

An AM1 Semiempirical Study

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Received April 17, 1995

A semiempirical AM1 theoretical study was carried out to examine the very low reactivity of thiophene; for example, the high reactivity of thiophene 1-oxide as a diene in the Diels Alder reactions. The reactivities of cyclopentadiene, thiophene, thiophene 1-oxide, and thiophene 1,1-dioxide were studied as dienes in the reaction with ethylene, cyclopropene, and benzoquinone. Ethylene was chosen as a standard, while cyclopropene, with its high strain energy was released in the course of a reaction making it relatively reactive. The benzoquinone has a lower LUMO energy, making it a very reactive dienophile for the Diels-Alder reaction. Frontier molecular orbital energy gap between the reactants was considered, and the disadvantage of this approach in studying the reactivity was demonstrated. For all combinations, the corresponding transition structures are generated and the activation energies are estimated. The estimated activation barrier for sulfur dioxide elimination from the adduct was used to explain the failure to accumulate the cycloadduct in the reaction mixture. The obtained results are compared with experimental data when available. An excellent agreement of theory and experiment was obtained.

J. Heterocyclic Chem., **32**, 1445 (1995).

Introduction.

The synthetic and theoretical study of heterocyclic five membered aromatic compounds as starting materials provide a solid foundation for the preparation of a wide variety of organic compounds [1,2]. There are only a handful of papers that deal with this problem, mainly because heterocyclic aromatic compounds are very stable and do not easily undergo [4+2] cycloaddition reactions. One of the most unreactive five member heterocycles is thiophene, due to its very high aromatic character. This effect was known for a long time and apparently Pauling first offered the idea that *d*-orbitals on the sulfur might be included into the aromatic resonance stability [3]. This idea stimulated many computational studies of aromaticity of the heterocycles [4]. Even from the highest quality *ab initio* calculations on thiophene, it is clearly indicated that *d*-orbital participation is not significant in the ground state [5]. Nevertheless, the fact remains that thermochemical determined resonance energy is as high as 117 kJ/mol for thiophene [6].

It is generally accepted that both thiophene 1-oxide and 1,1-dioxide do not have very pronounced aromatic properties. Thus, these compounds are expected to be more reactive and will participate as dienes in the Diels-Alder reactions [7]. Many other derived heterocycles participate unwillingly in the Diels-Alder reactions [8]. All three thiophenes can, in principle, participate as dienes in the Diels-Alder reactions. In general, there are three strategies that can increase the probability of the cycloaddition reaction. Using highly reactive dienophiles, increasing the potential reactivity of thiophene by the proper choice of substituents, and carrying out the reaction under high

pressure was shown to increase the reactivity due to negative activation volume of the reaction [9].

Diels-Alder reactions attract attention because of their unique capabilities. It is very frequently found, that, although the reaction could conceivably yield a number of structurally stereoisomeric products, one stereoisomer is strongly favored [10]. Significant progress has been made in understanding the nature of transition states and the level of *ab initio* theory required to reproduce the experimental kinetic data [11]. These reactions are generally assumed to be concerted cycloadditions, although a stepwise radical mechanism has been proposed [12], but has been rejected by high level *ab initio* calculations [13]. There are only a few examples of theoretical studies of heterocycles as dienes for the Diels-Alder reactions [14], although all carbon Diels-Alder reactions have been investigated extensively [15]. We would like to present an AM1 semiempirical study of thiophene and the oxy-derivatives as dienophiles for the Diels Alder reactions. We will demonstrate that by decreasing aromaticity of the thiophene ring through sulfur oxidation and by choosing some reactive dienophiles, the activation energy of the cycloaddition can be brought into a range of experimental performance.

Methodology.

All 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 6.0 [16]. The search for the transition states and their verification [17] was performed as described previously [18]. Vibrational and thermal analyses were performed on all optimized structures. The major problem with using AM1

for calculation of thiophene systems concerns the absence of 'd' orbitals. For example, errors in AM1 heats of formation for hypervalent sulfur containing molecules are generally quite large [19]. Since the oxidation state of the sulfur atom is unchanged in the Diels-Alder reaction, partial cancellation of such errors might occur. Thus, we expect, that unanticipated errors should be the same and the computed trends presented here should be qualitatively correct.

Results and Discussion.

In order to calculate the theoretical reactivity of thiophene and thiophene oxide in the Diels-Alder reaction, we have chosen AM1 semiempirical method [19]. Although activation energies for the Diels-Alder reactions with cyclobutadiene are not predicted correctly [20], this method has proven useful in the cases where polar cycloaddition reactions are involved, and when relative reactivity has to be predicted [21]. For the qualitative correlation of reactivity of thiophene and thiophene oxides in reaction with ethylene, cyclopropene, and benzoquinone, frontier orbital energy gap between reactants will be used. The frontier molecular orbital (FMO) [22] approach is a simple model that can, in many cases, give a satisfactory explanation and relative reactivity in cycloaddition reactions. This approach is based on the assumption that better overlap between orbitals will occur if they have similar energies. In other words, the most reactive reactant pair will be the one that

normally a HOMO diene controlled Diels-Alder reaction. Similarly, the dienes' behavior is predicted in reaction with cyclopentene (columns III and IV, Table 1), although, now only the cyclopentadiene reaction is a normal Diels-Alder reaction. The thiophene 1,1-dioxide is still predicted to be the most reactive followed by thiophene 1-oxide, thiophene, and cyclopentadiene. The most reactive dienophile predicted by AM1 method is benzoquinone. The reaction is now normal Diels-Alder cycloaddition reaction with the highest reactivity predicted for cyclopentadiene. Actually the predicted reactivity is inverse with that predicted for both ethylene and cyclopropene.

Energies of the reagents' frontier molecular orbitals were evaluated separately. As the reactants draw closer together the steric and electronic interactions between them become very important for determining the energies of a reactant pair system. One of the best approaches for explaining the reactivity of a species is to estimate the energy of the transition state for the corresponding reaction [23]. We will discuss the combined AM1 generated structures of transition states and their activation energies.

Addition of Ethylene.

The transition structures for the addition of ethylene to thiophene, thiophene 1-oxide, and thiophene 1,1-dioxide represent the concerted synchronous mechanism of the cycloaddition reaction (Figure 1). Thus, both newly

Table 1
Frontier Orbital Energies (eV) of the Reactants and their FMO Energy Gaps

Reactant	HOMO	LUMO	I	II	III	IV	V	VI
A	-9.07914	0.48161	11.51	10.51	10.30	10.12	11.37	7.34
B	-9.21756	0.23845	10.79	10.66	9.82	10.29	11.11	7.48
C	-9.64768	-0.67322	9.88	11.09	9.14	10.69	10.20	7.91
D	-11.03025	-1.41620	9.14	12.47	8.40	12.07	9.46	9.29
E	-10.55142	1.43778						
F	-9.81861	1.04223						
G	-10.87585	-1.73492						

A-Cyclopentadiene; B-Thiophene; C-Thiophene 1-oxide; D-Thiophene 1,1-dioxide; E-ethylene; F-cyclopropene; G-benzoquinone.

