

## SEMIEMPIRICAL STUDY OF THE OXAZOLE-ISOXAZOLE REACTIVITY IN DIELS-ALDER REACTIONS\*

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PM3 semiempirical calculations of the activation barriers for the cycloaddition reactions of ethylene, maleonitrile, and maleic anhydride to oxazole and isoxazole show why oxazole adducts are formed, contrary to isoxazole adducts which experimentally have not been generally observed. The calculated heats of formation for the oxazoles and the products of addition are in agreement with similar ab initio calculations for the case of ethylene addition. The frontier orbitals of the reactants were also computed and correlated.

**Keywords:** Semiempirical; PM3; Frontier orbital theory; Diels-Alder.

### INTRODUCTION

Oxazole is the only oxygen containing azole that readily undergoes Diels-Alder reactions. This reaction has been widely explored because the oxazole derivatives are a versatile source for the preparation of substituted pyridine bases [1]. The Kondrat'eva reactions, as the oxazole cycloadditions are known, are very useful for the preparation of pyridines including biologically important compounds – derivatives of nicotinic and isonicotinic acids, i.e. B6 vitamins and their analogues [2]. Ab initio quantum mechanical studies of heterodienophile additions to oxazole [3], as well as to other heterodienes [4] indicate that the heteroatom lone pairs play a decisive role in directing the regioselectivity of these reactions. However, there are no experimental reports on the Diels-Alder reactions with isoxazoles [5].

Most oxazoles which undergo Diels-Alder reactions contain electron-donating substituents indicating that oxazole functions as the electron-rich component. An attempt to rationalize the oxazole reactivity and the selectivity in the Diels-Alder reactions by  $\pi$ -electron density of localization energies and by frontier orbital theory have not been uniformly successful [6]. Recently Houk and coworkers reported an ab initio study of the ethylene addition to isoxazole and oxazole in terms of their different reactivity [7]. Since it would be of interest to quantum chemical practitioners, we would like to present a semiempirical study of the isoxazole-oxazole reactivity with ethylene, maleonitrile and maleic anhydride, and determine how these results correlate with available ab initio calculations.

### PROCEDURES AND METHODS

Chem-3D Plus on a Macintosh IIfx was used as a graphical interface for preparing and visualizing all structures which were initially minimized by the built in molecular mechanics force field. An internal coordinate file was generated for MOPAC 6.0 [8] calculations. All semiempirical calculations were performed on a DEC 7620 computer. The geometries of the

reactants, oxazoles, isoxazole, ethylene, maleonitrile, and corresponding transition structures were optimized by the PM3 method [9] without restricting any parameters. 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

Only the concerted pathways for the dienophile addition to oxazole or isoxazole were considered, although the non-concerted reaction pathways might

also be contemplated. The non-concerted mechanism involves the formation of intermediates that must be stabilized with substituents on the aromatic rings.

