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The reliability of PM3 for predicting the reactivity of cyanoethenes in Diels-Alder reactions with pyrrole was tested. Using frontier orbital theory it was predicted that the reaction is LUMO dienophile controlled, and the reaction should be facilitated in comparison to cyclopentadiene additions (pyrrole has higher HOMO energy). The transition structures were generated and compared with similar ones generated with both *ab initio* and PM3 calculations for cyclopentadiene additions: The geometries of the transition structures are similar, although the new CC forming bonds are 2-6% shorter, and the degree of asynchronicity is higher. The prediction of the activation barriers with the PM3 method failed totally. The preferred *exo* isomer in each case, indicated that the predicted stereoselectivity was incorrect. The prediction of the relative reactivity was also unreliable. Qualitative analyses of similar series of compounds can be obtained by frontier orbital energy correlations. All conclusions were made on the assumption that the reaction is concerted, which does not exclude the possibility that PM3 might be able to predict reliable reaction barriers if some other mechanisms are considered.

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## Introduction.

The addition of alkenes to aromatic five-membered heterocycles has been one of the major methods for the preparation of new heterocyclic compounds [1], and a source of new functionalities [2] on the long road in the preparation of natural products. It is generally accepted that these reactions are concerted, asynchronous cycloadditions. For the all-carbon Diels-Alder reactions there is an enormous body of theoretical study [3], while to the best of our knowledge, there is only one reported study of ethylene addition to oxazole and isoxazole [4]. We have been recently involved in the theoretical study of the all-carbon and heterodienophile additions to five membered aromatic heterocycles [5].

There are a number of experiments of substituted pyrroles participating as  $4\pi$  components in all-carbon Diels-Alder reactions [6]. Pyrrole and 1-alkylpyrroles generally react with  $\pi$ -deficient alkenes and alkynes to give Michael addition products or aromatic phthalic esters *via* a Diels-Alder adduct intermediate [7]. This procedure, for example, has been utilized in the synthesis of juncusol [8] where the formation of the bicyclic Diels-Alder intermediate is the slowest step in the transformation. Here we would like to present our test of the PM3 method as a tool for organic chemists in predicting the reactivity of different dienophiles in Diels-Alder reactions with pyrrole. The method was chosen because it is simple to use, it is relatively fast even on modest computational resources, and consequently can be widely applied.

## Methodology.

All calculations were performed on a DEC 7620 computer. Chem-3D Plus on a Macintosh IIx was used as a graphical interface for drawing and visualizing all structures and

for preparing input files for MOPAC [9]. The search for the transition states and their verification [10] was performed as described previously [11]. Vibrational and thermal analyses were performed on all optimized structures.

## Results and Discussion.

The geometries of the reactants and corresponding transition states were optimized by the PM3 [12] method. We considered only the concerted pathway for the dienophile addition to pyrrole, although the stepwise reaction pathway can also be contemplated. However, the non-concerted mechanism involves the formation of intermediates that must be stabilized with substituents on the aromatic rings. Since there are no such substituents, we excluded the stepwise mechanism from consideration.

PM3 was chosen over the other semiempirical methods because in the case of polar additions with heteroatoms very good agreement between theoretical studies and experimental results was observed [13]. There are several ways of determining the reactivity of different compounds in a reaction. One very popular, simple, and mostly qualitative method is determination of the energy gap between the frontier orbitals of the reactants. According to this frontier orbital theory [14] the rate of the reaction is determined largely by the degree of the HOMO-LUMO reactant interactions. If two frontier orbitals of the reactants have similar energies there will be better molecular orbital overlap, and the energy of the transition structure will be lower. In other words, in our case, the energy gap between the frontier orbitals will determine the order of the dienophile reactivity in the cycloadditions to pyrrole. The PM3 calculated energies of the frontier orbitals, and their energy gaps are presented in Table 1. According to frontier orbital theory the molecular orbital overlap in the transition state will occur

and the interaction will be productive when the orbitals have proper symmetry and they have similar energies. Thus the smaller energy gap between the frontier orbitals of the diene and the dienophile gets, the reactivity gets higher. In all cases the energy gap between HOMO of pyrrole and LUMO of the dienophile (column B, Table 1) is much lower than in the other combination (column A, Table 1). That makes this kind of addition LUMO dienophile controlled reaction and tetracyanoethene the most reactive dienophile ( $\Delta E = 6.55$  eV). Because the HOMO energy of pyrrole is 0.30 eV higher than cyclopentadiene, cycloaddition reactions of electron deficient dienophiles like tetracyanoethene should be more feasible with pyrrole than with cyclopentadiene.

