AM1 Semiempirical Searching for Suitable Thiophene Derivatives that Will Enable Thiophenes to Act as a Diene in the Diels-Alder Reactions

Branko S. Jursic* and Don Coupe

Department of Chemistry, University of New Orleans, New Orleans, Louisiana 70148

Received September 6, 1994

The AM1 semiempirical method was used for theoretical searching of activation of thiophene as a diene for the Diels-Alder reaction. The reactivity of thiophene, electron-withdrawing and electron-donating substituted thiophenes, as well as the *S*-methylthiophenium ion were studied as the diene for Diels-Alder reactions by evaluating their frontier orbital energies and by calculating reaction barriers with activated and deactivated dienophiles. It was demonstrated that slight activation of the thiophene ring can be obtained with both electron-donating and electron-withdrawing groups attached to the thiophene ring. It was predicted that the actual transformation of thiophenes into the corresponding *S*-methylthiophenium anions is the best means of activating the thiophenes. The calculated activation energies for normal (non-activated) dienophiles are moderate so mild reaction conditions are predicted. If dienophiles are activated with electron-donating substituents, AM1 calculations predict a two step cycloaddition reaction with a very small activation barrier.

J. Heterocyclic Chem., **32**, 483 (1995).

Introduction.

The search for versatile starting materials for the preparation of a wide variety of precious compounds is one of the major goals of organic synthesis [1]. Aromatic heterocyclic compounds can be synthons and can accomplish some synthetic transformations [2], but these reactions are under investigated because of their low reactivity due to the aromatic character of heterocycles [3]. Cycloaddition reactions between dienophiles and aromatic heterocyclic compounds is one of a few very promising methods to transform readily available materials into organic synthons [4]. Thiophene derivatives as the diene in hetero Diels-Alder reactions are desirable starting materials because sulfur extrusion from the cycloadduct is straightforward [5].

The thermal [4+2] cycloaddition reaction with thiophene as a diene is an allowed process. Nevertheless, the Diels-Alder reaction with thiophene as the diene is not very common. In fact, only a few examples of the reactions are known for the last two decades. In comparison with furan, lowered thiophene reactivity is unexpected. This discrepancy was in many cases explained by the role of *3d* orbitals in the cycloaddition reaction [6]. On the basis of perturbation theory it has been shown that *3d* orbitals stabilize the reactants but not the product of the reaction.

The first successful Diels-Alder addition of thiophene was a reaction with tetrafluorobenzyne to produce tetrafluoronaphthalene [7]. This discovery was followed with a couple of other benzyne derivatives as the dienophile in the Diels-Alder reaction with thiophene [8]. It has been shown that thiophene might react with less reactive dienophiles if the heterocycle is properly activated. Thus it has been shown that 2,5-dimethoxythiophene reacts with maleic anhydride followed by the usual sulfur extrusion leading to a diene that undergoes further cycloaddition reaction with maleic anhydride [9]. The Diels-Alder cycloadduct between unactivated thiophene and maleic anhydride can be obtained by applying very high pressure [10]. That is possible because the activation volume $\Delta V^{\ddagger}$ is negative, *i.e.* the volume of the transition state is smaller than the volume of the reactants, so the rate of the reaction will increase with increasing pressure. One of the characteristics of all cycloaddition reactions with thiophene mentioned above is the ratio of *exo* and *endo* adducts. The percentage of the *exo* isomer exceeds the amount usually found in classical Diels-Alder additions.

From the results of known Diels-Alder reactions with thiophene as the diene three strategies to promote a reaction can be suggested: use highly reactive dienophiles; increase the reactivity of the thiophene by choosing proper substituents, or carry out the reaction at very high pressure. To closely examine the reactivity of thiophene as a diene in the Diels-Alder reactions, and determine a new more efficacious path by forcing the thiophenes in the cycloaddition reaction, we have performed an AM1 semiempirical study. The results and a suggestion for performing the synthetic transformation of thiophene into Diels-Alder adducts are presented here.

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 [11]. The search for the transition states and their verification [12] was performed as described previously [13]. Vibrational and thermal analyses were performed on all optimized structures.

Results and Discussion.

