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Diels–Alder transition structures of hetero-dienophile addition to 4*H*-pyrazole calculated by ab initio methods

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Abstract

Transition structures for the hetero Diels–Alder additions of ethylene, formaldehyde, formaldimine, *cis*-diazene, *trans*-diazene, and nitrosyl hydride to 4*H*-pyrazole were obtained by ab initio molecular orbital calculations. The geometries of the transition structures and the reactants were optimized at the RHF/3-21G level of theory, whereas the energies were evaluated at the MP2/6-31G* level on the RHF/3-21G geometries. The transition structures are for a concerted mechanism, and they are fully synchronous with symmetrical dienophiles. The new forming bonds are shorter and the asynchronicity is higher than in the case of the corresponding all-carbon diene. Also, the activation energy for the reaction of 4*H*-pyrazole with ethylene is higher and with *cis*-diazene is lower compared to analogous reaction with cyclopentadiene. An exceptional energy difference (18.8 kcal mol^{-1}) was predicted for the exo/endo *cis*-diazene addition to 4*H*-pyrazole.

1. Introduction

In the course of our research on the preparation of heterocyclic compounds as intermediates in organic syntheses occasionally we have utilized hetero Diels–Alder reactions. Although there are a couple of excellent reviews [1] in this field, the reports on the theoretical study of these reactions are very rare [2], in marked contrast to the all-carbon Diels–Alder reactions [3]. Here we would like to present our results on the theoretical study of the heterodienophile addition to 4*H*-pyrazole. The system is a hetero analogue of the Diels–Alder addition to cyclopentadiene [4].

In this paper we will address the following points:

(1) The effect of the two nitrogens (diaza substitution) on the geometries and activation energies of the transition structures of the Diels–Alder reactions of 4*H*-pyrazole with hetero-dienophiles in comparison with the same reaction with cyclopentadiene.
(2) The influence of the symmetry of the dienophile and heteroatom lone-pairs on both dienophile and diene on the degree of asynchronicity, activation energy, and stereochemistry of these reactions.

2. Computational methods

The optimizations were carried out at the

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Table 1
HOMO–LUMO energies (eV) of the reactants calculated at the RHF/6-31G*//RHF/RHF/3-21G level

Reactant	E_{HOMO}	E_{LUMO}	E_A [a]	E_B [b]
4*H*-Pyrazole	−0.3942	0.1211		
Ethylene	−0.3748	0.1844	0.4959	0.5786
Formaldehyde	−0.43982	0.13196	0.56092	0.52616
Formaldimine	−0.41750	0.16317	0.53860	0.55737
cis-Diazene	−0.38110	0.14771	0.50220	0.54191
trans-Diazene	−0.38664	0.14689	0.50774	0.54109
Nitrosyl hydride	−0.42710	0.09039	0.54820	0.48459

[a] $E_A = \text{LUMO}_{\text{diene}} - \text{HOMO}_{\text{dienophile}}$; $E_B = \text{LUMO}_{\text{dienophile}} - \text{HOMO}_{\text{diene}}$.

restricted Hartree–Fock theory level with the 3-21G basis set in GAUSSIAN 92 [5]. The transition structures were located and optimized [6] prior to any ab initio calculations with the PM3 [7] method implemented in MOPAC [8]. Vibrational frequency analysis was performed for all transition states and they all had only one imaginary frequency corresponding to the formation of the two new bonds. The energy barriers of the reactions were also evaluated by single-point MP2/6-31G*//RHF/3-21G [9] calculations.