I-LUMO_{diene}-HOMO_{ethylene}, II-LUMO_{ethylene}-HOMO_{diene}, III-LUMO_{diene}-HOMO_{cyclopropene}, IV-LUMO_{cyclopropene}-HOMO_{diene}, V-LUMO_{diene}-HOMO_{benzoquinone}, VI-LUMO_{benzoquinone}-HOMO_{diene}

has the frontier orbitals with the lowest energy gap. The energies for frontier orbitals of thiophene derivatives and the dienophiles with frontier orbitals energy differences are presented in Table 1. The reactivity of thiophene and thiophene oxide will be compared with similar addition reactions with cyclopentadiene. According to FMO theory the most reactive diene for a nonactivated dienophile like ethylene would be thiophene 1,1-dioxide ($\Delta E = 9.14$ eV). The reaction is predicted to be LUMO diene controlled and it operates as a reverse Diels-Alder reaction. Although, ethylene addition to both cyclopentadiene and thiophene is nor-

formed C-C bonds have the same bond distance, although, these bonds differ from case to case. The shortest bond is with thiophene, and the longest with thiophene 1,1-dioxide. The structural parameters for ethylene addition to thiophene oxide are very interesting. There are two possible transition structures. One has an oxygen atom up (3) and other has oxygen down (4). They differ considerably in geometry. The transition state structure 3 is more similar to one with cyclopentadiene (1) than one with thiophene (2). The newly formed bond distance is 2.095 Å, only 0.012 Å shorter, and the dihedral angle is exactly the same as in 1.

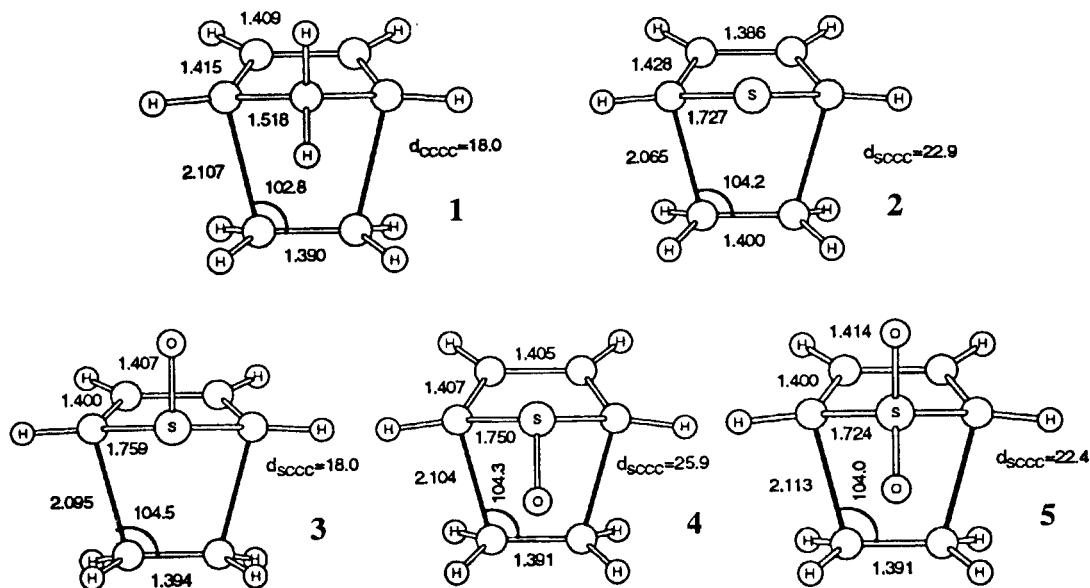


Figure 1. Transition state structures generated with AM1 for ethylene addition to the dienes.

In comparison with transition structure 3, transition structure 4, demonstrates two important effects occurring in most cycloaddition reactions, steric and electronic repulsion's in the course of bond formation. Due to repulsion interactions between the oxygen of thiophene 1-oxide moiety and ethylene, the two newly formed bonds are slightly longer ($\sim 0.030 \text{ \AA}$), and the ethylene group is pushed more *endo* in the transition state, and the thiophene ring diverges from the plane resulting in increasing the dihedral angle by 7.5° . The same effect is present in transition structure 5 for ethylene addition to thiophene 1,1-dioxide. Of course, these geometrical differences between two isomeric transition structures 3 and 4 can be explained by $n-\pi$ repulsion interactions present in transition state 4 between the oxygen lone pairs of thiophene 1-oxide, and the π orbitals of the ethylene moiety. Houk and coworkers [24], and we [25] have proposed a similar explanation for hetero dienophile addition to a diene. We believe, that the geometric parameters of the transition structures 4 and 5 are defined by both steric (oxygen-ethylene carbons) and electronic repulsion interaction ($n-\pi$) between reactant moieties.

On the basis of the structural parameters it is very hard to determine the diene's order of reactivity with ethylene. One can argue, that the progress of bond formation might be a criteria for determining reactivity by incorporating the Hammond postulate [26]. In a very simple application of the postulate, the longer newly formed bonds in the transition structure mean the transition structure is close in geometry to the reactants and consequently have a lower activation barrier. With respect to this the reactivity is 5, 1, 4, 3, and 2, in descending order. The only reliable approach is to calculate the activation barriers (Table 2). Surprisingly, the pre-

dicted order of reactivity based on the bond distance is quite close to one predicted by calculating the activation energy. Thiophene is unreactive toward [4+2] cycloaddition reactions as demonstrated by its high activation energy of 44.15 kcal/mol. There is a considerable reduction in the activation barrier when activated thiophene 1-oxide is used as a diene. Actually, it was predicted that this reaction is more feasible than ethylene addition to cyclopentadiene, while thiophene 1,1-dioxide is predicted to have a reactivity similar to cyclopentadiene. Although, experimental values for ethylene addition for both thiophene 1-oxide, and thiophene 1,1-

Table 2
AM1 Calculated Activation Energies (kcal/mol) for
Ethylene Addition to Cyclopentadiene, Thiophene,
Thiophene 1-Oxide, and Thiophene 1,1-Dioxide

Transition state	ΔE	$\Delta E + ZPVE$ [a]
1	28.50	29.45
2	44.14	44.15
3	31.58	28.99
4	30.16	27.65
5	28.50	29.81

[a] Zero point vibrational energy.

dioxide are not available. It is known, that their respective derivatives can engage in cycloaddition reactions with marginally activated dienophiles [27].

Addition of Cyclopropene.

It is expected that the addition of cyclopropene to dienes will be more feasible than a similar reaction with ethylene, because both are of higher HOMO energies and higher

heats of formation that will bring the energetic level of the reactants closer to the transition state. Because of *endo-exo* isomers, there are ten possible transition structures for cyclopropene addition to cyclopentadiene, thiophene, thiophene 1-oxide, and thiophene 1,1-dioxide (Figure 2). All transition structures for *endo* cyclopropene addition to the dienophiles are concerted and synchronous as can be expected, considering the reactants symmetry. *Exo* transition structures of cyclopropene addition to thiophene 1-oxide and thiophene 1,1-dioxide were not possible to generate,

due to strong steric interactions between the oxygen of the diene and the methylene hydrogen of cyclopropene. An AM1 search for transition structures always brought the transition structure that represented CC and OC rather than the two CC bonds. The activation energy for this reaction is around 35 kcal/mol. Because the energies are considerably higher than for the *endo* isomer and the yielded product might not be the Diels-Alder adduct.

