Computational Investigation of the Suitability of Heterocyclic Aromatic Compounds with Two Heteroatoms in the 1 and 3 Ring Positions as Dienes for the Diels Alder Reaction

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Semiempirical and density functional theory computational studies were carried out with the target determining the reactivity of five membered heterocycles with heteroatoms in the 1 and 3 positions as dienes for Diels-Alder reactions. The relative reactivity was evaluated in their reaction with acetylene, ethylene, and cyclopropene as dienophiles for cycloaddition. Qualitative criteria such as uniformity of heterocycle bond orders, change of bond orders and frontier molecular orbital energies in transformation of reactants into transition state structures were used to determine the relative reactivity in comparison with furan. These results are compared with the computed activation barriers as well as with experimental findings, where available. If cycloaddition is feasible with these heterocycles, a new synthetic transformation of simple organic compounds to valuable prostaglandin derivatives can be accomplished.

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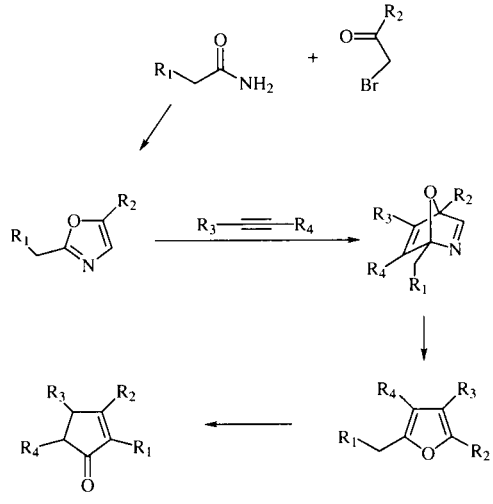
Introduction.

The preparation of valuable organic compounds from simple starting materials is always a desirable synthetic approach; it is worthwhile to explore for both synthetic and theoretical organic chemist. One class of compound that has drawn much attention in the organic chemistry community are prostaglandins [1]. The major reason for this attention comes from fact that they are active for wide variety of diseases [2]. There are many ways to prepare these valuable materials, though the majority of the synthetic procedures use relatively expensive starting materials [2]. The synthetic path outlined in Scheme 1 is one that is unique in many ways; it starts with simple amides, α-bromo ketones, and acetylenes for which synthetic procedures are well established in the literature. Some synthetic procedures such as the preparation 1,3-oxazole and the transformation of furan derivatives into 2-cyclopentenone are also well known and fairly well optimized. Although the synthetic procedure for the cycloaddition between isoxazole with various dienophiles has been described in the literature for some time [3], there are no systematic computational studies that include isoxazole cycloaddition reactions to other five-membered heterocycles with heteroatoms in the 1 and 3 positions. Here we would like to present semiempirical and density functional theory computational studies of these heterocycles with different dienophiles as intermediates for the preparation of natural products.

Computational Methods.

All semiempirical 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 [4]. In AM1 [5], bond order is defined as the sum of the squares of the density matrix elements containing any two atoms. For instance, the C-C bond orders for ethane, ethylene, and acetylene are, by definition, 1, 2, and 3, respectively [6].

Scheme 1. Synthetic Outline for the Transformation of an Amide and α-Bromo Ketone into Prostaglandin Derivatives.



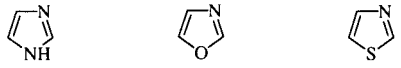
The transition state structures were localized, optimized, and verified as explained in our previous work [7]. Some computational studies are also performed with hybrid density functional theory methods [8].

Results and Discussion.

There are many ways to qualitatively determine the relative reactivity of a series of organic compounds that are involved in a given reaction [9]. This is especially true for dienes involved in the Diels-Alder reaction. Heterocycles are unique dienes because of their aromaticity and functionality introduced by the presence of heteroatoms. The aromaticity [10] and presence of heteroatoms decrease the heterocycles willingness to participate in cycloaddition reactions. Therefore, a comparison of the reactivity of the heterocyclic compounds with dienes such as butadiene and cyclopentadiene is not appropriate; it is rather more beneficial to compare the

reactivity of furan as a diene for the cycloaddition reaction with heterocycles. In this paper we will compare the reactivity of heterocycles with two heteroatoms in the 1,3 position (Scheme 2), using furan as an aromatic heterocycle and cyclopropene as a non-aromatic diene.

