



Ab initio transition structures for hetero Diels–Alder cycloadditions to furan

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Abstract

Ab initio calculations at the RHF/3-21G and RHF/6-31G*/RHF3-21G theory levels provide data on the reactivity and stereoselectivity of hetero dienophile additions to furan. The calculated activation energies for the hetero Diels–Alder reactions are usually small, and the newly formed bonds are shorter than in the corresponding all carbon Diels–Alder reactions. The formation of the endo isomer is predicted to be energetically more favorable due to n– π repulsion between the heteroatom lone pair and the π system of the furan ring. The activation energy for some hetero dienophiles is very low and the reaction is suggested to be of synthetic interest in the preparation of natural chiral compounds.

1. Introduction

Functionally substituted dihydro- and tetrahydrofuran structures play an important role as intermediates in the synthesis of highly functionalized natural products [1]. The Diels–Alder reaction has become a powerful tool in natural product chemistry because it combines C–C or C–heteroatom bond formation with regio- and diastereoselectivity at several centers [2]. Due to a supra–suprafacial reaction, and the polarity of diene and dienophile, very often only one pair of enantiomers is obtained out of the numerous possible isomers. The incorporation of functional groups, especially electron donating substituents in the Diels–Alder adducts, is most conveniently achieved by reactions with the corresponding

electron-rich 1,3-dienes and dienophiles, respectively. In hetero Diels–Alder reactions, it has been discovered that the interactions of N or O lone pairs with a π system can exert powerful stereochemical control [3]. The n– π repulsion which causes this phenomenon should be very important in controlling the stereochemistry in many complexation and reactivity events as well. To learn about the transition structures of such processes we investigated the reactions of furan with ethylene, formaldehyde, formalimine, diazene (diimide), and nitrosyl hydride with semiempirical and ab initio quantum mechanics methods.

2. Computational methods

The structures of the compounds were prepared and the results visualized with the CHEM-X [4] computational package. The semiempirical calculations were performed with the PM3 [5] method in MOPAC

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Table 1
PM3 Calculated Energies (kcal/mol) of the Hetero Diels–Alder Transition Structures in Respect to the Reactants

Dienophile	TS	Polar	Biradical
Ethylene	8	32.02	30.75
Formaldehyde	9	30.48	29.59
Formaldimine, <i>exo</i> H	10	30.78	28.36
Formaldimine, <i>endo</i> H	11	29.69	27.51
<i>trans</i> -Diazene	12	40.95	45.72
<i>cis</i> -Diazene, <i>exo</i> H	13	44.19	42.80
<i>cis</i> -Diazene, <i>endo</i> H	14	41.73	40.28
Nitrosyl hydride, <i>exo</i> H	15	42.15	40.35
Nitrosyl hydride, <i>endo</i> H	16	40.47	35.70

[6]. The transition states were optimized by the non linear least squares gradient minimization routine, NLLSQ [7]. These obtained geometries were used as input structures for the ab initio calculations which performed at the RHF level using GAUSSIAN 92 [8]. All structures were fully optimized with the 3-21G basis set, and characterized by vibrational frequency calculations. The transition states had one imaginary vibrational frequency, while the ground states had no imaginary vibrational frequencies. Single point energy evaluations were also performed at the RHF/6-31G**/RHF/3-21G level.

3. Results and discussion

Three different mechanisms in the hetero Diels–Alder reactions were considered: a stepwise and two concerted pathways. In the case of the reaction of formaldehyde with furan all possibilities that were considered will be explained. The two step mechanism can proceed through the formation of a carbon–oxygen bond first with an ionic or biradical intermediate. The same rationalization can be applied if the C–C bond is formed first. The concerted mechanism can proceed through formation of both bonds in the transition structure with small development of charges or it can be of biradical type. Our attempts to locate the first and second transition states both with PM3 and HF/STO-3G and HF/3-21G methods failed. The concerted transition states were located and activation energies were calculated for both the