The diene reactivity in cyclopropene cycloaddition reaction is almost impossible to predict on the basis of a transi-

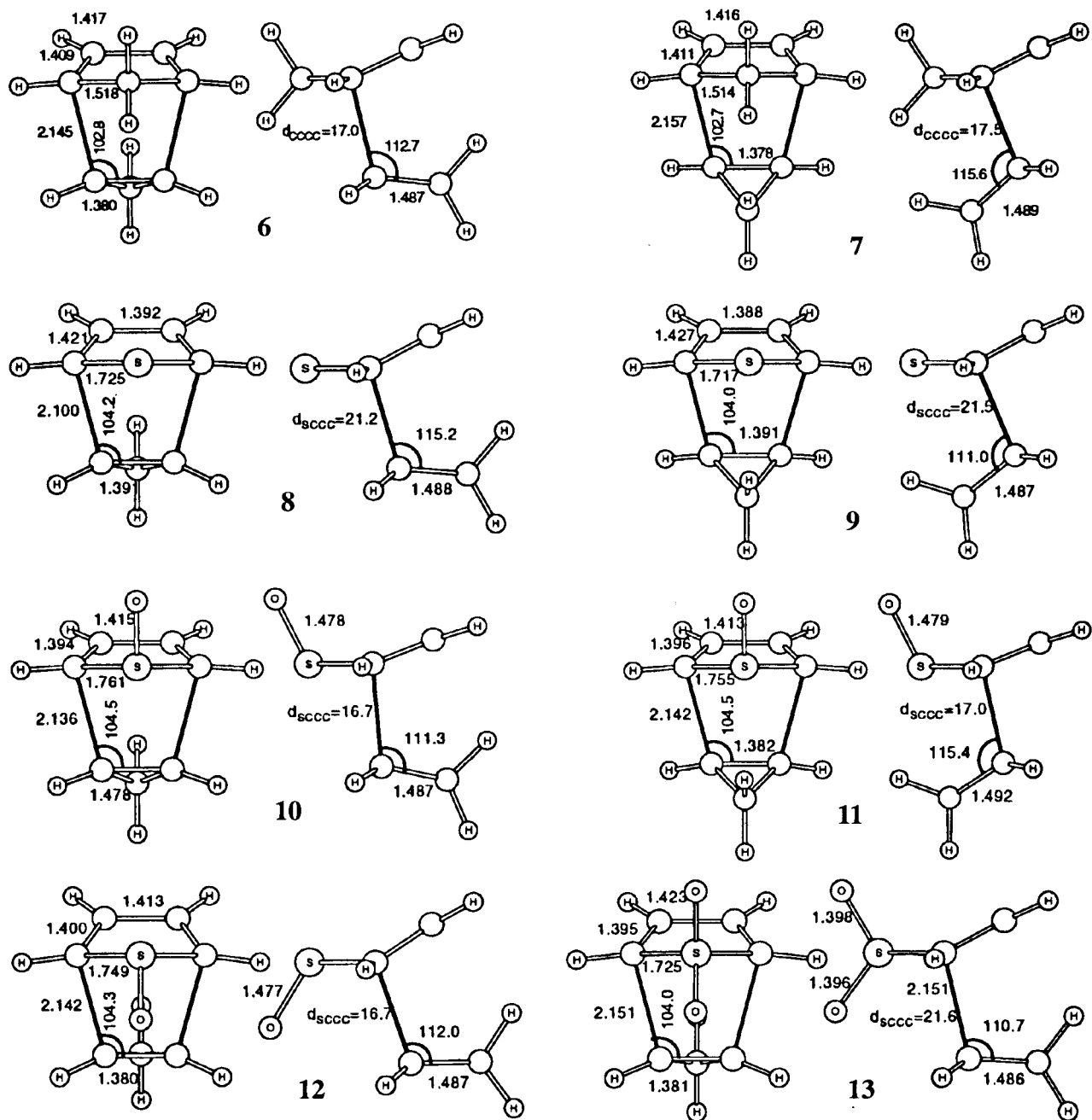


Figure 2. Transition state structure of cyclopropene addition to cyclopentadiene, thiophene, thiophene 1-oxide, and thiophene 1,1-dioxide generated by AM1.

tion structure without accepting at least two assumptions. First, the transition structure with *endo* addition will have lower energy than isomeric *exo*. Second, the transition structure with the longer newly formed CC bond will have the lower activation barrier because the transition states are closer in energy to the reactants. This might only be useful when very similar reactants of the same type in the reaction are considered. With this highly speculative approach the most reactive should be thiophene 1,1-dioxide, while low reactivity is predicted for the thiophene as a diene.

The activation barriers (Table 3) do indeed agree with these two predictions. It is interesting to note, that FMO energy gap correlation's favor cyclopentadiene as the least reactive. The predicted difference of *endo* cyclopropene addition to thiophene oxides are about 1.1 kcal/mol. As expected the addition of cyclopropene to thiophene (Table 3) has a lower reaction barrier by 4 kcal/mol compared with ethylene. The reaction will still not be experimentally feasible. By oxidation of thiophene the reaction barrier is decreased for more than 10 kcal/mol. The *endo* isomers are preferred over the *exo* species, except in the case of addition to thiophene. The trend of reactivity predicted by addition of cyclopropene is quite similar to the prediction obtained by calculating activation barriers for ethylene addition (Table 2). Although forceful reaction conditions are necessary for ethylene addition to cyclopentadiene, the reaction is experimentally possible. The experimentally determined activation barrier is 22.5 kcal/mol [28] which is 6 kcal/mol lower than the value predicted with AM1 calculation. Thus, it is reasonable to expect that cyclopropene addition to thiophene dioxide is around 20 kcal/mol and should be experimentally possible.

Table 3

AM1 Activation Barriers (kcal/mol) for Cyclopropene Addition to the Cyclopentadiene, Thiophene, Thiophene 1-Oxide, and Thiophene 1,1-Dioxide

Transition state	ΔE	$\Delta E + ZPVE$ [a]
6	27.13	27.63
7	29.55	29.92
8	40.48	40.46
9	40.00	40.08
10	29.31	29.33
11	32.23	32.11
12	28.90	28.88
13	27.83	27.76

[a] Zero point vibrational energy.

The [4+2] cycloaddition of thiophene dioxide with cyclopropene is facile and leads to a product in more than 95% yield [29]. The only limiting factor for the reaction is steric crowding on the methylene carbon of the cyclopropene moiety in the transition state. Thiophene dioxide

can be further activated by adding chlorine atoms. Tetrachlorothiophene 1,1-dioxide is a versatile, reactive but stable, cheletropic Diels-Alder reagent [30]. It undergoes [4+2] cycloaddition reaction with a variety of unreactive double bonds, followed by extrusion of sulfur dioxide, the net result being an annulation with tetrachlorobutadienediyl group [31].

