Theoretical Study of Thieno[3,4-d]thiepin and Furo[3,4-d]thiepin as Dienes in The Diels-Alder Reaction

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Theoretical study of thiophene and furan c-fused rings with unsaturated seven membered rings with oxygen or sulfur as dienes for Diels-Alder reactions was conducted with the semiempirical Austin Model 1 (AM1). Four approaches were considered: frontier orbital theory, resonance stability of the dienophiles determined through heat of hydrogenation, progress of the reaction through bond orders, and the estimation of the reaction barriers. It was determined that the most unreactive species with the highest resonance stability are sulfur heterocyclic compounds, while furan derivatives are the most reactive. Using o-quinonoid episulfide as an intermediate was rejected because the estimated activation energy for its formation is too high. The possibility of a three bond formation in the transition state of thieno[3,4-d]thiepin reaction with ethylene was considered and rejected on the basis of AM1 estimated activation energy. The S-methylated derivatives of thieno[3,4-d]thiepin were predicted to react with less reactive dienophiles like ethylene under moderate reaction conditions. If thieno[3,4-d]thiepin is not activated through S-methylation then a reactive dienophile and drastic reaction conditions are predicted to be necessary to force the cycloaddition reaction. The obtained results are in agreement with experimental evidence.

Introduction.

The Diels-Alder reaction has been the subject of extensive research since its discovery [1]. It is one of a few organic reactions that can start with reactants without any chiral center and produce a single product with four chiral centers. Although an extensive number of dienes and dienophiles have been used, there is still a need for readily available starting materials. An excellent source of the dienes for the Diels-Alder reaction can be five membered heterocyclic compounds [2]. Of particular interest, a diene such as thiophene and its derivatives can produce a product which through desulfurization [3] can be transferred into a plethora of cyclic products, not easily accessible by other routes. Although the hetero Diels-Alder reaction has been used extensively in preparation of natural heterocyclic compunds [4] there is little written on employing five membered heterocyclic compounds as dienes in organic chemistry [2,5]. Unfortunately, that is even worse in the case of thiophene and its derivatives, as the least reactive of all aromatic five membered heterocycles [6], which has been explained by the presence of d orbitals that are included in resonance stability of the thiophene system [8]. This assumption has stimulated many computational studies of aromaticity of thiophene [9]. The *ab initio* calculations on thiophene clearly indicate that d-orbital participation is not significant in the ground state [10]. Nevertheless, the fact remains that thermochemical determined resonance energy is as high as 117 kJ/mol for thiophene [11].

Experimentally, the reactivity of the thiophene derivatives as the diene for the Diels-Alder reaction can be increased by applying one of three general approaches [7]: a highly reactive dienophile should be used, the electron donating or electron withdrawing substituent should be put on the thiophene ring, and the reaction should be carried out under high pressure because intermolecular Diels-Alder reactions have negative activation volume [12].

Theoretical studies of Diels Alder reactions were carried out extensively [13]. There are also theoretical studies for hetero Diels-Alder reactions though considerably fewer in number [14], but there are only a few on Diels-Alder reactions with heterocycles as a source of dienes [15]. These reactions are generally assumed to be concerted [4+2] cycloadditions. A stepwise radical mechanism has been proposed [16], but has been rejected by high level *ab initio* calculations [17].

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 [18]. The search for the transition states and subsequent verification was performed as described previously [19]. Vibrational and thermal analyses were performed on all optimized structures. We are aware that MOPAC methods do not have d-orbitals, but the anticipated errors are expected to be in the same direction of the discussed physical effect. The computed trends are expected to be qualitatively correct but probably too large. That was also indicated for HF calculated energies of the Diels-Alder reaction of phosphole with ethyne by Bachrach [20]. Bond orders are calculated using a method that extends Mulliken population analysis. We are aware that these methods can produce unreliable numbers. Again, the bond order values will be compared between similar systems. Anticipated errors are expected to be in the same direction.
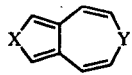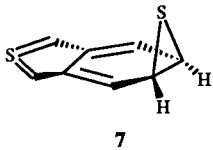
Results and Discussion.