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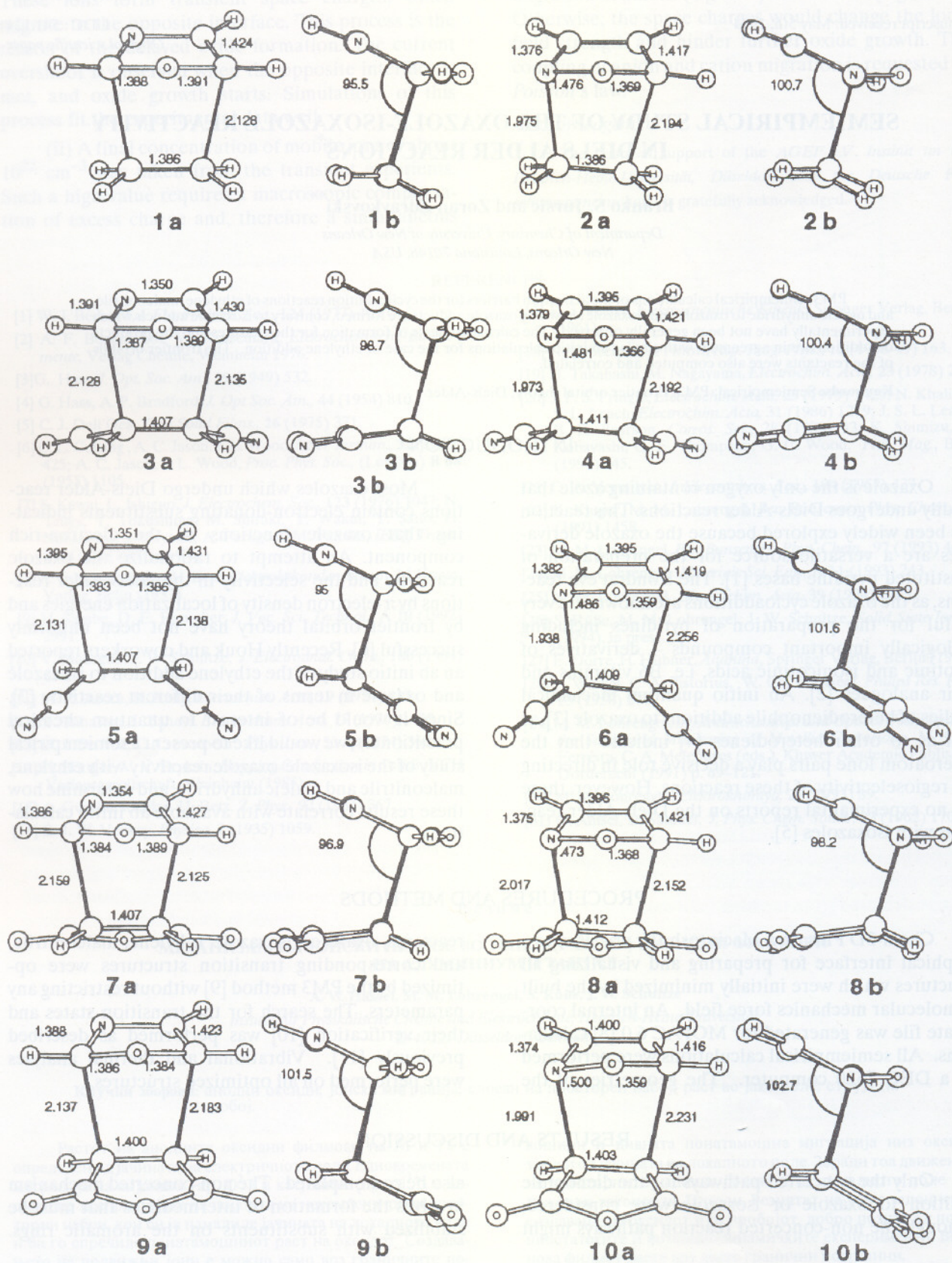


Fig. 1. PM3 optimized transition structures for the cycloaddition of ethylene, maleonitrile, and maleic anhydride to oxazole and isoxazole. (bond lengths in Å; bond angles in degrees)

However, in this case there are no such substituents, so the potential energy surface corresponding to the stepwise mechanism was not investigated.

The geometries of the concerted transition state structures are presented in Fig. 1. All ten transition state structures are slightly asynchronous, the isoxazoles having a higher degree of asynchronicity. The oxazole transition structures highly resemble the fully synchronous transition structures of the corresponding Diels-Alder additions to cyclopentadiene calculated by AM1, PM3 [12] and *ab initio* methods [13]. The new forming bonds in the transition structures **1**, **3** and **5** differ by only ~1% from those with cyclopentadiene [12]. In the oxazole series the highest synchronicity was observed in the transition structure of ethylene addition (structure **1**  $\Delta r = 0.018 \text{ \AA}$ ). As expected, the transition states with isoxazole are considerably asynchronous. The highest degree of asynchronicity was obtained with maleonitrile as dienophile (structure **6**). The forming bond lengths for the transition structure are 1.938  $\text{\AA}$  and 2.256  $\text{\AA}$ . One bond is shorter by 0.2  $\text{\AA}$  whereas the other longer by 0.118  $\text{\AA}$  compared to the Diels-Alder reaction of cyclopentadiene with ethylene [12]. There is a very small charge transfer from ethylene to oxazole or isoxazole, very similar to *ab initio* calculations [7].