For performing the study of the reactivity of thiophene in Diels-Alder reactions we have chosen the AM1 semi-

empirical method [14]. Although activation energies for Diels-Alder reactions with cyclobutadiene were not predicted correctly [15], this method was proven to be useful in the case of polar cycloaddition reactions [16]. Theoretical examination of thiophene derivatives as source of a diene in the Diels-Alder reaction will be examined first. As thiophene is an aromatic compound, it is reasonable to expect that it will be less reactive than its all-carbon analog, cyclopentadiene. In fact, the calculated heat of formation difference in hydrogenation of cyclobutadiene and thiophene is 21.9 kcal/mol due to resonance stabilization. That can be one of the contributing factors for low reactivity of thiophene as a diene in cycloaddition reactions. To determine the qualitative reactivity of the reactants in cycloaddition reactions, chemists have been using the Frontier orbital theory [17]. According to the frontier orbital theory the most reactive couple in the Diels-Alder reaction is one that has the smallest gap in HOMO energies of one reactant with LUMO energy of the other reactant. The addition of ethylene to cyclopentadiene has a frontier orbitals energy gap of 10.52 and 11.03 eV if LUMO and HOMO ethylene orbitals are involved in the cycloaddition reaction respectively. The same energy gap for ethylene addition to thiophene is 10.65 and 10.79 eV (Table 1). It is very interesting to point out that the energy frontier orbital gap that includes either HOMO or LUMO of thiophene is very narrow (energy difference only 0.14 eV), though slightly greater than one for ethylene addition to cyclopentadiene (10.54 eV). This observation inevitably predicts even lower reactivity of thiophene in cycloaddition reactions, but suggests that by properly choosing both electron-withdrawing and electron donating substituents, the frontier orbital energy gap the thiophenes and a dienophile will decrease considerably and the reactivity of the thiophenes will be increased. Thus by putting two methoxy groups on the thiophene ring the HOMO energy increased for 0.7 eV making the frontier orbital energy gap smaller. That relative narrowing of the frontier orbital gap will not significantly increase the probability of the reaction. One possibility is using electron deficient dienophiles. Three of them, 1,1-dicyanoethane, maleic anhydride, and tetracyanoethane are presented in Table 1. Their LUMO energy decreases in the same order making the frontier orbital gap of HOMO thiophene and LUMO of the dienophile to be 7.64, 6.70, and 6.00 eV, respectively. That suggests that the addition of these dienophiles to 3,4-dimethoxy- and 2,5-dimethoxythiophene should be experimentally achievable. This finding is in full agreement with the experimental evidence that cycloaddition of maleic anhydride to 2,5-dimethoxythiophene is feasible [9].

Table 1

LUMO and HOMO Energies (eV) of the Reactants Calculated by AM1 Semiempirical Methods

Compound	HOMO	LUMO
cyclopentadiene	-9.07914	0.48161
thiophene	-9.21756	0.23845
3,4-dimethoxythiophene	-8.31038	0.18188
2,5-dimethoxythiophene	-8.51587	0.20750
3,4-dicyanothiophene	-10.04298	-0.96027
2,5-dicyanothiophene	-10.22378	-1.44824
tetracyanothiophene	-10.78000	-2.31164
S-methylthiophene	-15.28210	-6.14392
ethylene	-10.55142	1.43778
diether **1**	-9.11463	1.48256
tetraether **2**	-8.35509	1.00126
disulphide **3**	-8.32267	0.28278
tetrasulfide **4**	-7.45510	-0.16779
1,1-dicyanoethane	-11.16684	-0.87843
maleic anhydride	-12.02287	-1.61890
tetracyanoethane	-11.52085	-2.52333

Another approach to activate the thiophene for cycloaddition reactions is by adding electron-withdrawing substituents to the thiophene ring. Thus, our calculations show that LUMO energy of cyano-substituted thiophenes is substantially decreased making the energy gap between LUMO energies and HOMO energy of ethylene 10.76, 9.59, and 8.24 eV for 2,5-dicyano-, 3,4-dicyano-, and tetracyanothiophene, respectively (Table 1). That certainly makes them more reactive than the original thiophene but impractical because the cyano groups have to be removed after completion of the reaction. Thus, a more general approach to activate thiophene derivatives is desirable. The transformation of thiophene into the corresponding thiophenium salts should be a straightforward process. The obtained *S*-methylthiophenium ion will be more reactive because of the expected lowering of the LUMO energy. In fact, the energy gap between HOMO of ethylene and LUMO of the *S*-methylthiophenium ion is now only 4.41 eV and should make this reaction experimentally feasible.