Addition of Benzoquinone.

As indicated by the FMO energy gap the addition of benzoquinone to thiophene should be the most reactive of all dienophiles studied here. There are ten possible transition structures. To enhance the clarity of presentation we will present benzoquinone addition to cyclopentadiene and thiophene (Figure 3), thiophene 1-oxide (Figure 4), and thiophene 1,1-dioxide (Figure 5) followed by their estimated activation energies separately. They are all concerted, synchronous [4+2] cycloaddition reactions with full symmetry. Steric interactions are clearly demonstrated when two isomeric transition structures **14** and **15** are compared. The transition structure for *exo* addition has a slightly longer newly formed CC bond and the methylene group of the diene is extended further than the *endo* transition structure **14**. The *exo* bond is only 0.007 Å longer and the *exo* dihedral angle is merely 1.5° wider than the *endo* structure dimensions. Although these steric differences are modest they have a profound influence on the energies of the transition states; favoring the one that has fewer steric interactions, transition structure **14**. The steric and electron repulsion's are even less visible (the differences for the distance is 0.005 Å and for the dihedral angle is 0.6°) for transition structures **16** and **17**. Regarding this case, we believe that the electronic effect, particularly n- π repulsion interactions between the reactant moieties, predominates in determining geometries and energies of the transition structures. Thus, we expect that transition structure **16** should have a slightly lower activation energy than **17**. The energy difference will be much smaller in comparison with the **14-15** couple. By comparison of bond distances for CC in formation we can predict that in this cycloaddition reaction the thiophene will have higher activation energy. FMO energy gap favors cyclopentadiene as a diene (Table 1). Our prediction of the stereoselectivity on the basis of steric and repulsive interactions in transition structures seems to be fully incorrect. Here AM1 predicts repulsive *endo* interaction. That is demonstrated on CCC angle that goes through the dienophile and a new CC bond. This is higher for *endo* transition structures, than for *exo* structures, indicating that these interactions might be responsible for contradicting the Alder rule. Because experimental data for these reactions are not available, one might assume that this effect is "real". There is more evidence to support the idea that the FMO energy gap (Table 1) predicts ben-

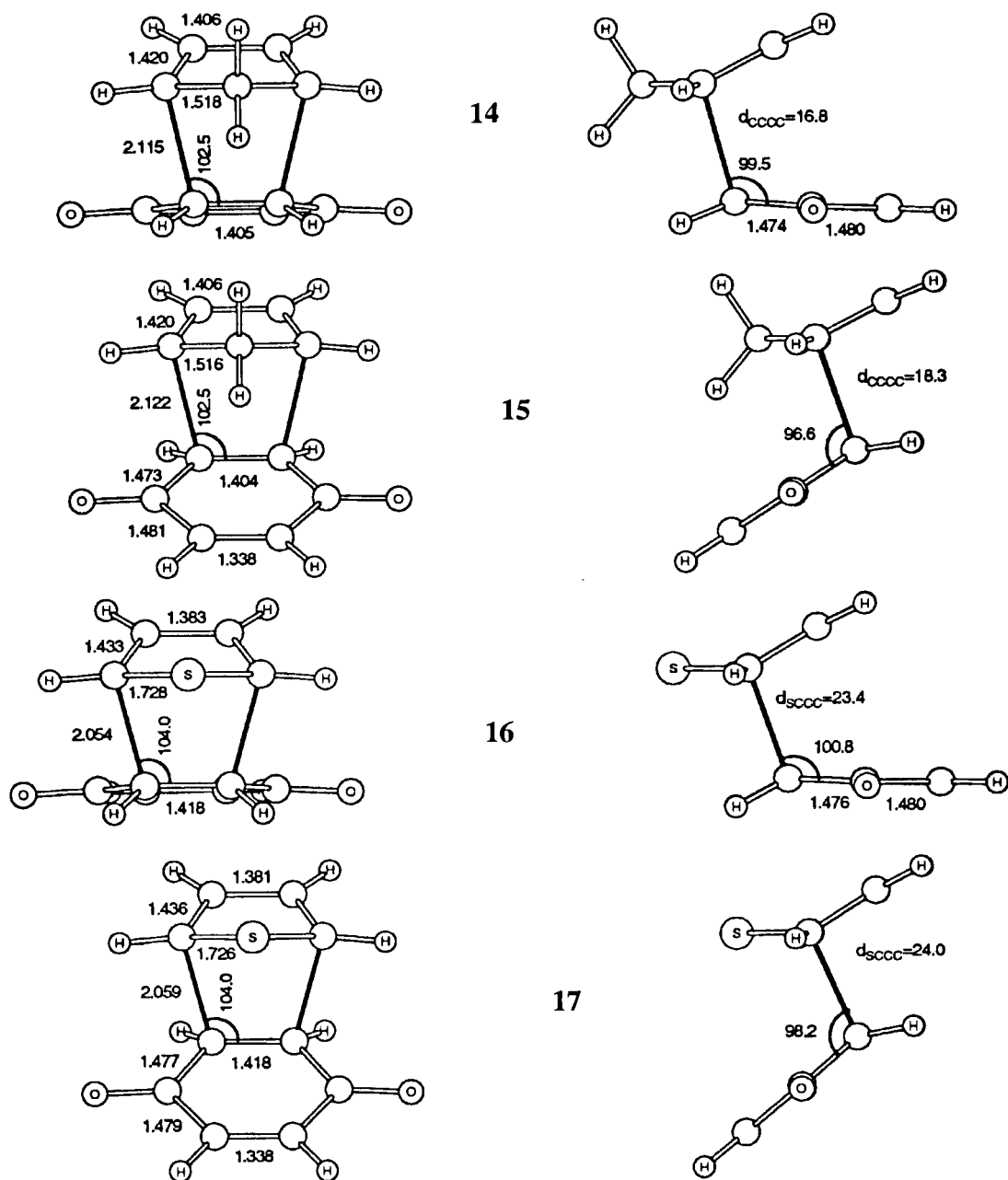


Figure 3. AM1 generated transition structures for benzoquinone addition to cyclopentadiene and thiophene.

zoquinone addition to be notably more facile than either ethylene or cyclopropene addition (Table 1). The AM1 predicted activation energies for benzoquinone as dienophile (Table 4) in the cycloaddition reaction with cyclopentadiene and thiophene are above the activation barriers predicted for the same reaction, using both ethylene (Table 2) and cyclopropene (Table 3). On the other hand, these results may indicate a weakness of semiempirical methods for calculating activation energies for reactive dienophiles. We have observed this problem in

Table 4
Activation Energies (kcal/mol) for Benzoquinone Addition to Cyclopentadiene and Thiophene

Transition state	ΔE	$\Delta E + ZPVE$ [a]
14	29.89	29.81
15	29.03	29.10
16	45.79	45.07
17	45.13	44.67

[a] Zero point vibrational energy.

the semiempirical study of cyanoethene addition to cyclopentadiene [20].