polar and the biradical mechanism with the PM3 method (Table 1). The activation energies for both polar and biradical transition structures prefer the *endo* isomer in all cases over the *exo* isomer. For almost all transition structures studied, the activation energy is lower for the biradical than for the polar TS. The only exception is *trans*-diazene which prefers the polar concerted mechanism over the biradical one [9]. The structures of some polar and biradical transition structures are presented in Fig. 1. It is quite clear that the optimized transition structures obtained for the concerted mechanism with the BIRADICAL keyword have a higher degree of asynchronicity (Fig. 1, structures denoted as **B**). Their newly forming bond lengths are considerably shorter than the corresponding polar transition structures (denoted as **P**) making them closer to the product structures and lowering their activation energies. Does this mean that the mechanism of the Diels–Alder cycloaddition of the heterodienophile to furan has indeed a biradical nature? According to the PM3 semiempirical method presented herein, the biradical mechanism is preferred by 1–2 kcal mol⁻¹.

In order to learn more about the transition states of such processes, we investigated these reactions with ab initio quantum mechanics methods. On the basis of a recent ab initio study [3(a)] of the mechanism of Diels–Alder reactions of heterodienophiles with butadiene, the concerted transition state for this cycloaddition was selected. The HF/3-21G optimized structures of the reactants are presented in Fig. 2, and the structures of the corresponding transition states in Fig. 3.

3.1. Asynchronicity and geometry of the transition structures

The transition structure for the reaction of furan with ethylene is fully symmetrical. Both C–C bonds seem to be formed at the same time. The bond distance (2.141 Å) is quite shorter than the one between butadiene and ethylene (2.205 Å) obtained by HF/3-21G [10]. The transition state structure for the addition of formaldehyde to furan is not symmetrical anymore. Both newly