Enhanced reactivity of the cycloaddition reaction with thiophene can be obtained if the reaction of the *S*-methylthiophenium ion is performed with an "activated" dienophile, a dienophile with considerable electron-donating ability. Thus by using ethers or sulfides the energy frontier orbital gap is considerably decreased (Table 2). The most reactive partners with the *S*-methylthiophenium ion are predicted to be dienophiles **3** and **4**.

Table 2

The Frontier Orbital Energy Gap (eV) Between LUMO of the *S*-Methylthiophenium Ion and HOMO of Dienophiles **1-4**

Dienophile	HOMO	ΔE
ethylene	-10.55142	4.41
diether **1**	-9.11463	3.00
tetraether **2**	-8.35509	2.21
disulphide **3**	-8.32267	2.18
tetrasulfide **4**	-7.45510	1.31

One of the major disadvantages of frontier molecular orbital theory is that the frontier orbital energies are calculated for separated reactants. In this way sterical and electronic interactions between the reactants that might occur in the course of the reaction are not incorporated. Thus correlation of frontier orbital energies for systems where these interactions are present will yield misleading results. For a more advanced approach to this problem we have optimized corresponding transition states and calculated their activation barriers.

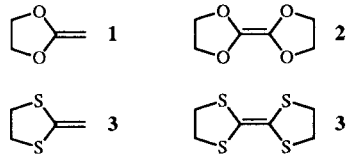


Figure 1. HOMO activated dienophiles for Diels-Alder reaction with *S*-methylthiophene.

Ethylene Addition to Thiophene.

The simplest of all Diels-Alder reactions with thiophene as the diene is the reaction with ethylene. The reaction cannot be performed experimentally and the results obtained will be used as a standard for determining reactivity in our theoretical search for thiophene activation. The AM1 generated transition structure is presented in Figure 2. The transition structure resembles in many ways the transition structure for the ethylene addition to cyclopentadiene [18]. The structure is for a concerted synchronous cycloaddition reaction. The calculated activation energy is 43.91 kcal/mol and 44.37 kcal/mol with a zero point vibrational energy (ZPVE) correction. The predicted energy is quite different from the one calculated for the ethylene addition to cyclopentadiene (28.0 kcal/mol) [15]. Of course, this inreactivity of thiophene can be explained by its high aromatic character, the highest of all five membered heterocycles that contain a single heteroatom. As mentioned above, we have predicted that the energy differences between cyclopentadiene and thiophene due to thiophene aromaticity is 21.9 kcal and, in large part, can be responsible for the high activation barrier. There is at least one more factor that can have considerable effect on the activation barrier of the reaction, that is, repulsion interactions between the lone pair orbitals located on sulfur and p-orbitals of the ethylene double bond. Similar interactions have been used by Houk and coworkers [19] and by us [20] for explaining the low reactivity in heterodienophile addition to dienes.

Diels-Alder Reactions with Thiophenes Activated with Electron-donating Groups.

Here we would like to demonstrate the effect of an electron-donating group on the thiophene reactivity for the example of the Diels-Alder reaction with 2,5-dimethyl- and 3,4-dimethylthiophene. Transition structures of ethylene addition to 3,4- and 2,5-dimethoxythiophene, and maleic anhydride addition to 2,5-dimethoxythiophene are presented in Figure 3. All generated transition structures are for the concerted reaction with the simultaneous formation of two C-C bonds. Although all reactants that are incorporated into transition structures **6-**

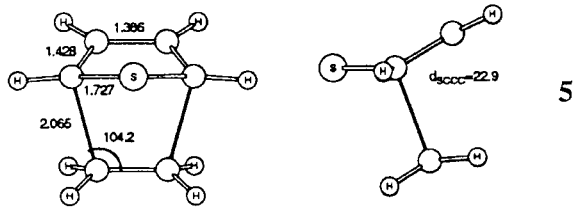


Figure 2. AM1 generated transition structure of the ethylene addition to thiophene.