Table 1  
PM3 Calculated HOMO and LUMO Energies (eV)  
for the Reactants in the Diels-Alder Reaction

Reactant	HOMO	LUMO	A	B
cyclopentadiene	-9.23217	0.32407		
pyrrole	-8.92826	1.11401		
ethylene	-10.64167	1.22833	11.75568	10.15659
acrylonitrile	-10.88535	-0.18751	11.99936	8.74075
fumaronitrile	-11.07960	-1.26615	12.19361	7.66211
maleonitrile	-11.04322	-1.21564	12.15723	7.71262
1,1-dicyanoethene	-11.16180	-1.10946	12.27581	7.81880
tetracyanoethene	-11.40151	-2.68041	12.51552	6.55176

A -  $\Delta E = \text{LUMO}_{\text{pyrrole}} - \text{HOMO}_{\text{dienophile}}$

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

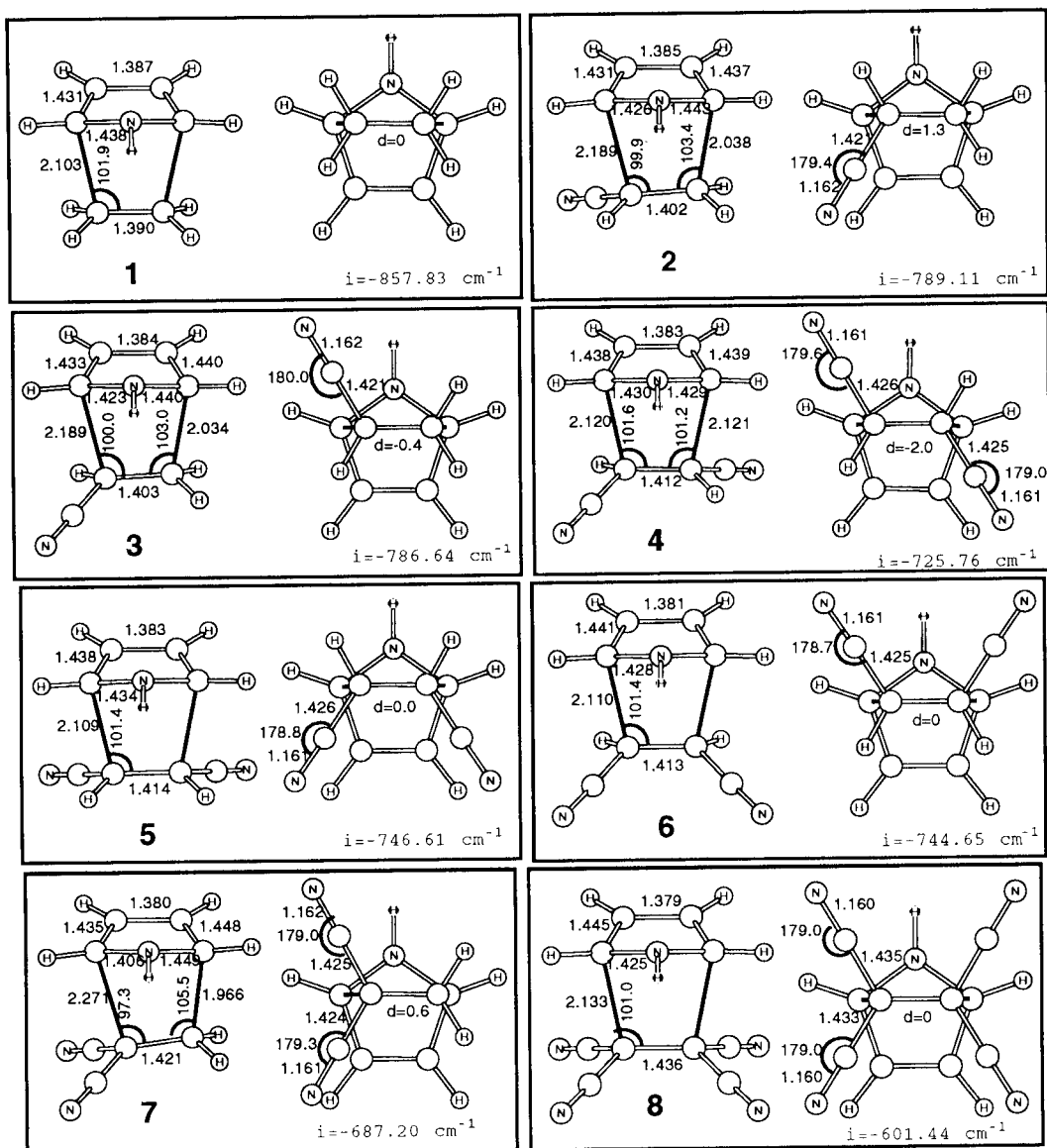


Figure 1. Geometries of the transition structures in the cyanoethene addition to pyrrole calculated by PM3. (bonds in angstroms, angles in degrees, i - imaginary frequency)

It is apparent that frontier orbital theory cannot predict the preferences in the formation of *exo-endo* isomers. Besides, the frontier energy correlation does not take into account the substituent interactions that are present in the transition structure, which are often of crucial importance in determination of the stereochemistry of the products. That can be overcome by correlation of the calculated reaction barriers. Prior to evaluation of the activation barriers we will discuss the structural features of the transition structures.

#### Geometries of Transition Structures.

The PM3 generated transition state structures are presented in Figure 1. In all transition states the N-H bond of pyrrole is pointing toward the dienophile. Our attempt to keep the N-H bond outward was unsuccessful; the structure has a 10 kcal/mol higher energy and the NLLSQ optimizer always transformed the structure into the one with lower energy. That can be explained by the  $n-\pi$  repulsion interactions which have been used to rationalize the stereoselectivity of the hetero dienophile additions to aromatic heterocycles [5].