Recently we have been involved in the theoretical and experimental [21] study of the suitability of thiophene and its derivatives as dienes for Diels-Alder reactions. We also determined that thiophene is not particularly suitable for the Diels-Alder reaction if not activated. The activation can be obtained by methylation of thiophene into the S-methylthiophenium ion [22], or by oxidation in thiophene 1-oxide or thiophene 1,1-dioxide [23]. Another approach that uses benzo[c]thiophene and its derivatives as the diene is possible because the corresponding transition state exhibits strong aromatic character [24]. It was reported by Schlessinger [25] and Ponticello that thieno-[3,4-d]thiepin and consequently its derivatives are reliable sources for preparation of benzo[c]thiophene Diels-Alder adducts. There is only one report on their reaction with highly reactive dienophiles like N-phenylmaleimide. To the best of our knowledge there are no reports of Diels-Alder reactions with unactivated dienophiles like non substituted alkenes. To closely examine this reaction we have run calculations using AM1. Although more reliable results can be obtained by *ab initio* calculations, these molecules are too big to be calculated with basic sets that will offer satisfactory results. The results of the cyanoethylene addition to butadiene and cyclopentadiene reveal that no accurate prediction of reactivity can be obtained on this system [26]. In contrast to this study, the AM1 method has proven to give reliable results when the Diels-Alder reaction is considered with thiophene as the diene. The absolute values of the energies are not necessarily correct but the general trend of the relative reactivity determined experimentally was obtained [21-24]. Because of these reasons we have chosen AM1 to study the reactivity of thieno[3,4-d]thiepin and related compounds as dienes for several Diels-Alder reactions.

For a qualitative correlation of reactivity of thieno-[3,4-d]thiepin and related compounds in reaction with ethylene and N-phenylmaleimide, the frontier orbital energy gap between reactants will be used. Frontier molecular orbital (FMO) [27] approach is based on a very simple model that has been shown to provide qualitative information for cycloaddition reactions [28]. The FMO approach is based primarily on maximum overlap between frontier orbitals of the reactants. The energies for frontier orbitals of thieno[3,4-d]thiepin and the related compounds as the diene and ethylene and N-phenylmaleimide as dienophiles with their energy gaps are presented in Table 1. The FMO energy gap strongly prefers thieno[3,4-d]thiepin as the most reactive diene studied here. According to the FMO energy gap the addition to thiophene 1 is even more preferred than addition to o-quinonoid episulfide 7 [29], which might be the intermediate of the reaction. The reaction seems to be HOMO diene and LUMO dienophile

controlled. The frontier orbital approach has one big disadvantage, it considers reactants separately. The FMO prediction should be totally wrong because furan derivatives, that are known to be more reactive than corresponding thiophene [30], are predicted here to be less reactive.

High aromaticity is the major reason why thiophene and the majority of its derivatives are not suitable as the diene for Diels-Alder reactions, thus making the difference in energy between the transition structure and the reactants too high. We will compare the stability of thieno[3,4-d]thiepin (1) with its carbon 2 and oxygen 3 analogs, as well as furan analogs 4-6 and the proposed intermediate 7 [25] for this reaction. In this way we can estimate the influence of sulfur on the stability of the thieno[3,4-d]thiepin system.

Table 1

Reactant	HOMO	LUMO	I	II	III	IV
ethylene	-10.55142	1.43778				
A	-9.14243	-1.24587				
1	-7.48116	-0.17940	10.37	8.92	9.32	6.23
2	-8.47256	-0.06042	10.49	9.91	9.20	7.22
3	-7.95733	0.00717	10.56	9.40	9.15	6.72
4	-7.70314	-0.23080	10.78	9.14	8.91	6.45
5	-8.80385	0.26537	10.82	10.24	9.41	7.55
6	-8.36004	-0.01130	10.56	9.80	9.13	8.11
7	-7.59875	-1.43533	9.11	9.04	7.70	6.35

A = N-phenylmaleimide; I-$LUMO_{diene}$-$HOMO_{ethylene}$, II-$LUMO_{ethylene}$-$HOMO_{diene}$, III-$LUMO_{diene}$-$HOMO_{N-phenylmaleimide}$, IV-$LUMO_{N-phenylmaleimide}$-$HOMO_{diene}$.

Aromaticity and resonance play a very important role in explaining many organic reactions and were accepted by both theoretical and experimental organic chemists very early on [31]. Qualitatively, there was no disagreement in the concept of aromaticity and it is generally considered that aromatic compounds are those that undergo substitution easier than addition reaction with an electrophile. There arose considerable difficulties when obtaining a value for aromatic stability because the definitions are vague and not easily applied in borderline cases [32]. It is broadly Table 1. Frontier orbital energies (eV) of the reactants and their FMO energy gaps accepted that aromaticity can be defined as the ability to sustain an induced ring current (diatropic components) [33]. This definition also has its flaws [34]. Here we will apply molecular orbital

theory and estimate the heat of hydrogenation for compounds **1-7**; although the most successful method compares calculated energies for the aromatic compound and its linear conjugated polyenes containing the same number of double bonds [35]. This approach will not be useful for our system because different results will be obtained for polyenes with sulfur in various positions in the chain. The AM1 estimated heat of hydrogenation is presented in Table 2. The heats of hydrogenation clearly demonstrate that heterocycle **1** has the highest degree of resonance stabilization, and consequently will be the most reluctant to withstand the Diels-Alder reaction. On the other hand, the heats of hydrogenation selects intermediate **7** as the most likely to accompany cycloaddition reaction. If this intermediate is present in the reaction mixture, the thieno-[3,4-d]thiepin (**1**) might be a suitable diene for Diels-Alder reaction. Furthermore, it supports the long standing knowledge that thiophene [36] is the most aromatic of all

of positive charge has to be located on the seven membered ring of **2** and **5** [37]. AM1 charge separation between five and seven membered rings are 0.0202 and 0.0769 electrons, respectively, supporting the positive