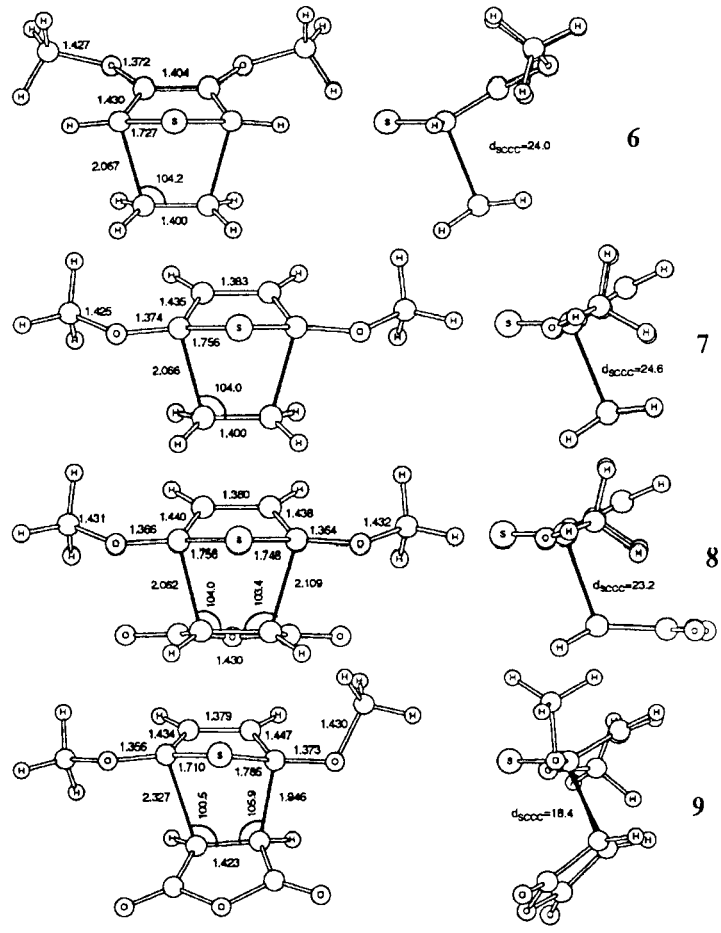


Figure 3. The transition state structures with donor activated thiophenes generated with AM1.

9 have a plane of symmetry, the transition structure **9** represents an asynchronous cycloaddition. The degree of asynchronicity is 0.381 Å. As predicted on the basis of the frontier orbital energy gap, the activation barrier for ethylene addition to both 3,4- and 2,5-dimethoxythiophene is quite similar to one obtained for the ethylene addition to thiophene (44.37 kcal/mol). Although frontier orbital favors transition structure **7** over **8** by 0.2 eV, the predicted activation energy for transition structure **8** is lower due to methoxy stabilization of a positive charge formed on C-2 and C-5 in the course of the reaction. The calculations prefer the *endo* isomer **8** over the *exo* isomer **9** which is in accordance with both experimental [9] evidence and the Alder rule. The cycloaddition reaction between maleic anhydride and 2,5-dimethoxythiophene is experimentally feasible, thus, the activation barrier predicted by AM1 must be overestimated.

Table 3

Activation Energies (kcal/mol) of Ethylene and Maleic Anhydride to Donor Activated Thiophene

Transition Structure	ΔE	ΔE+ZPVE [a]
6	44.14	44.15
7	42.28	42.37
8	36.80	35.63
9	42.61	41.46

[a] ZPVE-zero point vibrational energy.

Diels-Alder Reactions with Thiophenes Activated with Electron-withdrawing Groups.

The second approach to activate the thiophene ring as a diene in the Diels-Alder reaction is by attaching electron-withdrawing groups to the thiophene ring. We have studied cyano-substituted thiophene in the reaction with ethylene to determine the influence of electron-withdrawing substituents on the reactivity. All transition structures studied of the ethylene addition to cyanothiophenes are symmetrical, and the structures are for synchronous, concerted mechanisms. The bond distance for two bonds in the formations increases slightly from transition structure **10** to transition structure **12** indicating that structure **12** is more reactant-like and might have the lowest reaction barrier of all three transition states. That is also in agreement with the frontier orbital theory prediction discussed earlier. The order of calculated activation barriers for ethylene addition does not follow the predicted reactivity (Table 4). The most reactive cyanothiophene is 2,4-dicyanothiophene, and the activation barrier is just slightly lower than for ethylene addition to thiophene. Thus AM1 predicts that thiophenes with electron-withdrawing substituents might not be a suitable diene for Diels-Alder reactions. Our calculation for the frontier orbital energy gap suggests that *S*-methylthiophenium ions can serve this purpose much better.