Scheme 2. The Structures of Heterocycles with Two Heteroatoms in the 1 and 3 Positions Studied in this Paper



1,3-diazole 1,3-oxazole 1,3-thiazole

The traditional way to compare the reactivity of these heterocycles is through evaluation of their frontier molecular energy [11] difference between reactant pairs. This approach has played an increasingly important role in pericyclic reactions such as Diels-Alder type reactions [12]. According to this theory, the most reactive reactant pair will be the one with the smallest frontier orbital energy gap between reactant pairs. To evaluate the reactivity of 1,3-heterocycles, we have selected acetylene, ethylene, and cyclopropene as dienophiles in reaction with cyclopentadiene, furan and aromatic 1,3-heterocycles. The results of these studies are presented in Table 1. Considering the fact that both ethylene and cyclopropene can add to cyclopentadiene under normal reaction conditions, while furan can react only with cyclopropene, it should be possible to determine the reactivity of the heterocycle with the same dienophiles by comparing their relative frontier orbital energies. If the frontier orbital energy gaps with the heterocycles are lower than ones with cyclopentadiene and furan as dienes, then the reaction should be experimentally feasible. Regardless of the dienophile used, (Table 1) the cycloaddition with 1,3-diazole is a HOMO controlled reaction. The frontier orbital energy gap is slightly lower than in the case of comparable reactions with furan, but it is substantially higher than in the case of cyclopentadiene as a diene (Table 1). From these results, one would expect that 1,3-diazole should be an exceptionally well suited diene for cycloaddition. In contrary, cycloaddition with 1,3-oxazole and 1,3-thiazole as dienes is a LUMO controlled reaction. For the reaction with cyclopentadiene (Column F in Table 1), both 1,3-oxazole and 1,3-thiazole should be more reactive than cyclopentadiene, furan and 1,3-diazole. This finding seems questionable as far as our findings from previous studies. The major reason why this comparison cannot be taken with high certainty is due to the strong aromatic character of the heterocycles. In the course of cycloaddition the aromaticity of the heterocycle should be destroyed therefore this approach cannot produce reliable qualitative estimates of their reactivity.

Recently we have determined the relative aromaticity of some heterocyclic compounds through an imaginary

Table 1

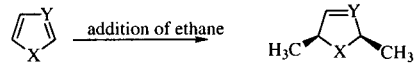
Frontier Molecular Orbital Energy (eV) Gap between the Heterocycles with Two Heteroatoms and Acetylene, Ethylene and Cyclopropene Computed with AM1 Semiempirical Method

Diene	A	B	C	D	E	F
cyclopentadiene	11.132	11.982	10.517	11.033	10.121	10.301
furan	11.370	12.223	10.755	11.274	10.359	10.542
1,3-diazole	11.212	12.477	10.597	11.528	10.201	10.796
1,3-oxazole	11.944	11.807	11.329	10.858	10.933	10.126
1,3-thiazole	11.751	11.290	11.136	10.341	10.740	9.609

LUMO = lowest unoccupied molecular orbital; HOMO = highest occupied molecular orbital; A = $LUMO_{acetylene}$ - $HOMO_{heterocycle}$; B = $LUMO_{heterocycle}$ - $HOMO_{acetylene}$; C = $LUMO_{ethylene}$ - $HOMO_{heterocycle}$; D = $LUMO_{heterocycle}$ - $HOMO_{ethylene}$; A = $LUMO_{cyclopropene}$ - $HOMO_{heterocycle}$; B = $LUMO_{heterocycle}$ - $HOMO_{cyclopropene}$.

1,3 ethylene cycloaddition reaction [8]. For the heterocycles studied in this paper the imaginary reaction is presented in Scheme 3. The computed heat for the proposed reaction is

Scheme 3. Imaginary Ethylene Addition to Cyclic Dienes



X = CH_2, O, NH, or S; Y = CH or N

presented in Table 2. It is obvious that the highest gain in energy is obtained in the transformation of cyclopentadiene into 3,5-dimethylcyclopentene (-16.7 kcal/mol). For the same reaction, for the transformation of furan into 2,5-dimethyl -2,5-dihydrofuran, the heat of the reaction (-9.2 kcal/mol) is substantially smaller and the difference of 4.5 kcal/mol between the heat of reaction for cyclopentadiene and furan can be attributed to the aromatic character of furan.