Table 2

Heats of Hydrogenation (kcal/mol) of Benzothiophenes and their Difference in Resonance Stability

Compound	ΔE	ΔE+ZPVE [a]	$\Delta\Delta E$	$\Delta\Delta E$+ZPVE [a]
1	-61.40	-28.64	0.00	0.00
2	-70.07	-36.81	-8.67	-8.17
3	-75.52	-42.04	-14.12	-13.40
4	-79.86	-46.43	-18.46	-17.79
5	-87.72	-53.71	-26.32	-25.07
6	-91.88	-57.69	-30.48	-29.05
7 [a]	-104.85	-72.78	-43.45	-44.14

[a] ZPVE-zero point vibrational energy. [b] The energy was calculated in comparison with the product of hydrogenation of **1**.
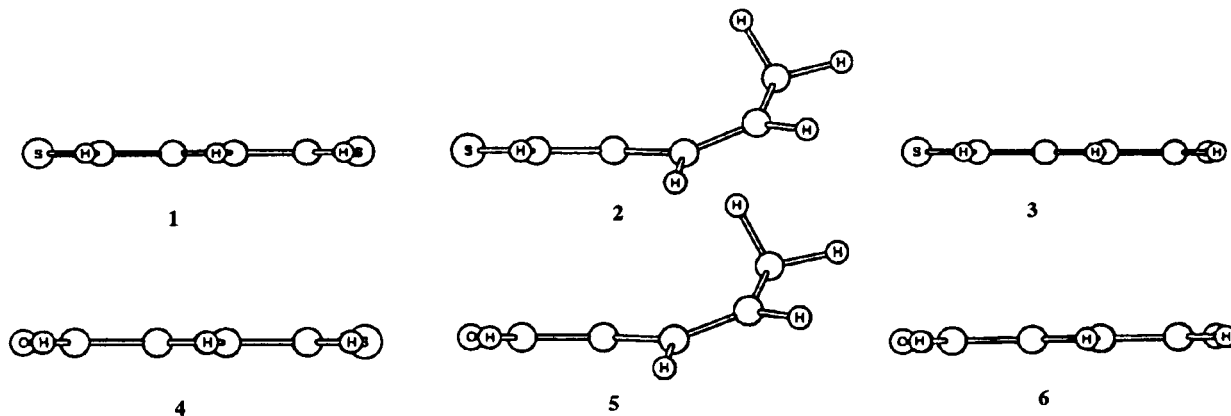

Figure 1. AM1 generated structures of the dienophiles **1-6**.

five membered aromatic heterocycles, and consequently the reactivity of furan derivatives **4-6** as the diene for the Diels-Alder reaction must be higher than the corresponding thio analogues. It is interesting that in the series where S is substituted with a methylene group, compounds **2** and **5**, have higher aromaticity than the corresponding oxygen compounds **3** and **6**. That can be explained by the homoaromatic character of the second ring of **2** and **5**. That is further supported by the fact that for thio derivatives **1** and **4** all heavy atoms are in one plane, while in compounds **2** and **5** the methylene group is above the plane in a position characteristic of homoaromaticity [37]. All of the structures have a π system that are interrupted by a hetero atom or a methylene group but their geometries still permit significant overlap of the p orbital across the insulating gap. In fact all dienes, except **2** and **5**, are planar and maximal p overlap can be obtained. To obtain homoaromatic stability for our systems, a certain amount

charge location on the seven membered ring as a prerequisite for homoaromaticity.

It is well known that bond orders [38] can be used to characterize the progress of the reaction. We have estimated the relative stability of the dienes (Table 2) and by calculating bond orders for new bonds formed it should be possible to characterize the reaction progress and relative reactivity of **1-7**. This study will be demonstrated by the example of an ethylene cycloaddition reaction with dienes **1-7**. The corresponding transition structures are presented in Figure 2. All of the transition states are for a synchronous concerted mechanism with two identical new bonds being formed. That is also demonstrated with bond orders (Table 3) of newly formed bonds. These are identical in the transition structure making the degree of asynchronicity (difference of bond orders of two bonds in formation) equal to zero.