Table 4

Activation Energies (kcal/mol) of Ethylene Addition to Cyanothiophenes

Transition Structure	ΔE	ΔE+ZPVE [a]
10	43.27	43.59
11	46.44	46.56
12	45.90	49.12

[a] ZPVE-zero point vibrational energy.

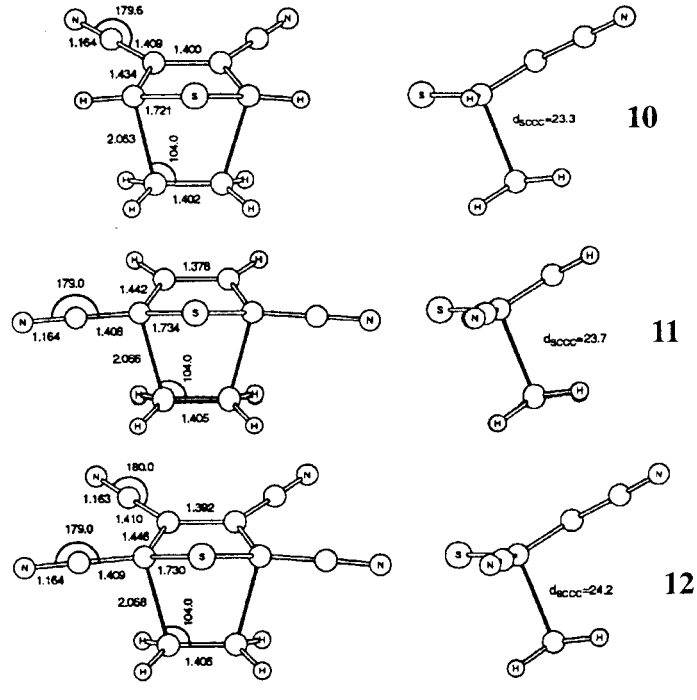


Figure 4. Geometric transition states of ethylene cyanothiophene generated by AM1.

Diels-Alder Reactions with *S*-Methylthiophenium Ion.

The possibility of preparing *S*-alkylthiophenium salts, and the question of whether or not such compounds would be aromatic, has been intriguing chemists for some time. The salt can be prepared only if very strong alkylating agents are used like the methyl ester of fluorosulfonic acid [21]. Although the salt of thiophene was not prepared by this method, 2,3,4,5-tetramethylthiophene gave the salt in more than 95% yield. It was also stated that thiophenium salts do not seem to undergo Diels-Alder addition [21]. One of the reasons that the experiment must be performed under absolutely anhydrous conditions is because *S*-alkylthiophenium salts undergo facile solvolysis [22] and consequently they are very good alkylation agents. Presented below is our theoretical study of the *S*-methyl-

thiophenium ion as the diene in the Diels-Alder reactions. The geometries of the transition structures of the ethylene addition to *S*-methylthiophenium ion are presented in Figure 5. There are two isomeric transition structures for the ethylene addition. One with the methyl group down, **13**, and another with the methyl group up, **14**. Both generated transition structures have a full plane of symmetry bisecting the structures in the way of two C-C bond formation. The bonds in formation slightly differ for two transition structures; that can be explained by steric repulsion between the methyl and ethylene moieties in transition structure **13**. This effect can be used to explain the greater value for d_{SCCC} dihedral angle in **13**.