3. Results and discussion

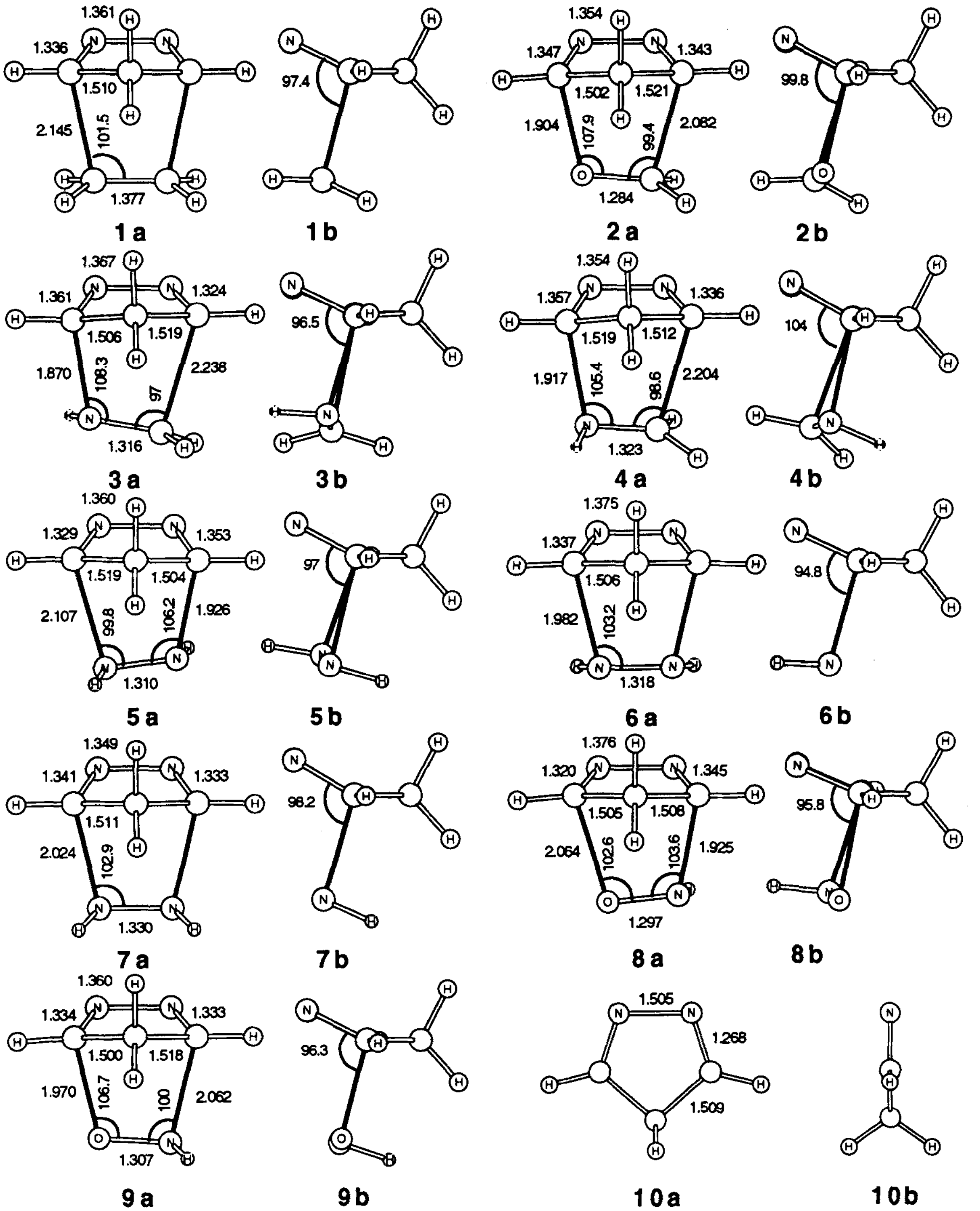
Transition structures were located for the reactions of 4*H*-pyrazole **10**, with ethylene, formaldehyde, formaldimine, *cis*- and *trans*-diazene, and nitrosyl hydride. In all cases when endo/exo isomers can be formed, they were both considered. Overall, nine transition structures were located and they are presented in Fig. 1. The transition structure for the reaction of 4*H*-pyrazole with ethylene (**1**) resembles that for the reaction of cyclopentadiene with ethylene [10] but the C–C forming bonds are 0.060 Å shorter.