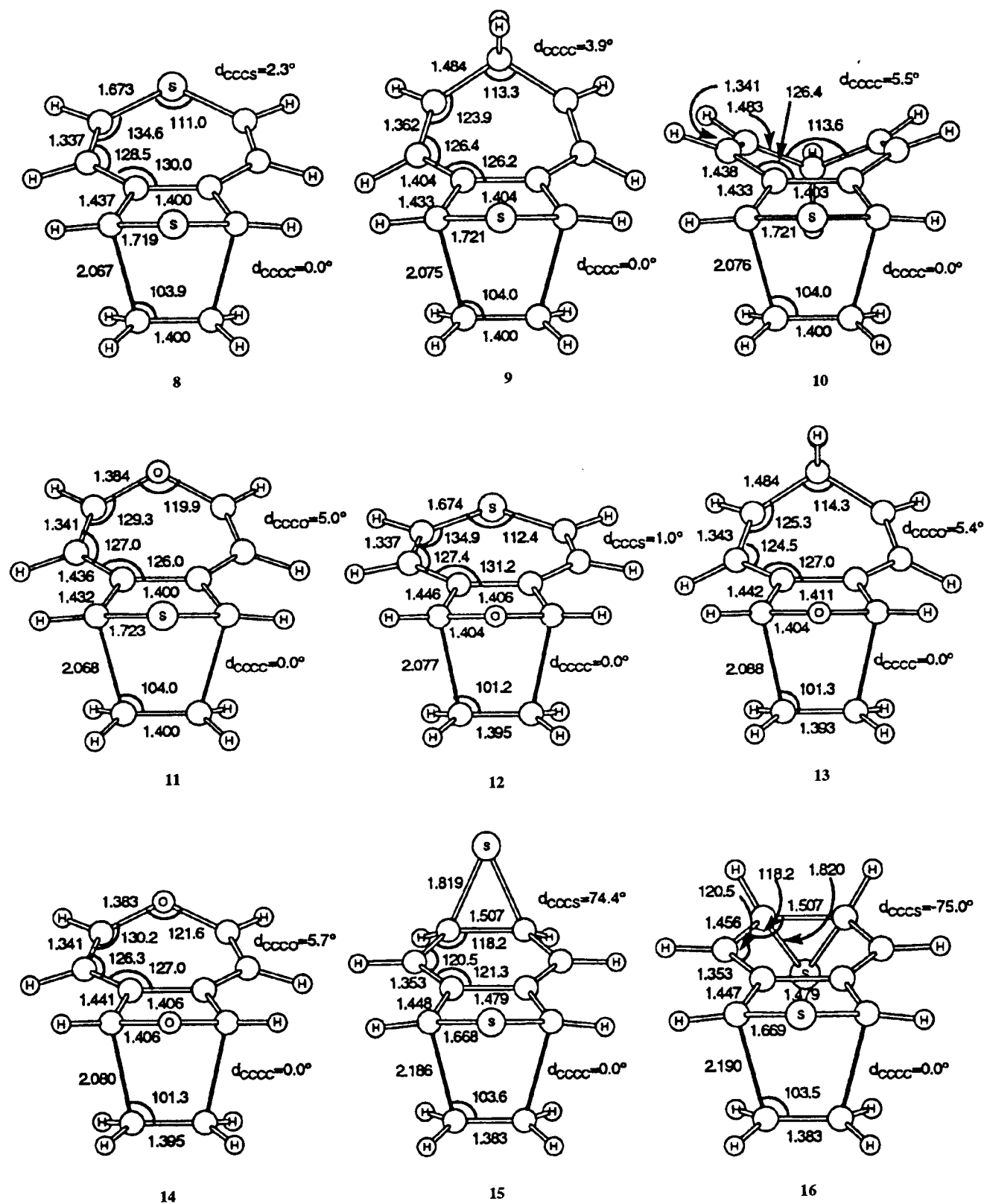There is one approach that organic chemists have been

Figure 2. Transition structures for Diels-Alder reaction between the dienes 1-5 and ethylene.

Table 3

Bond Orders for Newly Formed Bonds in the Transition States of Dienes 1-7 Cycloaddition Reaction with Ethylene

Transition Structure	A	B	A+B	A-B
8	0.457	0.457	0.914	0
9	0.453	0.453	0.906	0
10	0.454	0.454	0.908	0
11	0.458	0.458	0.916	0
12	0.433	0.433	0.866	0
13	0.425	0.425	0.850	0
14	0.432	0.432	0.864	0
15	0.372	0.372	0.744	0
16	0.368	0.368	0.736	0

A = bond order for the left newly formed bond in Figure 2. B = bond order for the right newly formed bond in Figure 2.

using for a long time to qualitatively predict the reactivity based on the Hammond postulate. According to the Hammond postulate the transition that is closer in geometry to the reactants will have lower activation energy [39] if the reaction is exothermic. In our case the smallest bond order means the lowest energy. There are three categories of compounds represented in Figure 2 and Table 3, the ethylene addition to the thiophene ring, transition structure 8-11, the ethylene addition to furan ring, 12-14, and ethylene addition to the highly reactive intermediate 7, transition structures 15 and 16. Apparently, the lowest activation energy is predicted for transition structure 15 and 16 where the reaction is advanced by only 37%, second is addition to furan derivatives, TS 12-14, with a reaction advance around 43% and finally thiophene derivatives with a reaction advance of about 46%. The differences in these three groups are so small that prediction of the reactivity is not possible considering only bond orders. If the heat of hydrogenation of the dienes 1-7 is considered together with bond orders, then the predicted reactivity is the same, 1 < 2 < 3 < 4 < 5 < 6 < 7. To predict which one of the two isomeric transition structures 9-10 and 15-16 will have lower activation energy is almost impossible. For example, smaller bond orders in TS 9 in comparison with 10 might mean that the transition structure 9 is closer to the reactants and consequently the activation energy should be lower. But in the case of comparing the reactivity of 15 and 16, the smaller bond orders for 16 might be caused mainly by steric repulsion interactions between the sulfur of thieno[3,4-*d*]thiepin moiety and ethylene and one can wrongly conclude that 16 will have lower activation energy.