It is well known that furan is one of few aromatic heterocycles that can be easily engaged in cycloaddition. In comparison with cyclopentadiene, an aromatic energy gain of 4.5 kcal/mol should diminish its capability to act as a diene for the Diels-Alder reaction but should not make it impractical. For all 1 and 3 heterocycles studied, the imaginary reaction with ethane is slightly endothermic. For instance the energy difference in the heat of reaction for 1,3-oxazole and cyclopentadiene is 19.7 kcal/mol, which indicates the strong 1,3-oxazole aromatic character. For this aromatic compound, the heat of the reaction is 12.2 kcal/mol more endothermic than for furan, indicating the substantially higher aromatic character of the 1,3-oxazole ring in comparison with furan (Table 1). Therefore, 1,3-oxazole should be quite a poor diene for the Diels-Alder reaction when compared to both cyclopentadiene and furan. This trend holds true for the other heterocycles (Table 2); therefore, our simple comparison of frontier orbital energy gaps

between different reactants pairs is obviously not a reliable way to determine the reactivity of heterocyclic compounds as dienes for Diels-Alder reactions.

Table 2
The AM1 Computed Heat for Imaginary Ethylene Addition to the Cyclic Dienes

Heterocycle	A	B	C
cyclopentadiene	37.1	3.0	-16.7
furan	3.0	-23.6	-9.2
1,3-diazole	50.8	34.4	1.0
1,3-oxazole	12.5	-1.9	3.0
1,3-thiazole	38.6	23.6	2.4

A = heat of formation (kcal/mol) computed for cyclic diene; B = heat of formation (kcal/mol) computed for 2,5-dihydroaromatic heterocycle; C = energy of imaginary reaction between the diene and ethylene; heat of formation for ethane is -17.4 kcal/mol.

There are also ways to qualitatively determine the reactivity of aromatic heterocycles as dienes for Diels-Alder reactions. One that we found to be quite reliable is the determination of bond order uniformity in the aromatic ring. Bond order is defined in such a way that it is one for the C-C bond in ethane, two for the C-C bond in ethene, and three for the C-C bond in acetylene. Therefore, for an aromatic system such as benzene, the C-C bond order is 1.5 indicating delocalization of the p molecular orbitals, thus indicating the high aromatic character of benzene. In the case of benzene, the bond order deviation from ideal bond order distribution in the ring is equal to zero. We have applied the same approach to determine the bond order deviation from an ideal distribution for cyclopentadiene as a non-aromatic ring. As one would expect, the deviation in cyclopentadiene is maximal (1.986) due to the strong localization of single and double bonds of the ring (Table 3). Due to de localization of the furan lone pair, the ring is becoming aromatic and the sum of the bond order deviation from ideal π molecular orbital de localization is smaller. Consequently, the ring's double and single bonds are less distinguishable than in the case of an ideal diene for the Diels-Alder reaction. This should have localized bonds that are two with bond orders of two and one. The reactivity of furan as a diene for the Diels-Alder reaction should be lower than for cyclopentadiene, which has more or less localized double bonds.

Similar distribution of the furan ring's order is observed in case of 1,3-oxazole (Table 3). One can assume that on the basis of the π molecular orbital distribution, 1,3-oxazole should be as reactive as furan. In contrary, both 1,3-diazole and 1,3-thiazole have substantially lower deviation from an ideal ring bond order distribution; therefore, they should have higher aromatic character than furan. They are also less reactive. The order of aromaticity computed through bond order deviation in 1,3-diazole is the highest, followed by 1,3-thiazole and the least aromatic is 1,3-oxazole (Table 3). Therefore, the order of reactivity obtained through frontier molecular orbital energy differences presented in Table 1 is incorrect due to the high aromatic character of the five membered heterocycles. We learned from many of our computational studies that bond order deviation, when compared between similar aromatic systems, is a reliable approach to determine the heterocycles aromaticity an therefore reactivity.

Table 3
The Ring Bond Orders and Bond Order Deviation for Heterocycles with Two Heteroatoms Computed with the AM1 Semiempirical Method

heterocycle	BO_{12}	BO_{23}	BO_{34}	BO_{45}	BO_{51}	SBO	ABO	BOD
cyclopentadiene	1.002	1.849	1.061	1.849	1.002	6.763	1.353	1.986
furan	1.104	1.670	1.190	1.670	1.104	6.738	1.348	1.290
1,3-diazole	1.171	1.567	1.394	1.554	1.174	6.860	1.372	0.798
1,3-oxazole	1.083	1.676	1.193	1.657	1.103	6.712	1.342	1.296
1,3-thiazole	1.159	1.632	1.257	1.590	1.186	6.824	1.365	0.985

BO_{X-Y} = bond order between atoms X and Y in the heterocycle ring; SBO = sum of ring bond orders; ABO = average bond order; BOD = sum of bond order deviation from the average ring bond order.