The transition structure of 4*H*-pyrazole with formaldehyde (**2**) is not synchronous, although it corresponds to a concerted mechanism of the reaction. The C–C forming bond is 0.063 Å shorter than in the case of the transition state **1**, and the C–O bond even shorter than the C–C bond which makes the transition state highly asynchronous (Δr = 0.178 Å). Two transition structures for the reaction of 4*H*-pyrazole with formaldimine can be conceived, one with endo N–H bond (**3**) and one with exo N–H bond (**4**). Both transition structures are asynchronous, although the endo isomer shows a higher degree of asynchronicity (Δr = 0.368 Å and Δr = 0.287 Å, respectively). The C–N forming bonds are considerably shorter (0.275 Å and 0.228 Å, respectively), whereas the C–C forming bonds are slightly longer (0.093 Å and 0.059 Å, respectively) in both isomeric transition states **3** and **4** when compared to the ethylene addition.

Besides the ethylene addition, the transition structures for the two *cis*-diazene additions are also symmetrical. Both transition structures that correspond to the endo **6** and the exo **7** N–H hydrogen addition of *cis*-diazene to the 4*H*-pyrazole, have shorter forming N–C bonds than the C–C bonds of ethylene addition to both cyclobutadiene (for **6** Δr = 0.223 Å) and 4*H*-pyrazole (for **6** Δr = 0.163 Å). On the other hand, the exo isomeric transition structure **7** has longer forming C–C bond (Δr = 0.042 Å) than the endo isomer **6**. It is interesting to mention that in the transition structure **5** for the asynchronous concerted addition of *trans*-diazene to 4*H*-pyrazole the endo C–N forming bond with endo N–H is shorter (Δr = 0.056 Å), and the exo C–N forming bond with endo N–H bond is longer (Δr = 0.083 Å) than in the case of the *cis*-diazene addition to 4*H*-pyrazole (Fig. 1). The transition structure of exo N–H addition of nitrosyl hydride to 4*H*-pyrazole (**9**) shows the highest degree of synchronicity (Δr = 0.092 Å) of all studied asymmetric dienophiles. Here again, the distance of the forming C–N bonds depends on the N–H orientation in respect to the ring. It is shorter for the exo N–H bond (1.925 Å) than for the endo N–H bond (2.062 Å) in the transition structure (Fig. 1, structures **8** and **9**).

Frontier molecular orbital [11] has been widely used to rationalize the reactivity in cycloaddition reactions. The HOMO and LUMO energies for both 4*H*-pyrazole and hetero-dienophiles are presented in Table 1.

Since 4*H*-pyrazole has lower HOMO energy (ΔE = 2.03 kcal mol^{-1}) than cyclopentadiene, the Diels–Alder reaction of 4*H*-pyrazole with ethylene,



1a **1b** **2a** **2b** **3a** **3b** **4a** **4b** **5a** **5b** **6a** **6b** **7a** **7b** **8a** **8b** **9a** **9b** **10a** **10b**

Fig. 1. 3-21G optimized geometries of the transition state structures of hetero-dienophile additions to 4*H*-pyrazole (front (**a**) and side (**b**) views).

Table 2
Total energies (atomic units) of reactants and transition structures for the Diels–Alder reaction of 4*H*-pyrazole with hetero-dienophiles

Species	RHF/3-21G	RHF/6-31G*//RHF/3-21G	MP2/6-31G*//RHF/3-21G
4*H*-pyrazole (**10**)	−223.4849229	−224.7607152	−225.4623995
Ethylene	−77.6009882	−78.0316943	−78.2840991
Formaldehyde	−113.2218198	−113.8623871	−114.1676329
Formaldimine	−93.4947805	−94.0256453	−94.3129884
trans-Diazene	−109.3547665	−109.9924702	−110.3083725
cis-Diazene	−109.3423988	−109.978457	−110.2948632
Nitrosyl hydride	−129.0382903	−129.7832474	−130.1235817
1	−301.0326923	−302.7304926	−303.7333391
2	−336.6533401	−338.5557299	−339.6022899
3	−316.9342256	−318.7269938	−319.7642627
4	−316.9186114	−318.7141758	−319.7501288
5	−332.7921402	−334.6841240	−335.7674379
6	−332.7937631	−334.6851063	−335.7687451
7	−332.7605845	−334.6562636	−335.7386976
8	−352.4935681	−354.4874054	−355.5906618
9	−352.4746900	−354.4699815	−355.5696200

formaldimine and diazene is HOMO dienophile controlled similarly to the addition of hetero dienophiles to 2-azabutadiene. Accordingly, Lewis acid catalysts should narrow the LUMO–HOMO gap via complex formation with 4*H*-pyrazole, increasing the reactivity of these compounds [12].