Until now we have discussed only the qualitative reactivity of dienes 1-7 for the Diels-Alder reaction, not considering the feasibility of the reaction itself. The best approach to this problem is to determine the activation barriers of the reaction. The AM1 evaluated activation barriers for ethylene addition to dienes 1-7 are presented

in Table 4. As predicted on the basis of the heat of hydrogenation of the dienes, thieno[3,4-*d*]thiepin is not an appropriate diene for the Diels-Alder reaction. It is less reactive than the corresponding furan derivatives with about 15 kcal/mol higher activation energy. The position of the methylene group, as well as sulfur seems not to have a profound influence on the activation energy, although isomers 9 and 15 have a little bit lower energy. The Diels-Alder reactions with diene 1 are not likely to happen because an activation energy of 43.59 kcal/mol cannot be achieved under "normal" reaction conditions; therefore, very high pressure and temperature should be applied. Cycloaddition [4+2] reactions with furan derivatives 4-6 have considerably lower activation energy, although this reaction will also require somewhat drastic reaction conditions. If we assume that a reaction with diene 1 will proceed through intermediate 7 then the activation energy is predicted to be similar to furan derivatives; again the reaction should not be achievable under normal conditions. Considering the predicted activation barriers for Diels-Alder reactions, it is not surprising that there is no experimental evidence indicating that these reactions are possible.

Table 4

The AM1 Activation Barriers (kcal/mol) for Ethylene Addition

Transition Structure	ΔE	ΔE+ZPVE [a]	Relative
8	43.37	43.59	0
9	41.70	42.08	-1.51
10	42.46	42.81	-0.78
11	43.39	43.64	0.05
12	29.53	30.04	-13.55
13	26.51	27.10	-16.49
14	27.69	28.15	-15.44
15	27.74	28.27	-15.32
16	27.69	28.15	-15.44

[a] ZPVE-zero point vibrational energy.

Further evaluation of the mechanism of the reaction of the diene 1 we have performed a theoretical study with ethylene when three bonds are formed in one reaction step. The AM1 generated transition structures for concerted mechanism are presented in Figure 3. The structures are symmetrical. Estimated activation energies with zero point vibrational energy corrections for transition structure 17 and 18 are extremely high (87.45 and 89.02 kcal/mol respectively) suggesting that if the reaction proceeds through intermediate 7 it should go in two steps: first formation intermediate 7 from 1, and then cycloaddition reaction of 7 with ethylene. The transition structure 19 of transformation of 1 to 7 (Figure 4) is predicted to have an extraordinary activation barrier of 54.95 kcal/mol

with zero point vibrational energy correction suggesting that the second step of the reaction has relatively low activation energy (28.15 kcal/mol) and might not occur at all. If this reaction proceeds at all it must do so directly with diene 1. In that case the reaction is not experimentally feasible, except if the reaction is carried out under high reaction pressure and temperature.
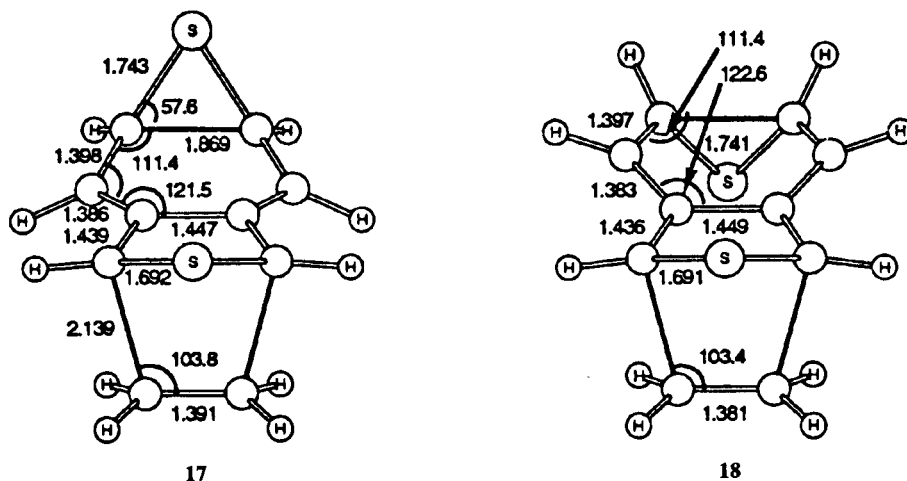
membered ring sulfur decreases the activation barrier by 10 kcal/mol, the cycloaddition reaction still has too high of an activation energy to be experimentally feasible. The same reaction with thiophene is predicted to have activation barrier of only 15.5 kcal/mol [22], indicating the extraordinary stability of the positive charge caused by the presence of the thiepin ring. The stabilization of the