There are a couple of ways to explain the different reactivity of isoxazole series in relation to the oxazole series. Most oxazoles which yield Diels-Alder adducts contain electron-donating substituents, so oxazole acts as the electron-rich component and the reaction should be governed by interaction of the highest occupied molecular orbital (HOMO) of oxazole with the lowest unoccupied orbital (LUMO) of the dienophile. The PM3 calculated HOMO and LUMO energies for oxazole, isoxazole, and the dienophiles studied are presented in Table I. According to frontier orbital theory [14] the rate of the reaction is determined largely by the HOMO-LUMO interactions of the reactants i.e. the smaller the energy gap between the frontier orbitals the greater the reactivity. When applied to these reactions, it predicts that the addition of ethylene to oxazole is a LUMO oxazole controlled addition [15]. Also, it is predicted that isoxazole should be somewhat more reactive than oxazole (1013.1 kJ/mol vs. 1047.9 kJ/mol) which is contrary to experimental [3, 4] and *ab initio* findings [7]. If the reaction is HOMO diene controlled, oxazole should be always more reactive than isoxazole because its HOMO energy is higher (Table I). In the addition of both maleonitrile and maleic anhydride to oxazole and isoxazole the frontier orbitals correctly predict that the reaction is HOMO oxazole controlled and that oxazole should be more reactive as an electron-donating diene in the Diels-Alder reactions. According to the frontier orbital energy gap, the adducts between oxazole and maleic anhydride should have the smallest activation energy of the discussed species. In order to confirm

this, the activation energies of these cycloadditions were calculated (Table II).

Table I  
HOMO and LUMO energies for the reactants in the Diels-Alder reactions.

Reactant	HOMO <sup>a</sup>	LUMO <sup>b</sup>	HOMOdiene-LUMOdienophile <sup>c</sup>	
			Oxazole	Isoxazole
Oxazole	967.46	21.06		
Isoxazole	996.33	13.56		
Ethylene	1026.81	118.52	1085.98	1114.85
Maleonitrile	1065.56	117.30	850.16	879.03
Maleic acid	1129.72	149.36	818.10	846.96

<sup>a</sup> HOMO -  $E(\text{HOMO})/\text{kJ} \cdot \text{mol}^{-1}$

<sup>b</sup> LUMO -  $E(\text{LUMO})/\text{kJ} \cdot \text{mol}^{-1}$

<sup>c</sup> HOMOdiene-LUMOdienophile -  $E(\text{HOMOdiene-LUMOdienophile})/\text{kJ} \cdot \text{mol}^{-1}$

Table II  
Calculated energies for the ethylene, maleonitrile and maleic anhydride addition to oxazole and isoxazole.

Dienophile	Diene	$\Delta E/(\text{kJ/mol})$	
		Endo	Exo
Ethylene	Oxazole	138.91	
	Isoxazole	169.45	
Maleonitrile	Oxazole	157.74	153.97
	Isoxazole	261.92	262.34
Maleic Anhydride	Oxazole	145.23	141.33
	Isoxazole	177.57	174.56

The calculated PM3 activation energies are consistent with the lack of reactivity of isoxazole in the Diels-Alder reactions. The activation energies in all five transition structures for the isoxazole reaction are higher than for the oxazole reaction. Also, the calculated activation energies for the addition of ethylene to oxazole and isoxazole are in agreement with the RHF/3-21G *ab initio* calculations (141.00 and 173.64 kJ/mol, respectively) [7]. It should be noted however, that the employed *ab initio* model chemistry is probably not adequate to describe this system with hetero atoms - higher levels of theory will give lower activation energy, in an even better agreement with the semiempirical value. From the data presented in Table II it can be concluded that the inability of isoxazole to par-

participate in Diels-Alder reactions stems from the high activation barrier.

The energy of formation of the azoles were also calculated. PM3 finds isoxazole to be less stable than oxazole. The calculated heat of formation for oxazole is  $-6.28$  kJ/mol and for isoxazole it is  $146.77$  kJ/mol. The values are quite different from the experimental data for the gas phase. They are  $-15.48$  kJ/mol for oxazole and  $78.66$  kJ/mol for isoxazole [14]. Surprisingly, the less stable isoxazole is the less reactive diene. This has been explained by the instability of the structures with nitrogen at the bridgehead as is the case with the isoxazole adducts [7]. In order to confirm this

we performed the calculation of the adducts **3-6** that are formed by addition of maleonitrile to oxazole and isoxazole (Fig. 2). The oxazole adducts **3p** and **5p** are more stable than the corresponding isoxazole analogues **4p** and **6p** by more than  $165$  kJ/mol. However, PM3 predicts lower activation energies for the exo adducts, contrary to the endo Alder rule. This seems to be a common limitation of the present semiempirical methods [12]. Consequently, in order to predict the correct regioisomer of the addition more expensive higher levels of ab initio calculations are necessary.