Let us now explore the electronic characteristics of the transition state structures for acetylene, ethylene and cyclopropene addition to 1,3-oxazole (Figure 1). The transition state structures with 1,3-diazole and 1,3-thiazole as dienes are similar to those presented for 1,3-oxazole and will not be discussed in this paper. The transitions state structures are for a cycloaddition mechanism in which both C-C bonds are formed simultaneously. Due to the asymmetry of the heterocycle, the transition state is also not symmetric. There is an indication that the C-C bond in formation pertaining to the carbon of heterocycle which is between the two hetero atoms, is forming a little bit later than the other bond. Otherwise, the transition state is typical for Diels-Alder cycloaddition.

Because transition state structures for other dienes are quite similar to this one, we believe that a comparison of

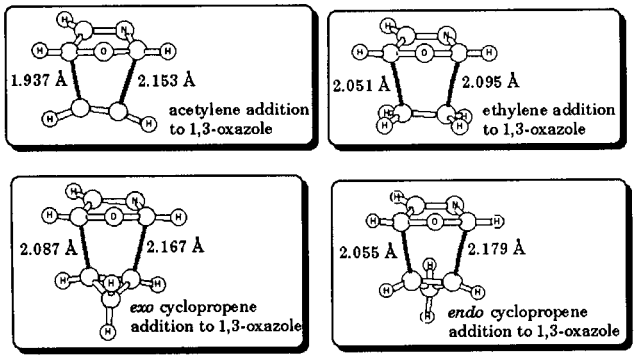


Figure 1. Transition state structures for acetylene, ethylene, and cyclopropene addition to 1,3-oxazole.

their electronic properties can be reliable for the evaluation of the heterocycles relative reactivity. To achieve this goal, we used two of our approaches; the necessary FMO energy change for the transformation of reactants into corresponding transition state structures, and the ring bond order reorganization required for the heterocycle to achieve the transition state reorganization.

For the sake of simplicity in our presentation, we are presenting only our results for *endo* cyclopropene addition to the heterocycles. All conclusions drawn from this study can be applied to the addition of acetylene and ethylene to the heterocycles, knowing that cyclopropene was the most reactive while acetylene was the least reactive dienophile. The frontier molecular orbital energies and frontier orbital energy changes for *exo* and *endo* cyclopropene addition to heterocycles which have heteroatoms in 1,3-position are presented in Table 4. The cycloaddition reaction with 1,3-diazole is for normal, LUMO dienophile and HOMO diene controlled Diels Alder reactions. On the other hand, both cycloaddition reactions with 1,3-oxazole and 1,3-thiazole were LUMO diene, and HOMO dienophile controlled. Recently we have introduced a postulate that is very similar to the Hammond postulate, which considers the relative reactivity of different reaction pairs. It was demonstrated

Table 4

Frontier Molecular Orbital (FMO) Energy (eV) for the Transition State Structure and the Necessary Changes in Reactants to Reach this Transition State of *endo* Cyclopropene Addition to Heterocycles which have Heteroatoms in their 1,3-Positions

TS	A	B	C	D	S_1	S_2
furan	0.926	0.424	1.488	-0.158	1.084	1.912
1,3-diazole	1.096	0.436	0.678	-0.613	1.709	1.114
1,3-oxazole	0.745	0.817	0.914	-0.179	0.924	1.731
1,3-thiazole	1.144	1.023	1.163	0.089	1.233	2.186

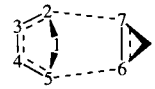
$A = HOMO_{TS} - HOMO_{cyclopropene}$; $B = HOMO_{TS} - HOMO_{heterocycle}$; $C = LUMO_{cyclopropene} - LUMO_{TS}$; $D = LUMO_{TS} - LUMO_{heterocycle}$; $S_1=|A|+|D|$; $S_2=|B|+|C|$.

that reactant pairs which experience the least structural or electronic changes should have the lowest activation energy. According to the FMO energy change, the most reactive was 1,3-oxazole, while the least reactive dienophile was 1,3-thiazole (Table 4). This reactivity order might not be correct because the same approach selected 1,3-oxazole to be more reactive than furan, which should not be true based on the experimental observations.