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18

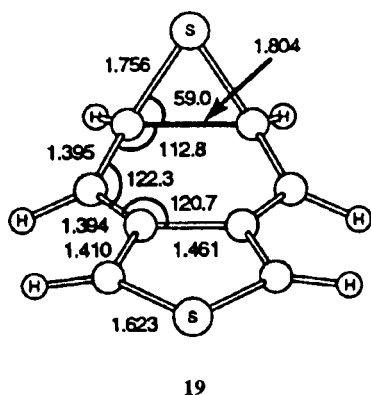Figure 3. Transition states for ethylene addition to 1 with three bonds in formation.

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Figure 4. The AM1 generated transition structure for 1 transformation into 7.

To search for suitable activation of thieno[3,4-d]thiepin we have applied the same approach we used for studying activation of the thiophene ring by S-methylation [22]. Here we can have methylation of one or both sulfur atoms in five and seven membered rings. The transition structures generated (Figure 5) are for a concerted mechanism of ethylene addition to the mono-cation and the di-cation of methylated 1. All transition structures in Figure 5, except 24, represent synchronous formation of both bonds. The corresponding activation energies are presented in Table 5. Although, methylation of the five

positive charge in the second, seven membered ring is very high, making the activation energy for transition structures 24 and 8 almost identical. To obtain an activation barrier as low as ethylene addition to S-methylthiopenium ion, the extra stabilized seven membered ring must be destroyed by using double methylated 1. With this diene the activation energy has been brought to 16.59 kcal/mol that is easily achievable experimentally.

Table 5

The AM1 Activation Barriers (kcal/mol) for Ethylene Addition

Transition Structure	ΔE	ΔE+ZPVE [a]	Relative
8	43.37	43.59	0
20	33.56	33.22	-10.37
21	38.11	37.86	-5.36
22	16.40	16.59	-27.00
23	21.62	22.00	-21.59
24	42.98	43.10	-0.49

[a] ZPVE-zero point vibrational energy.

To the best of our knowledge there is no experimental data available on the dimethyl dication of 1. There are experimental data for methylation of thiophene [40,41]. The ^1H nmr spectroscopy was used to study some S-methylthiophenium salts. It has been concluded [41] that the sulfur in these salts is sp^3 hybridized, and that the
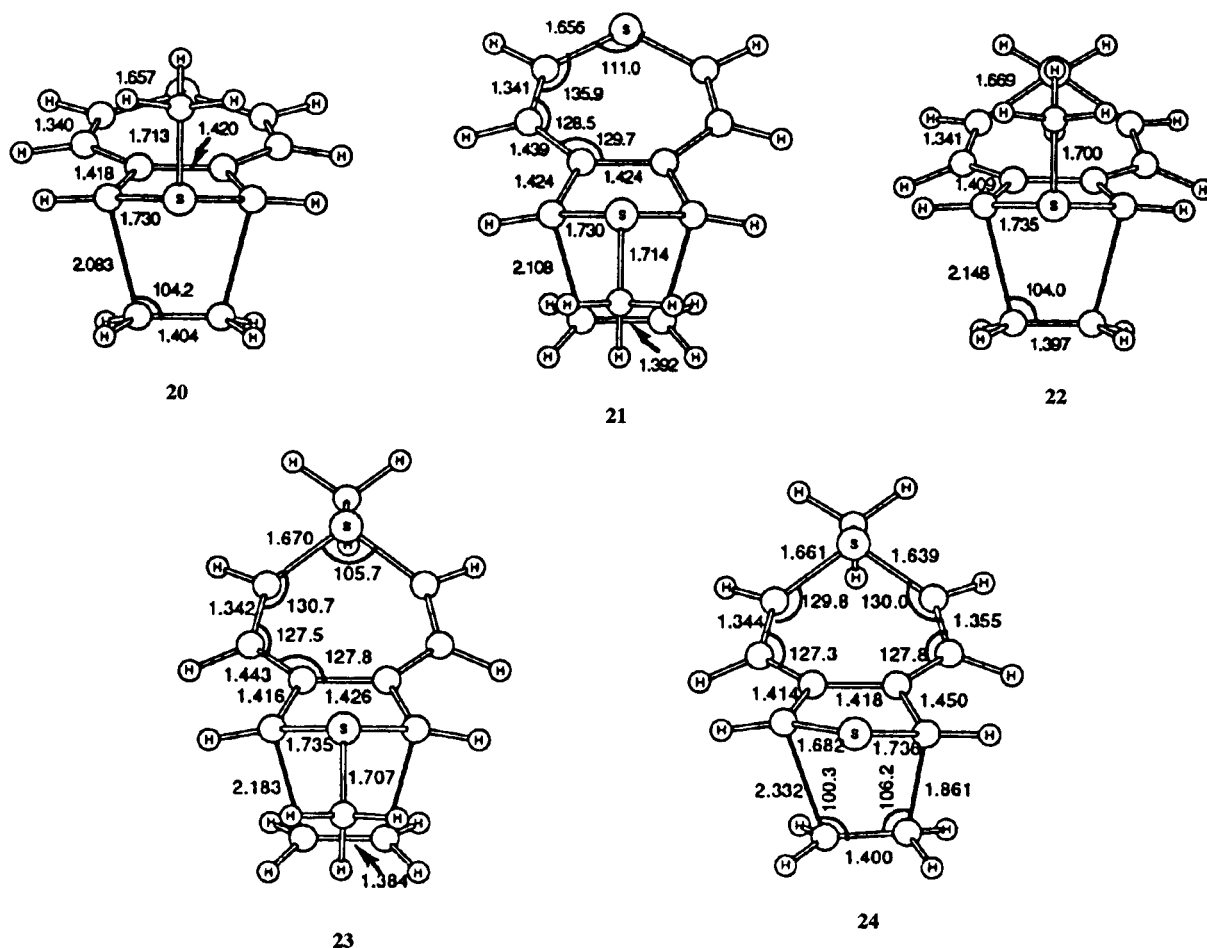
Figure 5. Transition structure for ethylene addition to *S*-methylated 1.