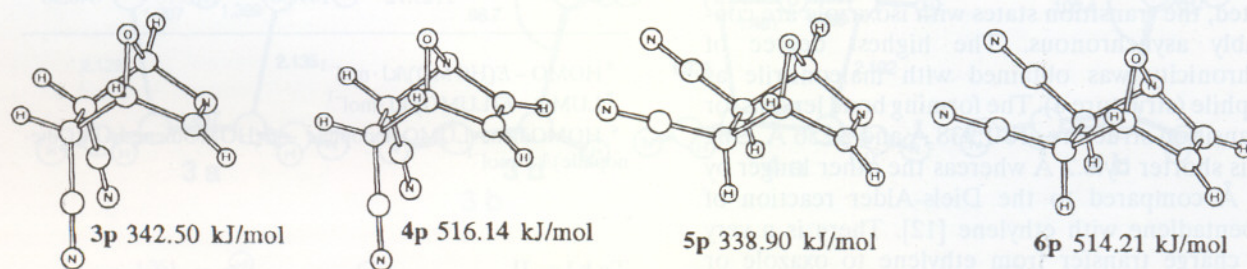


Fig 2. PM3 calculated heats of formations of possible Diels-Alder products of maleonitrile addition to oxazole and isoxazole.

## CONCLUSION

The HOMO energy level of oxazole is higher than the HOMO energy level of isoxazole and consequently, in normal electron demand Diels-Alder reactions, according to frontier orbital theory, oxazole should always be more reactive. The PM3 semiempirical method can predict the difference in the isoxazole-oxazole reactivity in the Diels-Alder reactions through

calculation of the activation barrier in the concerted mechanism. Although the PM3 Hamiltonian successfully explains the different reactivity of isoxazoles and oxazoles it fails to predict correctly the formation of the endo isomer in the cycloaddition reactions and therefore ab initio methods need to be applied.

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## Резиме

## ПОЛУЕМПИРИСКИ ИСПИТУВАЊА НА РЕАКТИВНОСТА НА ОКСАЗОЛ И ИЗООКСАЗОЛ ВО ДИЕЛС-АЛДЕРОВИТЕ РЕАКЦИИ

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Клучни зборови: PM3; полуемпириски, МОРАС; гранични орбитали.

Полуемпириските пресметувања на енергијата на активација за Диелс-Алдеровите реакции ги потврдуваат експерименталните сознанија за реактивноста на оксазолот и нереактивноста на изооксазолот со диенофилите етилен, малеонитрил и малеинскиот анхидрид. Овие резултати се во

согласност и со пресметките добиени од ab initio методи за реактивноста на етиленот со овие диени. Освен тоа беа пресметани и корелирани и енергиите на нивните гранични орбитали.

## INTRODUCTION

Platonic solids are regular convex polyhedra (2) which are used, among many other things, as structural models in chemistry (3, 4). A convex polyhedron is regular if its faces are regular polygons. A polyhedron is convex if every dihedral angle is less than  $180^\circ$ . The dihedral angle is the angle formed by two polygons joined along a common edge.

There are five Platonic solids: the tetrahedron (T), the cube (C) or the hexahedron, the octahedron (O), the icosahedron (I) and the dodecahedron (D). Their faces are either regular triangles (in three cases), squares (in one case) or regular pentagons (in one case). Platonic solids are depicted in Fig. 1. Their characteristic parameters are given in Table I.

Our aim in this report is to analyze the complexity of Platonic solids in terms of their numbers of spanning trees and to compare our results with some other attempts of this kind in the literature. In order to simplify the presentation we will use the graph-theoretical concepts and terminology throughout the report (5).



tetrahedron



cube



octahedron



icosahedron



dodecahedron

Fig. 1. The five Platonic solids.