If this problem is present in the case of cycloaddition of less reactive cyclopentadiene and thiophene, then it should be eliminated in the case of more reactive dienes like, thiophene 1-oxide and thiophene 1,1-dioxide (Figure 4). The transition structures are for synchronous cycloaddition reactions. In comparison with benzoquinone addition to

thiophene, the angle CCC through the newly formed bond is smaller for the *endo* isomer. That demonstrates that the repulsion interactions between reactants in transition structure 16 for thiophene (the angle is 100.8°) are now turned around into attractions, because the electron density on thiophene ring is now reduced (the angle for 18 is 97.8°). This should considerably decrease the activation barrier of the cycloaddition. This effect is obvious when the angle is

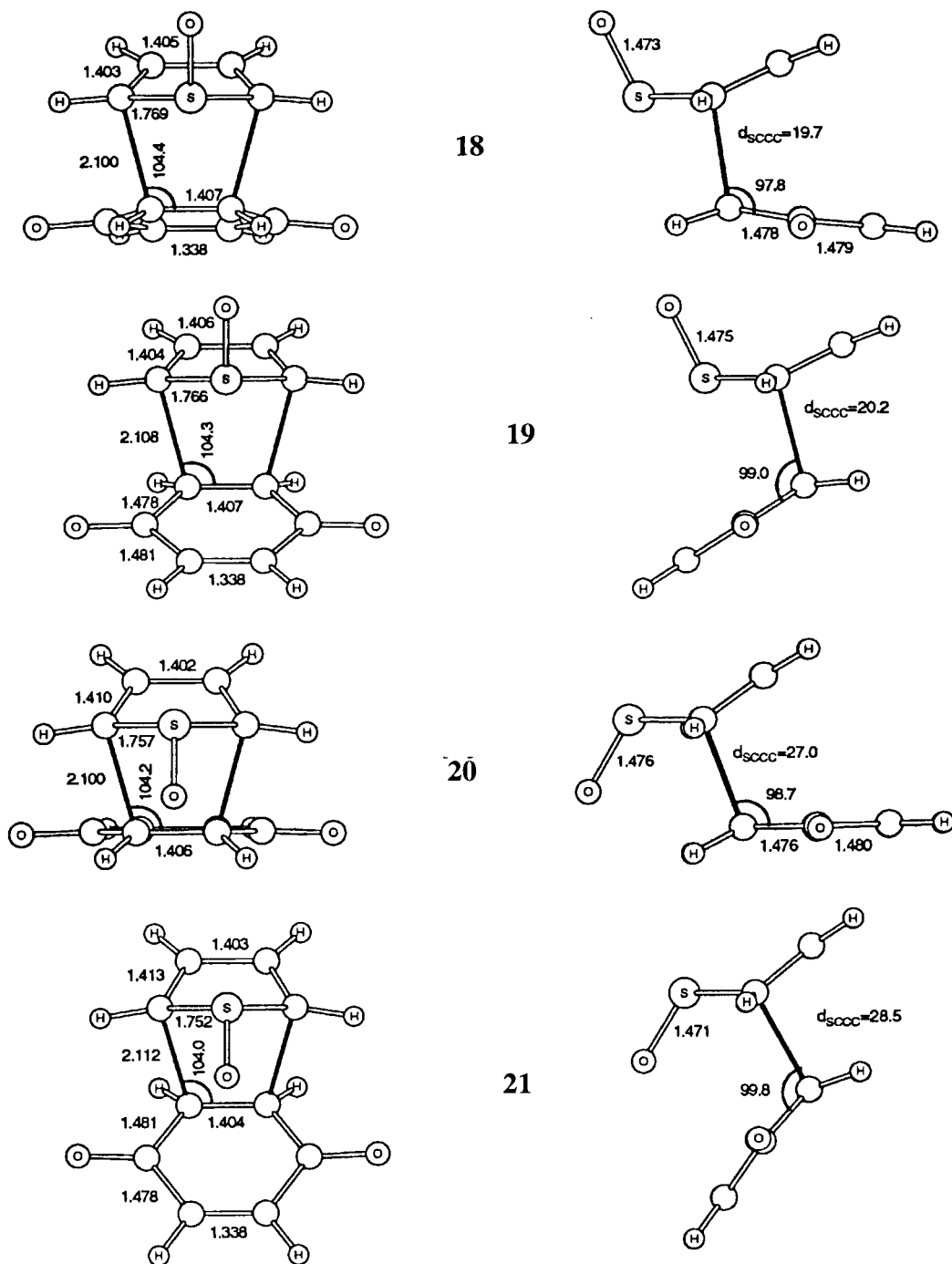


Figure 4. Transition structures for benzoquinone addition to thiophene 1-oxide.

compared with two isomer **16** and **17** for thiophene. The *endo* isomer has a wider angle at 2.9° . While in the case of **18/19**, the *exo* isomer has a wider angle at 1.2° , though that cannot be caused by steric interactions between thiophene 1-oxide oxygen and the benzoquinone ring as one can assume for structures **20/21**. It can be assumed that for both cycloaddition pairs the *exo* isomer will have lower energy. The difference should be more profound in transition structures **20/21**. We can also predict that thiophene 1-oxide should be considerably more reactive than thiophene despite FMO results (Table 1) that favor thiophene. As we already discussed, FMO theory considers separate reactants without incorporating the steric and electronic interactions that occur during the course of the reaction. To determine which transition states, **18** or **20**, will have a lower activation energy on the basis of structural parameters, is not an easy task. Of course, estimating the activation barrier, can better determine the reactivity (Table 5). As discussed, the activation barriers for *endo* benzoquinone additions are indeed lower. The predicted

Table 5
Activation Energies (kcal/mol) for Benzoquinone
Addition to Thiophene 1-Oxide

Transition state	ΔE	$\Delta E + \text{ZPVE [a]}$
18	15.41	14.73
19	16.87	16.23
20	12.80	12.22
21	16.40	15.95

[a] Zero point vibrational energy.

reactivity of thiophene 1-oxide on the basis of structural parameters; *i.e.*, the angle between the reactants, is correct. Thiophene 1-oxide is considerably more reactive than both cyclopentadiene and thiophene. What was difficult to determine on the basis of the geometric parameters, now shows that transition structure **20** has the lowest reaction barrier. The activation barriers are so low that the reaction is predicted not only to be feasible, but should require very mild conditions.

The [4+2] cycloaddition reaction with thiophene 1-oxide as the dienophile is well documented. The reaction requirements are, as determined theoretically, mild. By oxidizing 2,5-dimethylthiophene at 0° in the presence of benzoquinone the corresponding adduct was isolated [32]. Oxidation of thiophene by itself in the presence of benzoquinone will lead to the adducts, but now the oxidation can go further [32].

The cycloaddition of benzoquinone to thiophene 1,1-dioxide, based on chemical intuition and the result discussed above should yield an *endo* isomer, and the reaction should have a higher activation barrier. The first assumption is made on strong steric repulsion's between oxygen of the dioxide and benzoquinone in an *exo* transition structure. The second, is based on the AM1 estimated heat of hydrogenation of thiophene 1-oxide and thiophene 1,1-dioxide, making the energy of the dioxide species 4.75 kcal/mol lower. If all electronic interactions in *endo* transition structures with the oxide and the dioxide are the same then the reaction barrier might increase considerably because of FMO energy gap (Table 1).