alkyl (methyl) group is not coplanar with the thiophene ring. This results in reduced aromaticity (less effective overlap of lone pair on sulfur with the ring *p*-electrons); however, the effect of *d*-orbital participation seems to be unimportant. That is in full agreement with our calculations which predict a lower activation barrier for the thiophene sulfur methylated dienes in a cycloaddition reaction with ethylene.

Preparation of a double cation for the Diels-Alder reaction is not a practical choice for solving the problem of thieno[3,4-*d*]thiepin reactivity. The double cation must be even more unstable than *S*-methylthiophenium ion [41] and should be difficult to handle for the synthetic organic chemist. To find a suitable dienophile that can undergo reaction with thieno[3,4-*d*]thiepin we have performed a theoretical study with maleic anhydride and *N*-phenylmaleimide as dienophiles. Transition structures (Figure 6) indicate a concerted mechanism of [4+2] cycloaddition. The transition structures for maleic anhydride addition 25 and 26 have a bisecting plane representing synchronous formation two new bonds. The transition structures with

N-phenylmaleimide are no longer symmetrical as the phenyl group has rotated out of the dienophile plane. In the case of the *exo* addition the influence of the phenyl group in 27 is negligible and the bond distances for the two newly formed bonds are identical. In the *endo* transition structure the steric interactions now present cause the differences in the bond distance. Now the bond distance difference is 0.027Å, an extremely small deviation from synchronous mechanism of the cycloaddition reaction.

