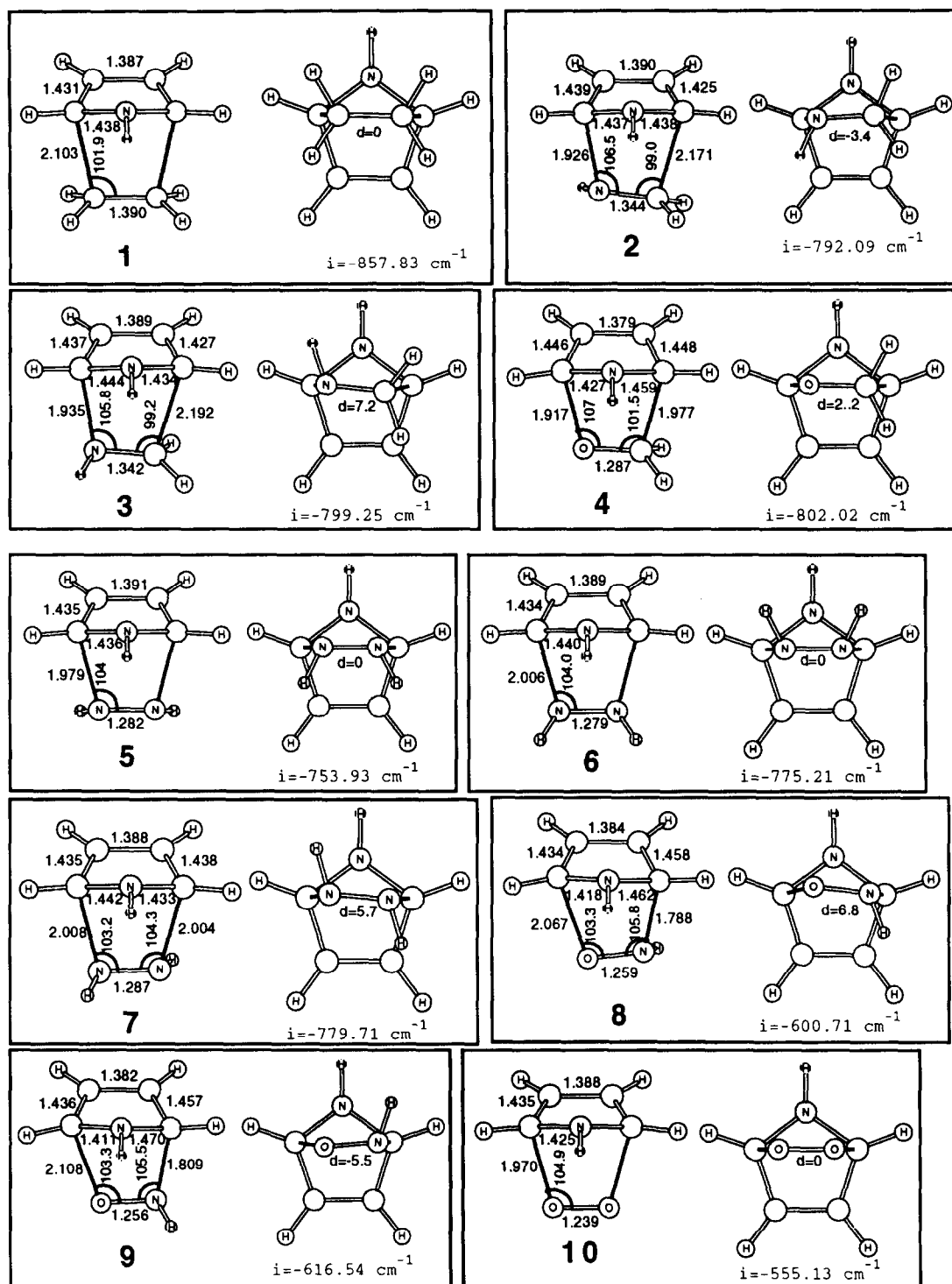


Fig. 1. PM3 calculated transition structures of heterodienophile addition to pyrrole (distances in ångströms, angles in degrees, $d \equiv$ dihedral C_2XXC_5).

reactions with pyrrole were undertaken: frontier orbitals, activation barriers, and geometry features of the transition state structures. According to frontier orbital theory, the reactions are LUMO dienophile controlled and are more favorable for the pyrrole than for the cyclopentadiene additions. In this series of heterodienophiles, frontier orbital theory predicts that all of them are more reactive than ethylene.

On the other hand, according to the PM3 calculated energy barriers, only oxygen is more reactive than ethylene. That is more reasonable in view of the fact that there are no experimental data for these heterodienophile additions to pyrrole. Frontier orbital theory cannot predict the stereoselectivity of the addition. Comparison of the activation barriers reveals that in all cases the endo hydrogen isomers are preferred over the exo hydrogen isomers which is in good agreement with ab initio calculations on both butadiene and cyclopentadiene.

Both the predicted reaction energy barriers and the geometries of the transition structures demonstrate the strong influence of the $n-\pi$ repulsion interactions. Generally, in the transition states with exo lone pairs, the new forming bonds are shorter and the asynchronicity is smaller. With endo lone pairs, the dienophile is pushed away and the dihedral angle is bigger. In other words, the exo lone pair transition structure is closer to the product and the activation energy is lower, while the endo isomer is closer to reactants and the activation energy is higher.

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