The structural parameters of two isomeric transition structures **22** and **23** (Figure 5) are very similar to values

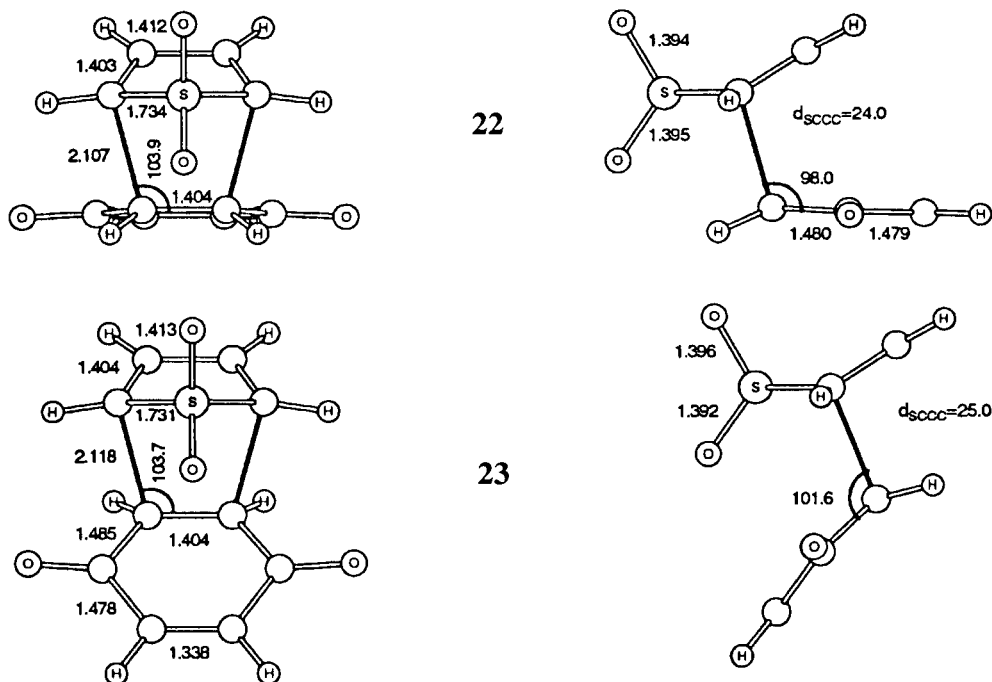


Figure 5. Transition structures for benzoquinone addition to thiophene 1,1-dioxide

Table 6
Activation Energies (kcal/mol) for Benzoquinone
Addition to Thiophene 1,1-Dioxide

Transition state	ΔE	$\Delta E + \text{ZPVE [a]}$
22	35.43	34.72
23	40.36	39.36

[a] Zero point vibrational energy

with thiophene 1-oxide (Figure 4). Both are for synchronous formation of the cycloadduct. The activation barriers (Table 6) for these reactions are higher than those predicted for thiophene 1-oxide. The *endo* isomer is preferred for about 5 kcal/mol. This predicted activation barrier is remarkably high in comparison with thiophene 1-oxide (Table 5) and this reaction must be performed under vigorous conditions. As demonstrated, thiophene 1-oxide

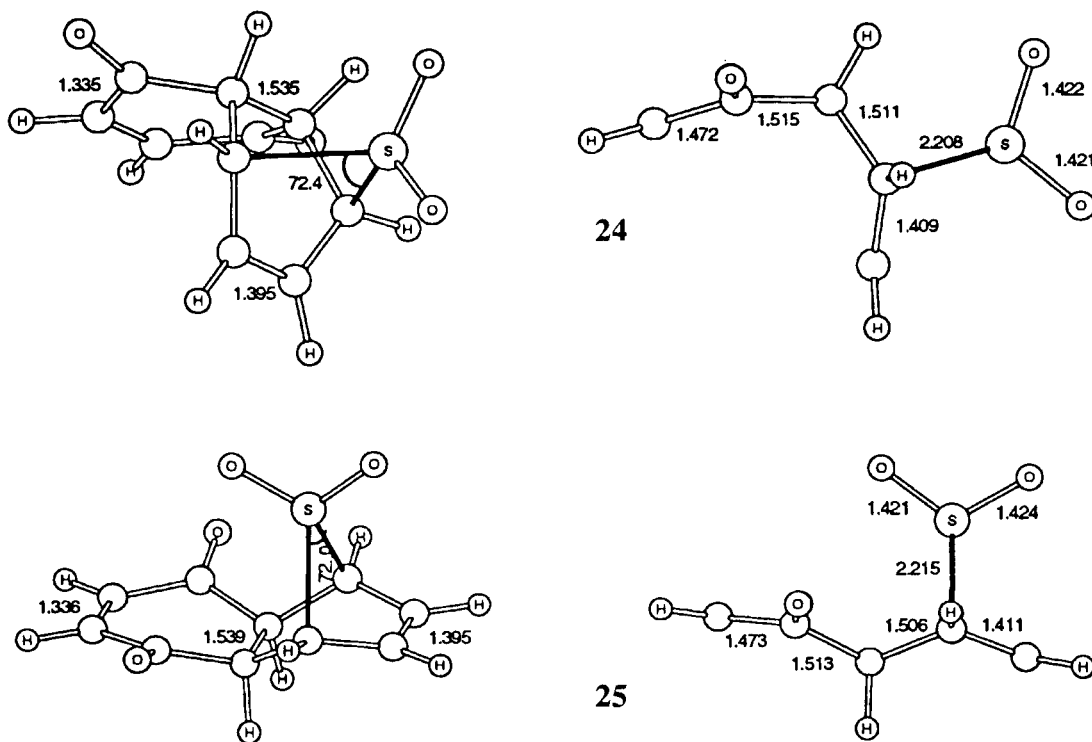


Figure 6. The transition structures for thermal sulfur dioxide elimination.

is much more reactive than thiophene 1,1-dioxide although the cycloadduct can be obtained under vigorous reaction condition [32].

Both thiophene 1-oxide, and thiophene 1,1-dioxide when involved in cycloaddition reactions as dienes rarely produces the expected cycloaddition product. The cycloadduct usually undergoes elimination of H_2SO or sulfur dioxide [32,33]. We will determine the activation barriers of sulfur dioxide elimination with examples of

benzoquinone adducts to thiophene 1,1-dioxide. The transition structures **24** and **25** (Figure 6) represents the concerted mechanism of sulfur dioxide elimination. Both of the transition structures have a plane of symmetry, that is defined by eliminating a molecule of sulfur dioxide. Both bonds are breaking at the same time with the same bond distance making the transition structure synchronous. Transition structure **25** has two CS bonds breaking at a slightly greater distance due to steric interactions between the leaving group and benzoquinone moiety. Considering that the reaction is exothermic (calculated by AM1), transition structure **24** is closer to the product resulting in lower activation energy. That is demonstrated on AM1 estimated activation energies (Table 7) for sulfur dioxide elimination. The activation energy is only 14.42 kcal/mol and is much lower than 34.72 (Table 6) predicted for *endo* benzoquinone addition to thiophene 1,1-dioxide.