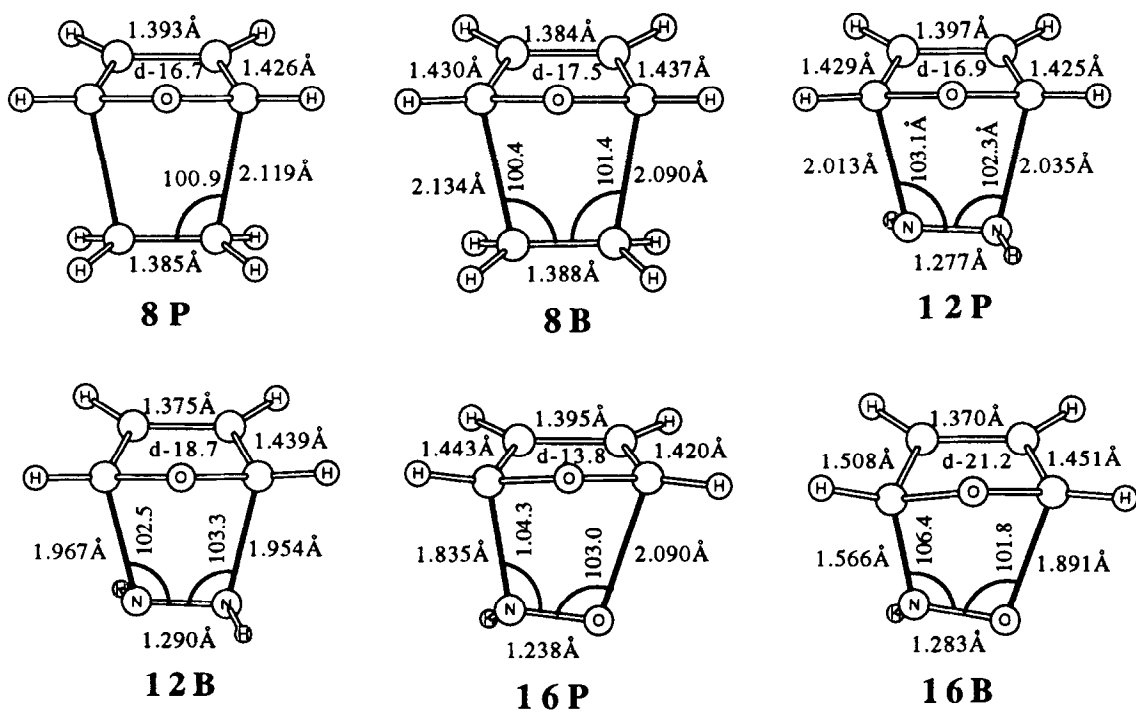


Fig. 1. PM3 generated polar and biradical concerted transition structures of Diels–Alder addition of heterodienophile to furan.

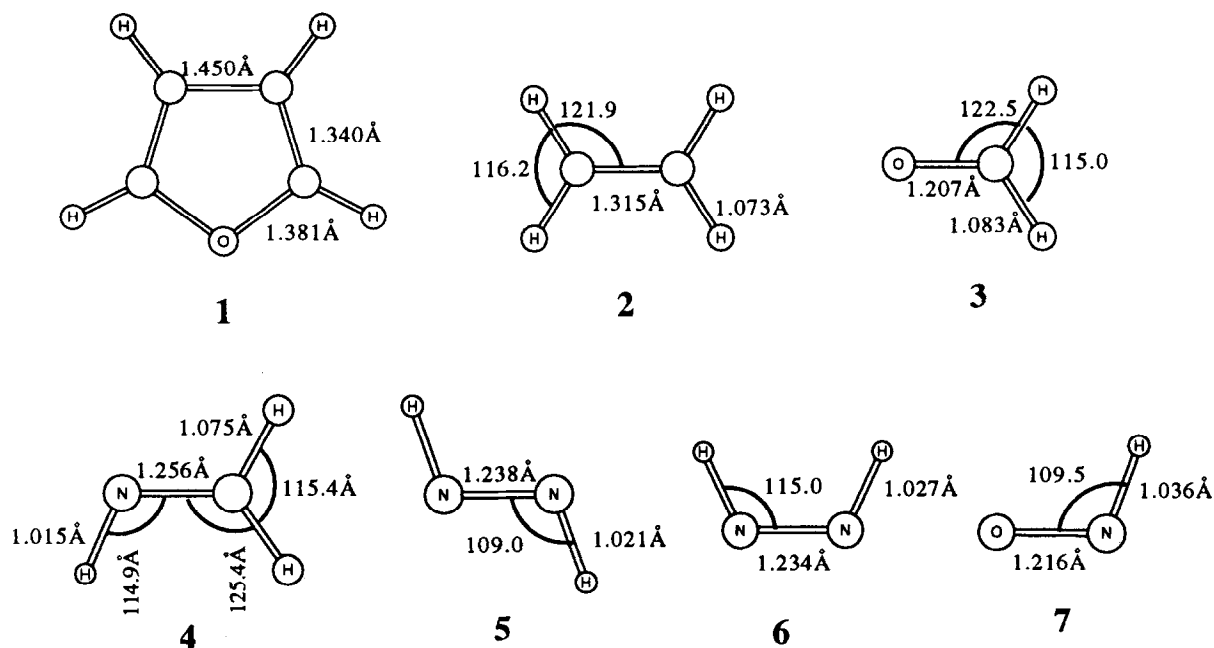


Fig. 2. HF/3-21G structures of the reactants, furan and heterodienophiles.