The calculated energy barriers can give answers not only about the reactivity but also the regioselectivity in these reactions. The calculated total energies for the reactants, the transition structures and the energies are given in Tables 2 and 3. The predicted activation barrier for all studied theory levels, agree with the frontier orbital prediction that the addition of ethylene to 4*H*-pyrazole will be much more disfavored than the addition of ethylene to cyclopentadiene [10].

Experimentally there is no evidence that ethylene reacts with 4*H*-pyrazole but there are literature reports of efficient *cis*-diazene derivative additions to 4,4-dimethyl-3,6-diphenyl-4*H*-pyrazole [13]. As mentioned above the addition of formaldehyde and ethylene to 4*H*-pyrazole are $\mathrm{LUMO}_{\mathrm{dienophile}}$–$\mathrm{HOMO}_{\mathrm{diene}}$ controlled (Table 1). In this case formaldehyde must be more reactive than ethylene because formaldehyde has a lower LUMO energy. However, the calculated activation barriers at all three theory levels prefer ethylene. The anomaly can be explained by the repulsive

Table 3
Calculated activation energies (kcal mol^{-1}) for the Diels–Alder reaction of 4*H*-pyrazole with hetero-dienophiles[a]

Dienophile	TS	RHF/3-21G	RHF/6-31G*//RHF/3-21G	MP2/6-31G*//RHF/3-21G
Ethylene	**1**	33.4 (0.0)	38.9 (0.0)	8.3 (0.0)
Formaldehyde	**2**	33.5 (0.1)	42.3 (5.4)	17.4 (9.1)
Formaldimine, endo H	**3**	28.5 (−4.9)	37.2 (−1.7)	7.0 (−1.3)
Formaldimine, exo H	**4**	38.3 (4.9)	45.3 (6.4)	15.8 (7.5)
trans-Diazene	**5**	29.8 (−3.6)	43.3 (4.4)	2.1 (−6.2)
cis-Diazene, endo H	**6**	21.1 (−12.3)	33.9 (−5.0)	−7.2 (−15.5)
cis-Diazene, exo H	**7**	41.9 (8.5)	52.0 (14.0)	11.6 (3.3)
Nitrosyl hydride, endo H	**8**	18.6 (−14.8)	35.5 (−3.4)	−3.0 (−11.3)
Nitrosyl hydride, exo H	**9**	30.4 (−3.0)	46.4 (7.5)	10.3 (2.0)

[a] Values in parenthesis, relative to the etyhlene addition.

interactions of the oxygen lone pair with the 4*H*-pyrazole π-system, similarly to previously reported heterocycloadditions to butadiene [2(a)]. The side view (Fig. 1, **2b**) shows that the formaldehyde oxygen is somewhat pushed away from 4*H*-pyrazole, increasing the distance from the endo lone pair to C–N, but significant n–π repulsion is still present in the transition state. The lone pairs on the two nitrogens do not have influence on the bond distance through nitrogen–oxygen n–n repulsion interactions, because the nitrogen lone pairs are pointing away from the CNNC plane of 4*H*-pyrazole. The nitrogen atom in the diene ring increases the positive charge on the carbon atoms, considerably shortening the new forming bonds in the transition states. Thus, the C–O new forming bond in the formaldehyde addition to 4*H*-pyrazole is 7% shorter, while the C–C new forming bond is only 3% shorter than in the case of formaldehyde addition to cyclopentadiene [14]. Nevertheless, the activation barrier for the formaldehyde addition to 4*H*-pyrazole is 4.4 kcal mol^{-1} higher than the corresponding addition to cyclopentadiene [14] at the same MP2/6-31G*//RHF/3-21G level.