Table 7
Activation Energies (kcal/mol) for Sulfur Dioxide from Benzoquinone
Adducts to Thiophene 1,1-Dioxide

Transition state	ΔE	$\Delta E + \text{ZPVE [a]}$
24	17.48	14.42
25	18.86	16.58

[a] Zero point vibrational energy.

Conclusion.

Although the AM1 method will not accurately predict activation barriers for the Diels-Alder reactions, this method can be useful for the correlation of relative reactivity of similar dienes. The calculation of frontier molecular orbital energy gap with reactants fails when there is considerable steric and/or electronic interaction in the course of the reaction. This was clearly demonstrated in the example of benzoquinone addition to cyclopentadiene, thiophene, thiophene 1-oxide, and thiophene 1,1-dioxide. The reactivity is predicted to decline in the same order. This contradicts experimental evidence, that selects thiophene 1-oxide as the most reactive dienophile in the series studied. The calculation of activation barriers predicts that the most reactive diene is indeed thiophene 1-oxide with an activation barrier of only 14.73 kcal/mol. Furthermore, that activation energy required by mild reaction conditions, is in agreement with experimental data. Thiophene is predicted to be less reactive with an activation barrier of 45.07 kcal/mol. This value precludes the cycloaddition reaction and justifies the absence of experimental data for thiophene as diene in the Diels-Alder reaction. Intermediate reactivity was predicted for thiophene 1,1-dioxide, with estimated activation barrier for cyclopentadiene addition of 27.76 kcal/mol and benzoquinone addition of 34.72 kcal/mol. Knowing that AM1 overestimates the activation energies, it was predicted that the reaction will proceed only under vigorous conditions. Finally, in these kinds of thio- reactions, the cycloadduct was rarely isolated but instead the product of sulfur dioxide elimination. The AM1 reaction barrier for sulfur dioxide elimination from a benzoquinone adduct to thiophene 1,1-dioxide is predicted to be only 14.42 kcal/mol. Finally, the semiempirical AM1 method helps to explain the high reactivity of thiophene 1-oxide and the low reactivity of thiophene as diene in the Diels-Alder reactions.

REFERENCES AND NOTES

- [1] For recent reviews of organic syntheses in general see: D. Seebach, *Angew. Chem., Int. Ed. Engl.*, **29**, 1320 (1990); B. Helmut, H.-D. Scharf, N. Hoffmann and P. Esser, *Angew. Chem., Int. Ed. Engl.*, **30**, 477 (1991); E. J. Corey, *Angew. Chem., Int. Ed. Engl.*, **30**, 455 (1991); L. F. Tietz and U. Beifuss, *Angew. Chem., Int. Ed. Engl.*, **32**, 131 (1993).
- [2] For more general application of five membered aromatic heterocycle in organic syntheses see: A. I. Meyers, *Heterocycles in Organic Synthesis*, E. C. Taylor and A. Weissberger, eds, Wiley, New York, 1974; B. H. Lipshultz, *Chem Rev.*, **86**, 795 (1986); T. Masayoshi and Y. Gosei, *Kagaku Kyokaiishi*, **51**, 399 (1993); P. A. Jakobi, K. M. Touchette and H. G. Selnick, *J. Org. Chem.*, **57**, 6305 (1992).
- [3] G. W. Wheland and L. Pauling, *J. Am. Chem. Soc.*, **57**, 2086 (1935); V. Schomaker and L. Pauling, *J. Am. Chem. Soc.*, **61**, 1769 (1939); H. C. Longuet-Higgins, *Trans Faraday Soc.*, **45**, 173 (1949).
- [4] Some of them that concern thiophene are M. J. S. Dewar and N. Trinajstic, *J. Am. Chem. Soc.*, **92**, 1453 (1970); W. G. Salmund, *Q. Rev. Chem. Soc.*, **22**, 253 (1968); N. D. Epitotis, W. R. Cherry, F. Bernadi and W. J. Here, *J. Am. Chem. Soc.*, **98**, 4361 (1976).
- [5] U. Gelius, B. Roos and P. Siegbahn, *Theor. Chim. Acta*, **69**, 284 (1972).
- [6] K. Pihlaja and E. Taskinen, *Phys. Methods Heterocyclic Chem.*, **6**, 199 (1974).
- [7] S. Rajappa, Thiophene and their Benzo Derivatives: (ii) Reactivity in: *Comprehensive Heterocyclic Chemistry*; A. K. Katritzky and C. W. Rees, eds, Pergamon Press, New York, 1984, Vol 4, p 741.
- [8] For an excellent book on hetero dienophile in Diels-Alder see: D. L. Boger and S. N. Weinreb, *Hetero Diels-Alder Methodology in Organic Synthesis*, Academic Press, New York, 1987; S. M. Weinreb and R. R. Staib, *Tetrahedron*, **38**, 3087 (1982); E. Wenkert, P. D. R. Moeller and S. R. Piettre, *J. Am. Chem. Soc.*, **110**, 7188 (1988); J. Hamer, ed, 1,4-Cycloaddition Reactions, Academic Press, New York, 1967; T. Kametani and S. Hibino, *Advances in Heterocyclic Chemistry*, Academic Press, New York, 1987, Vol 42, Chapter 4; S. D. Larsen and P. A. Grieco, *J. Am. Chem. Soc.*, **107**, 1768 (1985); P. A. Grieco, P. D. Bailey, R. D. Wilson and G. R. Brown, *Tetrahedron Letters*, 6781 (1989); M. Maggini, M. Prato and G. Scorrano, *Tetrahedron Letters*, 6243 (1990); M. M. Midland and R. W. Kooops, *J. Org. Chem.*, **55**, 5058 (1990); M. Terada, K. Mikami and T. Nakai, *Tetrahedron Letters*, 935 (1991); K. F. McClure, J. W. Benbow and S. J. Danishefsky, *J. Am. Chem. Soc.*, **113**, 8185 (1991); A. Bahsas, *J. Org. Chem.*, **52**, 5746 (1987); P. A. Grieco, S. D. Larsen and W. F. Fobare, *Tetrahedron Letters*, 1975 (1986); H. Waldmann, *Angew. Chem., Int. Ed. Engl.*, **27**, 274 (1988); H. Waldmann, *Liebigs Ann. Chem.*, 231 (1989); L. Stella, H. Abraham, J. Feneau-Dupont, B. Tinant and J. P. DeClerq, *Tetrahedron Letters*, 2603 (1990).
- [9] H. Kotsuki, S. Kitagawa, H. Nishizawa and T. Tokoroyama, *J. Org. Chem.*, **43**, 1471 (1978); H. Kotsuki, H. Nishizawa, S. Kitagawa, M. Ochi, N. Yamasaki, K. Matsuoka and T. Tokoroyama, *Bull. Chem. Soc. Japan*, **52**, 544 (1979).
- [10] For review see: J. Sauer and R. Sustmann, *Angew. Chem., Int. Ed. Engl.*, **19**, 779 (1980); W. Carruthers, *Cycloaddition Reactions in Organic Synthesis* Pergamon Press, New York, 1990.
- [11] For recent review see: K. N. Houk, Y. Li and J. D. Evansek, *Angew. Chem., Int. Ed. Engl.*, **31**, 682 (1992) and references therein.
- [12] M. J. J. Dewar, S. Olivella and J. J. P. Stewart, *J. Am. Chem. Soc.*, **108**, 5771 (1986); M. J. S. Dewar, *Acc. Chem. Res.*, **25**, 537 (1992) and references therein.
- [13] K. N. Houk and Y. Li, *J. Am. Chem. Soc.*, **115**, 7478 (1993).
- [14] B. S. Jursic and Z. Zdravkovski, *J. Chem. Soc., Perkin Trans 2*, 1877 (1994); B. S. Jursic and Z. Zdravkovski, *J. Org. Chem.*, **59**, 7734 (1994); B. S. Jursic and Z. Zdravkovski, *J. Phys. Org. Chem.*, in press; B. S. Jursic and Z. Zdravkovski, *J. Mol. Struct. (THEOCHEM)*, in press; B. S. Jursic and Z. Zdravkovski, *J. Heterocyclic Chem.*, **31**, 1429 (1994); B. S. Jursic and D. Coupe, *J. Heterocyclic Chem.*, in press; J. Gonzalez, E. C. Taylor and K. N. Houk, *J. Org. Chem.*, **57**, 3753 (1992).
- [15] O. Kikuchi, *Tetrahedron*, **27**, 2791 (1971); M. V. Basilevsky, V. A. Tikhanov and I. E. Chenlov, *Theor. Chim. Acta*, **23**, 75 (1971); J. W. McIver, Jr., *Acc. Chem. Res.*, **7**, 72 (1974); M. V. Basilevsky, A. G. Shamov and V. A. Tikhanov, *J. Am. Chem. Soc.*, **99**, 1369 (1977); M. J. S. Dewar, S. Olivella and H. S. Rzepa, *J. Am. Chem. Soc.*, **100**, 5650 (1978) and reference therein; M. J. S. Dewar, S. Olivella and J. J. P. Stewart, *J. Am. Chem. Soc.*, 5771 (1986); J. Pancir, *J. Am. Chem. Soc.*, **104**, 7424 (1982); K. N. Houk, Y.-T. Lin and F. K. Brown, *J. Am. Chem. Soc.*, **108**, 554 (1986); F. K. Brown and K. N. Houk, *Tetrahedron Letters*, **25**, 4609 (1984); K. N. Houk, R. J. Loncharich, J. F. Blake and W. L. Jorgensen, *J. Am. Chem. Soc.*, **111**, 9172 (1989); W. L. Jorgensen, D. Lim and J. F. Blake, *J. Am. Chem. Soc.*, **115**, 2936 (1993).
- [16] All calculations were carried out with MOPAC version 6.0. Quantum Chemistry Program Exchange (QCPE), Program Number 455 (1990).
- [17] The transition state has to have only one imaginary frequency and that has become the major criteria for proving the transition state. For example see: W. J. Hehre, L. D. Burke, A. J. Shusterman and W. J. Pietro, *Experiments in Computational Organic Chemistry*,