The activation energies are presented in Table 6. Surprisingly, the activation barrier does not decrease considerably when the reaction is performed with ethylene, or maleic anhydride and *N*-phenylmaleimide as the dienophiles. The predicted activation energies are around 40 kcal/mol. It is well documented that AM1 will overestimate [42] the activation energy when a strongly electron deficient dienophile is involved. Nevertheless, an activation energy that is close to 40 kcal/mol is not easy to reach thermally. Schlessinger and Ponticello [25] experimentally performed the cycloaddition reaction between thieno[3,4-*d*]thiepin (1) and *N*-phenylmaleimide under
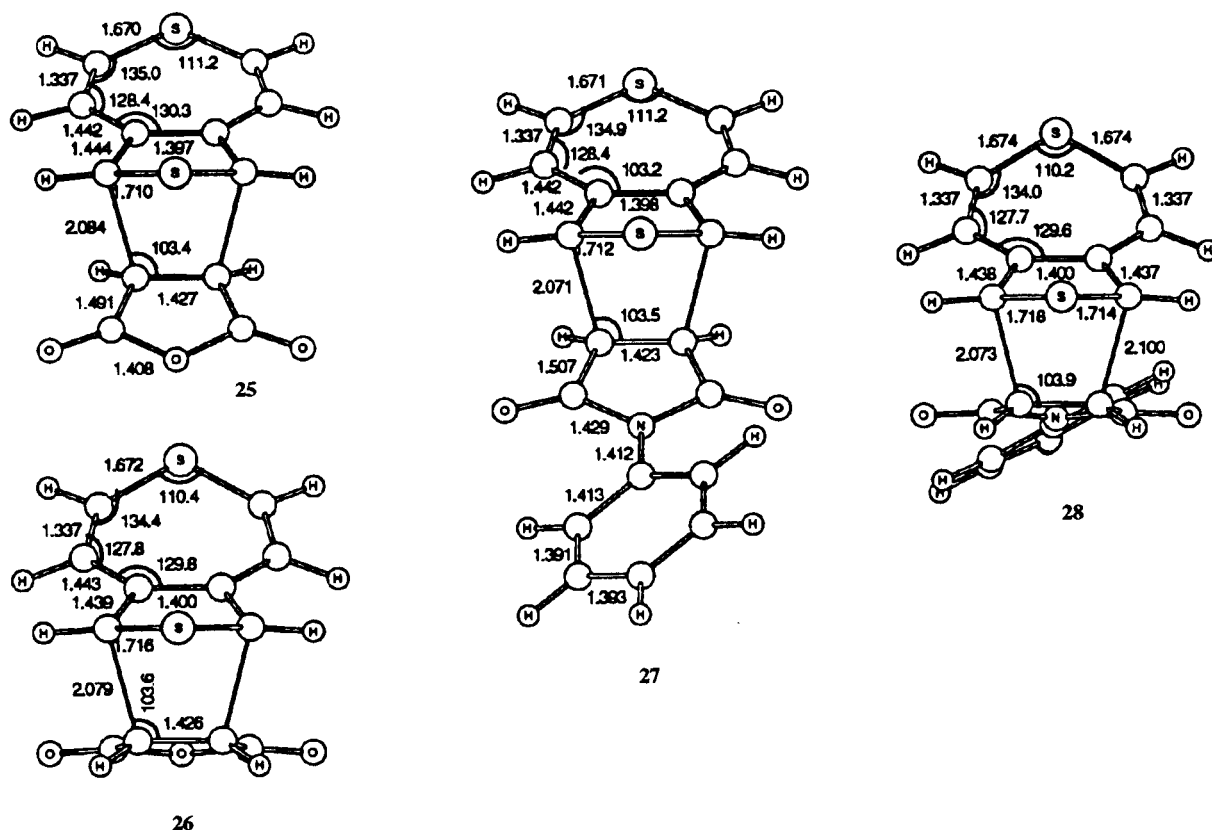
Figure 6. AM1 transition structures for maleic anhydride and N-phenylmaleimide addition to thiepin 1.

rather drastic reaction conditions. When heated above its melting point, thiepin 1 was found to decompose slowly into a mixture of products. This does not occur when 1 was heated at 150° in N-phenylmaleimide as the solvent. A single crystalline product in nearly quantitative yields was isolated and shown to be similar to the cycloadduct that is formed from transition structure 27. AM1 correctly predicts that the major product of a cycloaddition will be an *exo* isomer. Furthermore, a high activation energy predicted with AM1 calculation is in agreement with the drastic reaction conditions necessary to force the cycloaddition reaction.

Table 6

The AM1 Activation Barriers (kcal/mol) for Maleic Anhydride and N-Phenylmaleimide Addition to Thieno[3,4-d]thiepin

Transition Structure	ΔE	ΔE+ZPVE [a]	Relative
8	43.37	43.59	0
25	41.57	40.70	-2.89
26	42.86	41.87	-1.72
27	42.05	41.15	-2.44
28	43.55	42.54	-1.05

[a] ZPVE-zero point vibrational energy.

Conclusion.

The AM1 calculation might not necessarily predict absolute values of the activation energies of the cycloaddition reactions, but rather gives preference for some reactants in a series of the same reaction. Evaluation of the reactivity of the thiophene, and furan ring fused with seven membered unsaturated heterocycles by FMO orbitals totally fails because, as predicted, the least reactive thieno[3,4-d]thiepin is the most reactive diene in the study series. A more reliable method for determining resonance stability of the heterocycle proved to be calculating heat of the hydrogenation. This method predicted correctly that thieno[3,4-d]thiepin is the least reactive in the series because of high aromatic stability. The o-quinonoid episulfide intermediate 7 was rejected as a suitable dienophile in transformation 1 to the cycloadduct because the estimated activation energy for its transformation is too high (~55 kcal/mol). An alternative mechanism with three bond formation in the cycloaddition reaction (one is formation episulfide ring) is predicted to have even higher activation energy (87.45) and therefore rejected. By using very reactive dienophiles like N-phenylmaleimide the activation energy was predicted to drop considerably, yet the reduction in activation energy was negligible thereby

requiring drastic reaction conditions as necessary to force the reaction in the targeted direction. This is in full agreement with the experimental evidence.

There is one way of activation for thieno[3,4-d]thiepin in a Diels-Alder reaction with non activated dienophiles by S-methylation. AM1 predicts the activation energies with these dienes to be below 20 kcal/mol and consequently experimentally feasible. The methylation must be on a five membered ring, because S-methylation of the seven membered ring is predicted not to have substantial influence on the diene reactivity.

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