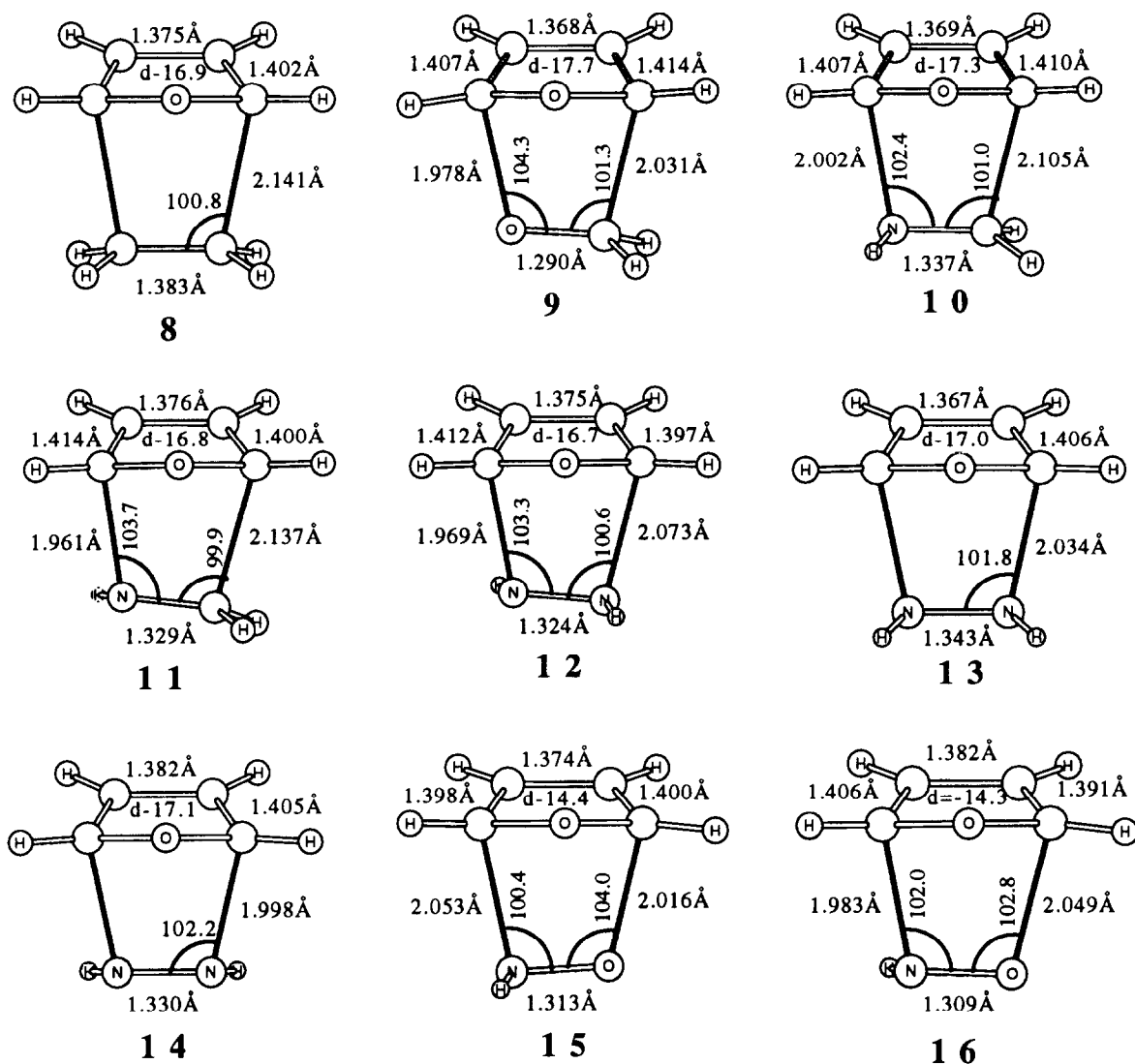


Fig. 3. HF/3-21G transition structures for the Diels–Alder cycloaddition of furan with heterodienophiles.

formed bonds are considerably shorter than in the addition of ethylene. Our results indicate that the C–C bond is more fully formed than in ethylene.