The other method to determine reactivity for reactions with synchronous concerted cyclic transition state structures is through evaluation of the transition state ring aromaticity, considering bond order deviation [8]. The results of the *exo* cyclopropene addition to the heterocycles and to cyclopentadiene are presented in Table 5. The higher the sum of the bond order deviation from average bond order (x) is, the lower the aromatic character the transition state structure possesses. The most reactive dienophile was cyclopentadiene, followed by furan, followed by the other heterocycles. The most reactive heterocycle with heteroatoms in 1,3-position was 1,3-oxazole, as was predicted on the basis of the FMO energy changes (Table 4). The least reactive was 1,3-diazole, as one would expect on the basis of experimental observations. It is quite difficult to rely on the transition state structure bond order deviation to determine the experimental feasibility of a reaction;

Table 5

Bond Order Uniformity for a Six-membered Transition State Structure of an *exo* Cyclopropane Addition to a Heterocycle with Two Heteroatoms



diene	BOC_{23}	BOC_{34}	BOC_{45}	BOC_{56}	BOC_{67}	BOC_{27}	SBOD
cyclopentadiene	1.433	1.390	1.433	0.362	1.482	0.362	0.234
furan	1.286	1.530	1.286	0.378	1.471	0.378	0.449
1,3-diazole	1.235	1.620	1.181	0.451	1.400	0.413	0.702
1,3-oxazole	1.298	1.545	1.243	0.406	1.455	0.378	0.487
1,3-thiazole	1.274	1.598	1.208	0.440	1.411	0.420	0.603

Average bond order deviation is computed from the formula 6X + 4 = sum of the ring bond orders as explained in Scheme 4; BOC_{X-Y} = bond order change of bonds between atoms X and Y in the heterocycle ring required to achieve transition state structures; SBOD = sum of the bond order deviations.

because SBOD for furan and 1,3-oxazole were very similar, one can conclude that the cycloaddition with 1,3-oxazole is also experimentally feasible.

To verify our qualitative reactivity assessment on the basis of FMO energy changes and transition state bond order deviation, we computed activation barriers for those Diels-Alder reactions (Table 6). It was quite obvious that the order of reactivity of dienophiles, regardless of the heterocycle, was cyclopropene, ethylene, and then acetylene. This order of reactivity was true for many Diels-Alder reactions. The predicted order of reactivity through the FMO energy changes (Table 4) is in full agreement with computed activation barriers: the most reactive diene was 1,3-oxazole whereas 1,3-thiazole was the least reactive heterocycle (Table 6). Considering activation barriers, cyclopropene addition should be experimentally feasible to all three heterocycles; while in the case of alkenes, the reaction that should have practical applications should be the reaction with 1,3-oxazole as a dienophile. This was also confirmed experimentally [57].

Table 6

The AM1 and the B3LYP/6-31G(d) Computed Activation Barriers for Acetylene, Ethylene, and Cyclopropene Addition to 1,3-Diazole, Oxazole and Thiazole

reactant or reaction	HOF	ΔE_I	ΔE_{II}
endo furan + cyclopropene		27.4	18.7
exo furan + cyclopropene		26.1	18.4
acetylene + 1,3-diazole	148.0	42.4	33.9
ethylene + 1,3-diazole	101.8	34.5	30.8
exo cyclopropene + 1,3-diazole	157.0	31.4	21.2
endo cyclopropene + 1,3-diazole	158.5	32.9	22.9
acetylene + 1,3-oxazole	103.9	36.6	29.4
ethylene + 1,3-oxazole	57.0	28.0	24.8
exo cyclopropene + 1,3-oxazole	113.4	26.1	16.8
endo cyclopropene + 1,3-oxazole	115.1	27.8	18.6
acetylene + 1,3-thiazole	142.3	48.9	37.7
ethylene + 1,3-thiazole	96.6	41.5	31.9
exo cyclopropene + 1,3-thiazole	152.2	38.8	23.5
endo cyclopropene + 1,3-thiazole	152.7	39.3	24.3

HOF = heat of formation computed by AM1; ΔE_{II} = activation barrier (kcal/mol) computed with the semiempirical method; ΔE_{II} = activation barrier (kcal/mol) computed with the density functional theory method on geometry computed with the semiempirical method

Conclusions.

There are at least two strong conclusions that can be drawn from the results presented in this paper. Our computational approach to evaluate qualitative reactivity of heterocyclic aromatic compounds through bond order deviation from ideally, and bond order uniformity of the transition state structures are in agreement with computed activation barriers as well as experimental results for cycloaddition reactions. Similar conclusions can be obtained on the basis of frontier orbital energy changes necessary for reactants to adapt to be transformed into transition state structure. All these finding agree that the suitable heterocycle for realization of synthetic pathways presented in Scheme 1 should be oxazole because its reactivity in regard to furan is higher; a second dienophile addition can be controlled with subsequent transformation to prostaglandin derivatives. If realize, this synthetic transformation might become one of the simplest route for preparation of prostaglandins.

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