The addition of formaldimine to 4*H*-pyrazole shows lower activation barrier (2.4 kcal mol^{-1}) for the endo and higher barrier (1.8 kcal mol^{-1}) for the exo isomer in comparison to the cyclopentadiene addition [14]. The asymmetricity is higher, and the C–N new forming bond in the endo isomer is 8% shorter than in the case of cyclopentadiene addition. The energy difference for the exo–endo formaldimine addition is 8.8 kcal mol^{-1} which is considerably higher when compared to the all carbon Diels–Alder reaction [10]. The difference can be again explained by the repulsive interactions of the formaldimine nitrogen lone pair in the exo N–H addition with the occupied π orbital in 4*H*-pyrazole. That is apparent on the side view of **4b** where the N–H is pushed away from the pyrazole moiety. An excellent demonstration of the n–π repulsive interactions is the case of *trans*-diazene addition to 4*H*-pyrazole. The activation energy is lower (Table 3) than in the case of both formaldimine additions and is in agreement with what was predicted by frontier orbital interactions (Table 1), but in comparison to cyclobutadiene [14] it is 0.4 kcal mol^{-1} higher. The two new forming N–C bonds are not equivalent. The N–H bond in the exo position of the transition structure **5a** has the nitrogen lone pair in endo position. The n–π repulsive interactions make this bond considerably longer than the other, endo N–C new forming bond. Furthermore, because of the C–N bond polarization in 4*H*-pyrazole, the endo new forming N–C bond in transition structure **5a** is shorter than in the case of cyclopentadiene [14].

According to the n–π repulsive interactions the N–H endo *cis*-diazene addition to 4*H*-pyrazole should have lower activation barrier than the exo addition. That was confirmed by calculations, and the energy differences for the exo–endo *cis*-diazene addition is very large, 18.8 kcal mol^{-1}. That suggests that the addition should be extremely stereoselective. Also, as expected, the activation energy for the *trans*-diazene addition is between the activation barrier of exo and endo *cis*-diazene addition to 4*H*-pyrazole (Table 3). Besides, the N–H endo *cis*-diazene addition to 4*H*-pyrazole has quite lower activation barrier than in the addition both to butadiene (24.8 kcal mol^{-1}) [2(a)] and cyclopentadiene (2.6 kcal mol^{-1}) [14].

According to frontier orbital theory the addition of nitrosyl hydride to 4*H*-pyrazole is HOMO diene and LUMO dienophile controlled reaction and should be the most reactive in the studied series. It is not quite so. The endo N–H *cis*-diazene addition has the lowest activation barrier. That can be again explained by the n–π repulsion interactions. In the case of endo N–H *cis*-diazene addition there are no n–π repulsive interactions, whereas in the case of endo N–H nitrosyl hydride there is an oxygen lone pair that is in the exo position. These interactions considerably increase the activation barrier and make *cis*-diazene the most reactive dienophile studied here (Table 3). The stereoselectivity of nitrosyl hydride addition to 4*H*-pyrazole should be quite higher because the energy difference between exo and endo addition is 10.9 kcal mol^{-1}.

4. Conclusion

The transition structures for the hetero Diels–

Alder reactions of 4*H*-pyrazole with formaldehyde, formaldimine, diazene, and nitrosyl hydride, are similar to the all carbon Diels–Alder reactions. In all cases where symmetrical dienophiles were used, fully synchronous transition structures were obtained. With asymmetric dienophiles asynchronous transition structures were obtained and the degree of asynchronicity is higher than in the case when cyclopentadiene was used as a diene. The new forming bonds are shorter and the activation energy for addition of ethylene is little higher than the all carbon Diels–Alder reaction. The most reactive hetero dienophile is predicted to be *cis*-diazene. The endo N–H addition is by 15.5 kcal $\mathrm{mol^{-1}}$ preferred over ethylene, and the energy difference of the activation barrier between the exo–endo isomers is 18.8 kcal $\mathrm{mol^{-1}}$ making the stereoselectivity of the addition exceptional. Overall, 4*H*-pyrazole is comparable to cyclopentadiene as a diene in hetero Diels–Alder reactions.

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