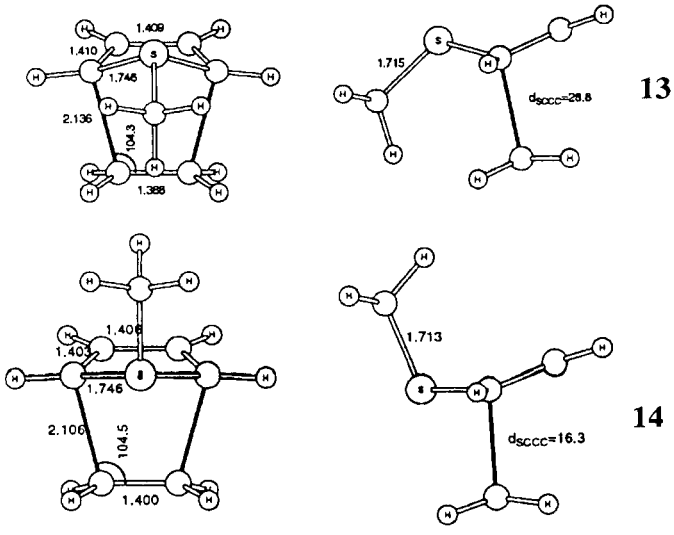


Figure 5. Transition structures for synchronous ethylene addition to the *S*-methylthiophenium ion.

On the basis of the frontier orbital energies for the reactants, the reactivity of the *S*-methylthiophenium ion as the dienophile in the Diels-Alder reaction is predicted to be considerably higher than thiophene due to lower LUMO *S*-methylthiophenium ion energy. Furthermore on the basis of steric interactions between the methyl group and the ethylene moiety of transition structure **13**, it is reasonable to expect that the transition structure **14** will have a lower reactivity barrier. Thus one can predict that the reactivity order will be **5**, **13**, and **14**. AM1 calculated activation barriers are 43.91 (44.37), 21.11 (22.55), and 15.55 (16.66) kcal/mol respectively. This demonstrates the extraordinary reactivity of the *S*-methylthiophenium ion as a diene in Diels-Alder reactions.

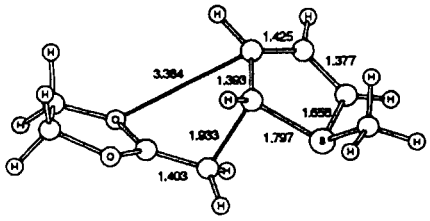
Spectroscopy (^{1}H nmr) was used to study some *S*-ethylthiophenium salts. It has been concluded [22] that the sulfur in these salts is sp^3 hybridized, and that the alkyl (methyl) group is not coplanar with the thiophene ring. This results in reduced aromaticity (less effective overlap of the lone pair on sulfur with the ring p-electrons); however, the effect of *d*-orbital participation seems to be unimportant. This finding is in full agreement with our calculations that predict a very low activation barrier (15.55 kcal/mol) for ethylene addition to the *S*-methylthiophenium ion. Furthermore ^{13}C nmr spectroscopy has been used for location of the position of the positive charge on the thiophenium carbon atoms [21]. It was determined that going from thiophene to the *S*-methylthiophenium ion, the chemical shift of carbon atoms 3 and 4 moved downfield by 16 ppm, whereas the change in carbons 2 and 5 was only 1.4 ppm. This finding is in agreement with the electrostatic picture of a positive charge located on carbons 3 and 4 of the *S*-methylthiophenium ion. If the charge can be stabilized in the Diels-Alder transition structure the reaction barrier might be reduced. To take advantage of charge location on the ring we have performed calculations of the transition state with dienophiles **1-4**. These dienophiles can stabilize the positive charge of the *S*-methylthiophenium moiety by oxygen or sulfur participation. We have shown by the example of ethylene addition to the *S*-methylthiophenium ion that the transition state with the methyl group up (transition structure **14**) has a substantially lower activation barrier, so hereafter only the transition structures with the methyl group up will be considered. The transition structures are presented in Figure 6. It was predicted on the basis of the frontier orbital energy gap that addition of dienophiles **1-4** should be those most preferable to study. Now, because there is an extraordinary possibility to stabilize the positive charge by the dienophiles, the concerted mechanism of the cycloaddition reaction is no longer preferred, instead the stepwise mechanism has considerably lower activation energies. Of the two steps, the first one is rate determining, so we are presenting only the transition structures for the first step. In transition structure **15** the additional stabilization of the charge located on C-3 of the thiophenium ring is minimal, based on the distance of the C-O bond, 3.384 Å. It is expected that additional stabilization of the transition structure is negligible. That effect is somewhat more pronounced in transition structure **16** where now the C-O bond distance is 3.043 Å. This addition should have an activation barrier that is lower than for **15** also because its HOMO energy is higher (Table 1) and the frontier orbital energy gap between the reactants is lower (Table 2). The stabilization of positive charge in the transition structure with a dienophile seems to be evident in transition structure **17**. The C-S bond distance is only 1.855 Å and is slightly longer than normal C-S bond. In transition structure **18** this effect is reinforced with an additional stabilization of the positive charge on the thiophenium sulfur with the