The geometries of the transition structures are in many ways similar to the ones obtained in the cyclopentadiene addition to the same dienophiles calculated by PM3 [15]. The two new forming C-C bonds in the symmetrical transition state **1** of ethylene addition to pyrrole are 0.035 Å shorter than in the addition to cyclopentadiene. Thus the transition state seems to be closer to the product than in the case of cyclopentadiene addition.

Because acrylonitrile is asymmetric dienophile its addition to the symmetric diene must produce asynchronous transition structure. Two diastereomeric transition structures **2** and **3** were located. The asynchronicity strongly depends on the polarity of both the dienophile and the diene, as well as the electronic and steric interactions between the constituents in the transition structures. The degree of asynchronicity for structure **2** is 0.151 Å and is 0.041 Å higher, while the bonds are shorter, than in the case of the cyclopentadiene reaction [15]. The isomeric transition structure with the nitrile group in *exo* position **3**, has structural features that follow a similar pattern. The structure has higher asymmetry (0.155 Å) than in the case of cyclopentadiene addition with both new forming bonds shorter (0.126 Å) [15]. The addition of fumaronitrile to pyrrole should also result in formation of an asynchronous transition structure, although both reactants have symmetry. The two new forming C-C bonds have almost equivalent distances. That suggests that PM3 cannot account for the *endo* interactions that are responsible for the formation of *endo*-substituted products of Diels-Alder addition, better known as the Alder rule. This finding is also demonstrated on the C-C forming bond distances of the two isomeric transition structures **5** and **6** that represent the addition maleonitrile to pyrrole.

Because of the symmetry of both reactants it is not surprising that both transition state structures are fully synchronous. The surprising fact is that both transition states have the same new forming C-C bond distances, so the Alder rule is not accounted for in these two transition structures. Again, in comparison to cyclopentadiene [15] the new forming C-C bonds are 0.034 Å and 0.049 Å shorter, respectively.