The degree of synchronicity is not as high as in the case of formaldehyde addition to butadiene [3(a)]. There is no experimental evidence that formaldehyde reacts with furan. Two diastereomeric structures, **10** and **11**, were found for the reaction of formaldimine with furan. Both of them are asynchronous, the endo transition structure having a higher degree of asynchronicity. Again all

distances are shorter than in the case of ethylene addition. In comparison with available literature transition structures for addition of formaldimine to butadiene, the transition structure has a higher degree of synchronicity (Δr is 0.435 Å for the endo addition of formaldimine to butadiene [3] and 0.176 Å for furan). Interestingly, the transition structure for addition of *trans*-diazene shows asynchronicity that is very close to the one obtained with butadiene, but contrary to the endo and exo *cis*-diazene addition to butadiene [3(a)], the

Table 2
Total Energies (in au) of Reactants and Transition Structures for the Diels–Alder Reaction of Furan with Heterodienophiles

Species	HF3/3-21G	HF/6-31G*//HF/3-21G
1	–227.35008	–228.62267
2	–77.60099	–78.03169
3	–113.22182	–113.86239
4	–93.49478	–94.02564
5	–109.35477	–109.99247
6	–109.34240	–109.97846
7	–129.03829	–129.78325
8	–304.89583	–306.58053
9	–340.52391	–342.42033
10	–320.78810	–322.57637
11	–320.79367	–322.58039
12	–336.66172	–338.54107
13	–336.64108	–338.52740
14	–336.65052	–338.53110
15	–356.35666	–358.33496
16	–356.36030	–358.34380

transition structure for furan addition is fully symmetric. The nitrosyl hydride addition transition structures show a certain degree of asynchronicity which is again not so pronounced like in the case of butadiene. It appears that symmetric *cis*-heterodienophiles add to furan through a fully synchronous transition structure.

3.2. Energetics of the transition structures

The calculated total energies for the reactants, the transition structures and the energies with respect to the reactants for heterodienophile addition to furan are given in Tables 2 and 3.

The activation energy for the addition of

ethylene to furan calculated by HF/6-31G*//HF/3-21G is higher than in the addition of ethylene to either butadiene (45.9 kcal mol^{–1}) [10]. Although the Hartree–Fock theory overestimates the energy barrier and correlational energy has to be taken into account, it seems that non activated alkenes will not undergo Diels–Alder reaction with furan. To the best of our knowledge, there is no experimental evidence in the literature for this kind of cycloaddition.

Both HF/3-21G and HF/6-31G*//HF/3-21G predict a lower activation energy of reaction for formaldehyde with furan than in the reaction of ethylene with furan (Table 3). This finding is contrary to the one obtained for the addition of formaldehyde to butadiene (energy difference for HF/6-31G*//HF/3-21G is +3.0 kcal mol^{–1}) [3(a)]. Nevertheless, experimentally formaldehyde does not react with either 1,3-butadiene or furan [12].

Two structures **10** and **11** for the addition of formalimine are quite different (Fig. 3), causing a difference in the activation energies. The *exo* form has very similar activation energy to the one in the addition of ethylene to furan and thus the reaction is energetically not favorable. The *endo* structure **11** is predicted to have a 2.5 kcal mol^{–1} (6-31G*) lower activation energy than **10**. This is considerably larger than the *endo* preference for Diels–Alder reactions of activated ethylene with butadiene and cyclopentadiene [10,11,13]. The formation of hydrogen bonds in the transition structures **10** and **11** between the formalimine hydrogen and the furan oxygen in both cases is not favored either by the geometry or the orbital interactions (the H–O distance in the *exo* isomer is

Table 3
Calculated Energies (kcal/mol) of Hetero Diels–Alder Transition Structures with Respect to Reactants