Table 5

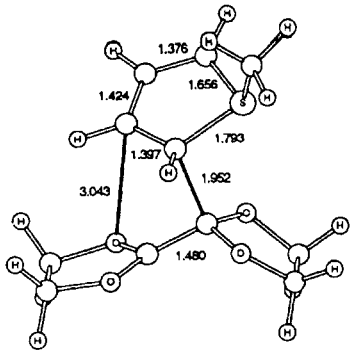
Activation Energies (kcal/mol) of Dienophile **1-4** Addition to *S*-Methylthiophenium Ion Calculated by AM1

Transition Structure	ΔE	ΔE+ZPVE [a]
15	1.43	1.98
16	1.50	1.50
17	-7.18	-4.96
18	-3.29	-2.28

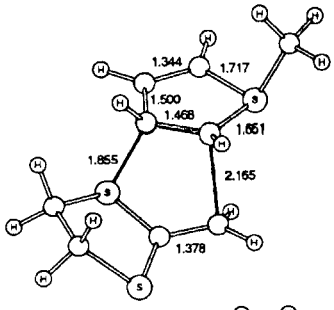
[a] ZPVE-zero point vibrational energy.



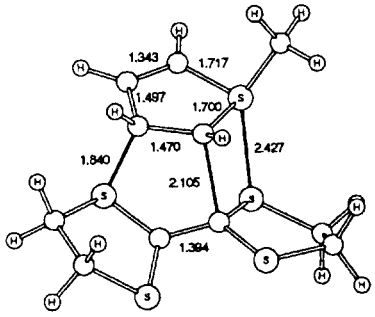
d_{SCCC}=4.5 **15**



d_{SCCC}=3.5 **16**



d_{SCCC}=-1.4 **17**



d_{SCCC}=7.2 **18**

Figure 6. Transition states of dienophiles **1-4** addition to *S*-methylthiophenium ion.

dienophile **4**. On the basis of structural characteristics of transition structures **15-18** one can expect that the reactivity will be **15**, **16**, **17**, and **18**. To confirm this assumption we have calculated the activation barriers (Table 5). All of these reactions were initiated with minimal or without activation barriers. The calculated negative activation barrier was due to the very high energy of the *S*-methylthiophenium ion that was stabilized in the solvent, and might effect a modest increase in the activation barrier. The semiempirical calculation is performed in the gas phase and the solvent interactions with the reagents were excluded. Nevertheless this calculation demonstrated that the cycloaddition reaction between the *S*-methylthiophenium ion and activated dienophiles such as **1-4** will proceed under very mild reaction conditions.

Conclusions.

The calculations presented of the Diels-Alder transition states with thiophene derivatives as dienophiles was performed with the objective to increase thiophene reactivity in cycloaddition reactions. The frontier orbital energy calculations indicate that both electron-donating and electron-withdrawing substituents should increase the thiophene reactivity. The estimated activation energies reveal that these substituents will slightly increase the thiophene activity, as was also demonstrated experimentally. To perform the reaction experimentally, rather stringent reaction conditions are required. That was the result of only a slight change of thiophene aromaticity with the substituents. Dramatic changes in electronic properties were determined by transforming thiophene into the *S*-methylthiophenium ion. That ion does not have high aromaticity, and the activation energy of ethylene addition was predicted to be only 15.55 kcal/mol. The Diels-Alder reaction with activated dienophiles that can stabilize a positive charge on C-3 of the thiophenium ion moiety of the transition structure is predicted to be stepwise with a negligible activation barrier. Thus it is suggested that thiophene transformed into the *S*-methylthiophenium ion is an excellent way to use thiophenes as a diene for Diels-Alder reactions.