The new forming C-C bonds in transition structure **7** of 1,1-dicyanoethene addition to pyrrole must have different length because the dienophile does not have a plane of symmetry bisecting the CC double bond. The CH<sub>2</sub>-pyrrole new forming CC bond is 0.275 Å shorter than the C(CN)<sub>2</sub>-pyrrole new forming bond. Both bonds are shorter than in the cycloaddition reaction with cyclopentadiene [15].

The addition of the highly symmetric tetracyanoethene to pyrrole must produce synchronous transition structure **8**. Furthermore, because of higher steric interactions between the dienophile and the diene than in the case of ethylene and maleonitrile the new forming CC bonds have to be little longer than in transition structures **1**, **5**, and **6**. Those structural features were actually confirmed by PM3 calculations.

#### Activation Energies.

The activation energies of the cyanoethene additions to pyrrole are presented in Table 2. The most reactive species according to the activation energies predicted by PM3 calculations is 1,1-cyanoethene. There are no

Table 2  
PM3 Calculated Activation Energies of  
Cyanoethene Additions to Pyrrole

Transition structure	<i>E</i> /kcal·mol <sup>-1</sup>	<i>E</i> <sub>0</sub> /kcal·mol <sup>-1</sup>
<b>1</b>	35.3 (0.0)	36.5 (0.0)
<b>2</b>	35.7 (0.4)	36.3 (0.2)
<b>3</b>	34.3 (-1.0)	34.9 (-1.6)
<b>4</b>	35.3 (0.0)	35.5 (-1.0)
<b>5</b>	37.2 (1.9)	37.3 (0.8)
<b>6</b>	34.2 (-0.9)	34.3 (-2.2)
<b>7</b>	33.5 (-1.8)	33.6 (-2.9)
<b>8</b>	35.6 (0.3)	35.0 (-1.5)

experimentally obtained activation energies for cyanoethene additions to pyrrole, but as already discussed, according to molecular orbital theory the most reactive should be the dienophile with more electron withdrawing groups. If we compare the reactivity of these dienophiles in the cyclopentadiene addition, certainly the reactivity should increase with the number of cyano groups on ethylene, and in case of *endo-exo* isomers, the one with an *endo* cyano group should have the lower activation energy. A relatively good correlation of the activation barrier with their LUMO energies is also expected. That is not quite so.

The most reactive dienophile is predicted to be 1,1-dicyanoethene but not tetracyanoethene. In all cases the calculated *exo* isomers have lower energy than the *endo* isomers which is opposite to the Alder rule. The PM3 calculated activation energies with pyrrole as diene seems to suffer from the same problems as in the case of cyclopentadiene as dienophile [15]. The relative reactivity for all *exo* isomers seems to follow the expected order, but the differences in the energy are far too small and the prediction of the stereoselectivity of the product is incorrect.

The same analysis was performed with other heterocyclic compounds (oxazole, isoxazole, imidazole, and triazole) as dienophiles in cyanoethylene cycloaddition reaction with the same results. However, we have presented only the results with pyrrole since they best depict the advantages and disadvantages of the PM3 method.

### Conclusions.

The presented calculations of the Diels-Alder transition states of addition cyanoethylene to pyrrole are based on the assumption that in the reaction two C-C bonds will be formed simultaneously. In comparison with known *ab initio* and PM3 calculations, the transition structures of pyrrole as diene closely resemble the ones obtained in the cyanoethene addition to cyclopentadiene. The two new forming CC bonds are generally 2-6% shorter, and the transition structures with asymmetric dienophiles are more asynchronous than in the case of cyclopentadiene.

Frontier orbital theory generally predicts the correct order of reactivity that has been experimentally observed for the addition to cyclopentadiene. The PM3 energy barriers for the cycloaddition reactions are too high, especially when ethylenes with more cyano groups are involved. It is interesting to mention that PM3 always gives preference to the incorrect isomer, contrary to the Alder rule.

There are two possible interpretations of these results: Either the semiempirical method cannot handle the synchronous mechanism of the Diels-Alder addition reaction to pyrrole or the reaction is not synchronous at all, and goes through a stepwise mechanism. The anomalies of predicted results are the same as in the case of cyanoethene addition to cyclopentadiene.

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