Dienophile	TS	HF/3-21G	HF/6-31G*//HF/3-21G
Ethylene	8	34.7 (0.0)	46.3 (0.0)
Formaldehyde	9	30.1 (–4.6)	40.6 (–5.7)
Formaldimine, <i>exo</i> H	10	35.6 (+0.9)	45.1 (–1.2)
Formaldimine, <i>endo</i> H	11	32.1 (–2.6)	42.6 (–3.7)
<i>trans</i> -diazene	12	27.1 (–7.6)	46.5 (+0.2)
<i>cis</i> -diazene, <i>exo</i> H	13	32.2 (–2.5)	46.3 (0.0)
<i>cis</i> -diazene, <i>endo</i> H	14	26.3 (–8.4)	43.9 (–2.4)
Nitrosyl hydride, <i>exo</i> H	15	19.9 (–14.8)	44.5 (–1.8)
Nitrosyl hydride, <i>endo</i> H	16	17.6 (–17.1)	39.0 (–7.3)

2.5 Å, in the endo isomer it is 3.2 Å, and in both cases the N–H bond is parallel to the C–O–C plane). The effect can be explained by the fact that the Diels–Alder reaction prefers the exo lone pair transition structure [14]. It has been calculated that Diels–Alder reactions with N-methylformaldimine still prefer the exo lone pair by 4 kcal mol⁻¹ [15]. There is significant twisting between furan and formaldimine in both structures. The dihedral angle of C–C–N–C is 65.5° for the exo **10** and 79.3° for the endo transition structure **11**, which shows an attraction of the imino hydrogen to the π electrons of the furan ring thus freeing the lone pair. The corresponding values for the butadiene–formaldimine system where such effects are absent, are -27° for the exo and 20° for the endo adduct [3(a)].

Azo compounds are very reactive dienophiles and are extensively used in organic syntheses [16]. Azo compounds with electron-withdrawing groups play very important roles in syntheses of natural products. They can exist both in the trans and cis forms. In diazene, the trans form is 6–7 kcal mol⁻¹ more stable than the cis form [17]. Our calculations predict 7.8 kcal mol⁻¹ (HF/3-21G) and 8.8 kcal mol⁻¹ (6-31G**/3-21G), respectively. As was mentioned above, the transition state with *trans*-diazene is asynchronous, but with *cis*-diazene the transition state is synchronous. The lone pair effect is shown in structure **12**, which causes one of the newly forming bonds to be slightly shorter ($\Delta r = 0.104$ Å). The effect is also present in the activation energy that follows the simple rule, lower energy–exo lone pair.

The largest decrease in the activation energy for the compounds studied in comparison with ethylene is calculated for the endo nitrosyl hydride addition to furan (-17.1 kcal mol⁻¹ with HF/3-21G and -7.3 kcal mol⁻¹ with HF/6-31G**//HF/3-21G). Surprisingly enough, both transition structures **15** and **16** show only a slight degree of a synchronicity ($\Delta r = 0.037$ Å and 0.066 Å, respectively). The activation energy differences between the endo and the exo transition structures are again caused by an n– π repulsion which is indicated by the shorter C–N bond length than the C–O bond in **15**. This large decrease in the activation energy and the moderate difference in exo/endo activation

energy might be useful in designing enantioselective Diels–Alder reagents that could prefer the reaction in relatively mild conditions [18].

4. Conclusion

The ab initio transition state structures for the Diels–Alder reactions of hetero dienophiles with furan are surprisingly synchronous and similar to Diels–Alder reactions with cyclopentadiene. The newly formed C–heteroatom bonds are mostly much shorter than the corresponding C–C bonds in the transition state structures. If the dienophile is symmetrical, a fully synchronous transition state structure is generated both for the endo and the exo case. Almost all hetero dienophiles show a higher reactivity in the addition to furan than to ethylene. In all cases the endo isomer has lower activation energy which is explained by repulsion of the lone pairs on N or O with the π system of the furan ring. This repulsion interaction might be very important for stereochemical control of the Diels–Alder reactions and related cycloaddition reactions as well.

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