REFERENCES AND NOTES

[1] D. Seebach, *Angew. Chem., Int. Ed. Engl.*, **25**, 1320 (1990); B. Helmut, H.-D. Scharf, N. Hoffmann, and F. Esser, *Angew. Chem., Int. Ed. Engl.*, **30**, 477 (1991); E. F. Corey, *Angew. Chem., Int. Ed. Engl.*, **30**, 455 (1991); L. F. Trietze and U. Beifuss, *Angew. Chem., Int. Ed. Engl.*, **32**, 131 (1993).

[2] A. I. Meyers, Heterocycles in Organic Synthesis, E. C. Tayler and A. Weissberger, eds, John Wiley and Sons, New York, NY, 1974; B. H. Lipshutz, *Chem. Rev.*, **86**, 796 (1986); T. Masayoshi and Y. Gosei, *Kagaku Kyokaishi*, **51**, 399 (1993); P. A. Jacobi, K. M. Touchette, and H. G. Selnick, *J. Org. Chem.*, **57**, 6305 (1992).

[3] Comprehensive Heterocyclic Chemistry, Vol **1-8**, A. R. Katritzky and C. W. Rees, eds, Pergamon Press, New York, 1984.

[4] D. L. Boger and S. N. Weinreb, Hetero Diels-Alder Methodology in Organic Synthesis, Academic Press, New York, NY, 1987; R. R. Schmidt, *Acc. Chem. Res.*, **19**, 250 (1986).

[5] For sulfur elimination from organic compounds see: E. Block, The Chemistry of Functional Groups, S. Patai, ed, Supplement E, Part 1, Wiley, New York, 1980, p 585; L. I. Belen'kii and V. N. Belen'kii, Chemistry of Organosulfur Compounds, Ellis Horwood, Chichester, 1990, p 192; G. R. Pettit and E. E. van Tamelen, *Org. React.*, **12**, 356 (1962); H. Hauptmann and W. F. Walter, *Chem. Rev.*, **62**, 347 (1962); J. Schut, J. B. F. N. Engberts and H. Wynberg, *Synth. Commun.*, **2**, 415 (1972); Y. Kikugawa, *J. Chem. Soc., Perkin Trans. 1*, 609 (1984).

[6] P. W. Lert and C. Trindel, *J. Am. Chem. Soc.*, **93**, 6392 (1971).

[7] D. D. Callander, P. L. Coel, and J. C. Tatlow, *J. Chem. Soc., Chem. Commun.*, 143 (1966).

[8] D. D. Callander, P. L. Coel, J. C. Tatlow, and A. J. Uff, *Tetrahedron*, **25**, 25 (1969); P. L. Coel, G. M. Pearl, and J. C. Tatlow, *J. Chem. Soc. (C)*, 604 (1971); D. Del Mazza and M. G. Reinecke, *Heterocycles*, **14**, 647 (1980).

[9] J. M. Barker, P. R. Huddleston, and S. W. Shutler, *J. Chem. Soc., Perkin Trans. 1*, 2483 (1975).

[10] 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).

[11] All calculations were carried out with MOPAC version 6.0. Quantum Chemistry Program Exchange (QCPE), Program Number 455, 1990.

[12] The transition state has to have only one imaginary frequency and that has become the major criteria for proving the transition state. 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).

[13] B. S. Jursic and Z. Zdravkovski, *J. Mol. Struc. (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).

[14] M. J. S. Dewar, *J. Am. Chem. Soc.*, **107**, 3902 (1985); M. J. S. Dewar and E. G. Zoebisch, *J. Mol. Struc. (Theochem)*, **180**, 1 (1988).

[15] B. S. Jursic and Z. Zdravkovski, *J. Mol. Struc. (Theochem)*, **309**, 249 (1984).

[16] B. S. Jursic and Z. Zdravkovski, *J. Mol. Struc. (Theochem)*, **309**, 241 (1994) and references therein.

[17] 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).

[18] K. N. Houk, Y.-T. Lin and J. D. Evansek, *Angew. Chem., Int. Ed. Engl.*, **31**, 682 (1992) and references therein.

[19] 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).

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

[21] R. F. Heldeweg and H. Hogeveen, *Tetrahedron Letters*, **15**, 75 (1974).

[22] R. M. Acheson and D. R. Harrison, *J. Chem. Soc. (C)*, 1764 (1970).