Wavefunction, Irvine, California, 1993; J. B. Fresman and Æ. Frisch, *Exploring Chemistry with Electronic Structure Methods*, Gaussian, Pittsburgh, PA, 1993.

[18] B. S. Jursic and Z. Zdravkovski, *J. Mol. Struct. (Theochem)*, **303**, 177 (1994). For more detail on location of the transition states with the MOPAC semiempirical methods in the Cope rearrangement see: M. J. S. Dewar, E. F. Healy and J. J. P. Stewart, *J. Chem. Soc., Faraday Trans. II*, **3**, 227 (1984).

[19] M. J. S. Dewar and Y.-C. Lin, *Inorg. Chem.*, **27**, 3881 (1990).

[20] B. S. Jursic and Z. Zdravkovski, *J. Mol. Struct. (THEOCHEM)*, **309**, 249 (1994).

[21] B. S. Jursic and Z. Zdravkovski, *J. Mol. Struct. (THEOCHEM)*, **309**, 241 (1994) and references therein.

[22] K. Fukui and H. Fujimoto, *Bull. Chem. Soc. Japan*, **40**, 2018 (1967); K. Fukui and H. Fujimoto, *Bull. Chem. Soc. Japan*, **42**, 2018 (1969); K. Fukui, *Angew. Chem., Int. Ed. Engl.*, **21**, 801 (1982).

[23] For the perspective of the transition state theory see: W. J. Albery, *Transition-State Theory Revisited in Adv. Phys. Org. Chem.*, **28**, 139 (1993); R. A. Marcus, *Skiing the Reaction Rate Slopes in Science*, **256**, 1523 (1992), I. W. M. Smith, *Probing the Transition State in Nature*, **358**, 279 (1992).

[24] M. A. McCorrick, Y.-D. Wu and K. N. Houk, *J. Org. Chem.*,

58, 3330 (1993); J. Gonzalez and K. N. Houk, *J. Org. Chem.*, **57**, 3031 (1992); M. A. McCorrick, Y.-D. Wu and K. N. Houk, *J. Am. Chem. Soc.*, **114**, 1499 (1992).

[25] B. S. Jursic and Z. Zdravkovski, *J. Org. Chem.*, **59**, 3015 (1994).

[26] G. S. Hammond, *J. Am. Chem. Soc.*, **77**, 334 (1955); W. J. Le Noble, A. R. Miller and S. D. Hamann, *J. Org. Chem.*, **42**, 338 (1977); A. R. Miller, *J. Am. Chem. Soc.*, **100**, 1984 (1978).

[27] S. D. Turk, R. L. Cobb, in *1,4-cycloaddition Reactions*, J. Hamer, ed, Academic Press, New York, 1967, p 320; M. S. Raasch, *J. Org. Chem.*, **45**, 856 (1980); K. Kanematsu, K. Harano and H. Dantsuji, *Heterocycles*, **16**, 1145 (1981); M. S. Raasch, *J. Org. Chem.*, **45**, 867 (1980).

[28] R. Walsh and J. M. Wells, *J. Chem. Soc., Perkin Trans. 2*, 52 (1976).

[29] D. N. Reinhoudt, P. Smael, W. J. M. van Tiborg and J. P. Visser, *Tetrahedron Letters*, 3755 (1973).

[30] M. S. Raasch, *J. Org. Chem.*, **45**, 867 (1980).

[31] M. S. Raasch, *J. Org. Chem.*, **45**, 856 (1980); K. Kanematsu, K. Harano and H. Dantsuji, *Heterocycles*, **16**, 1145 (1981).

[32] K. Torrsel, *Acta Chem. Scand., Ser. B*, **30**, 353 (1976).

[33] B. Iddon and R. M. Scrowston, *Adv. Heterocyclic Chem.*, **11**, 177 (1970); P. Grieco, *Synthesis*, 67 (1975).