π-Facial Diastereoselectivity in Diels-Alder Reactions
of 2,5-Dimethylthiophene Oxide

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Abstract: A series of [4 + 2] cycloadditions with 2,5-dimethylthiophene oxide (**2**), generated *in situ* by peracid oxidation of 2,5-dimethylthiophene (**1**), are described. In all cases the *syn* adduct (with respect to the sulfoxide oxygen) is formed exclusively.

Recently the π-facial diastereoselectivity encountered in Diels-Alder reactions, where the addends possess two different reactive faces, has received increased attention.[1] In many of these cycloadditions, in which the diene contains an allylic stereogenic centre, the dienophile reacts preferentially with the more sterically hindered *syn* face. This is particularly true of C-5 substituted cyclopentadienes in which the allylic group contains an electronegative heteroatom such as oxygen, nitrogen, or chlorine.[2,3] In contrast, a sulfur substituent reverses the facial selectivity and *anti* adducts result.[3]

A number of vinyl sulfoxides have been examined as dienophiles[4] and a stereogenic sulfinyl group directed a pyrone cycloaddition to give a 88:12 diastereomer ratio.[5] Frequently, the interpretation of the results with acyclic systems is complicated by the necessity of determining the relative contribution and reactivity of various conformers in which the heteroatom is aligned "inside" as predicted by electronic factors or "outside" as favoured on steric grounds. Cyclic dienes avoid this complication and examples that are plane-nonsymmetric afford insight into the "addition directing" influence of diverse functional groups. Thiophene oxides provide a model to assess the relative importance of the competition between a lone pair and sulfur-oxygen bearing face. We wish to report that many diactivated, *endo* selective dienophiles, add preferentially to the *syn* oxygen face. Thiophene oxides thus represent latent butadienes that react with exclusive facial control.
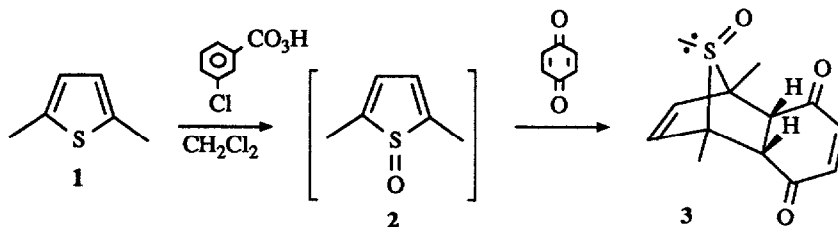

In contrast, to the cycloadditions of thiophene-1,1-dioxides thiophene oxides have received much less

attention.[6] Upon oxidation thiophene undergoes a Diels-Alder dimerization to thiophene sesquioxide (4)[7] whose structure and stereochemistry was assigned on the basis of its nmr spectra.[8] Torssell established that *in situ* peracid oxidation of 2,5-dimethylthiophene (mClPhCO$_3$H, CH$_2$Cl$_2$, -5 to 21° C) in the presence of benzoquinone afforded an adduct (33%) but the stereochemistry about sulfur was not determined.[9] This reaction was repeated, the product recrystallized from acetonitrile-diethyl ether, and structure 3 established by X-ray diffraction. Addition occurred exclusively in a contrasteric manner *syn* to the sulfur-oxygen bond.

In order to assess the generality of this result, other dienophiles were investigated as summarized in the Table. These included naphthaquinone, tetracyanoethylene, N-phenylmaleimide, and 2-chloroacrylonitrile. In each case the structure of the adduct was established by X-ray analysis and confirmed the cycloadditions were *anti* to the lone pair bearing face. The structural features for all the adducts were very similar and thus only the ORTEP drawing for 3 is reproduced in Figure 1. An adduct was also isolated from the reaction with maleic anhydride but was unsuitable for crystallographic analysis. The isolated yields of crystalline material were low 10 - 30% under the conditions employed, (m-ClPhCO$_3$H, 5 to 21° C, CH$_2$Cl$_2$, 1-5 days), but were not optimized. They do however represent the only Diels-Alder adducts, as established by both GC-MS and ^{1}H nmr analysis of the total reaction mixtures. Recrystallization of the tetracyano adduct 6 from methanol resulted in an addition-cyclization to form the heterocycle 7 as a consequence of the close spacial proximity of the two *endo* nitrile groups. The structure of 7 was also confirmed by X-ray analysis.

In order to gain preliminary insight into the relative reactivity of thiophene oxides the 2,5-dimethylthiophene oxide, generated *in situ*, was treated with phenylacetylene, methyl vinyl ketone, methyl maleate, and 2,3-dimethylmaleic anhydride but no adducts could be isolated. The use of dimethyl acetylenedicarboxylate afforded dimethyl 3,6-dimethylphthalate directly. It was possible to detect the adduct in the crude reaction mixture but the sulfoxide bridge was extruded during chromatography. No adducts were obtained from reactions with N-phenylmaleimide or tetracyanoethylene with either thiophene oxide or 2,5-bis(chloromethyl)thiophene oxide.
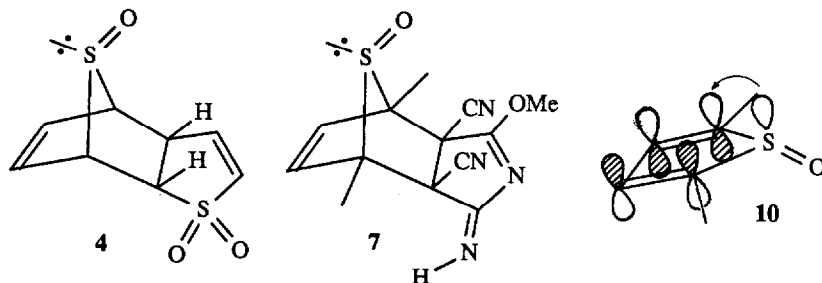
On the basis of electrostatic interactions Kahn and Hehre concluded that electrophilic dienophiles should add preferentially to the more nucleophilic diene face, *syn* to "a lone-pair-containing allylic substituent".[10] Unfortunately this explanation does not satisfy the *anti* addition we have observed in C-5 substituted cyclopentadienes.[3] A satisfactory explanation is based on the relative σ donor ability of the adjacent bonds and their interaction with the developing incipient bonds. This concept of transition state stabilization by sigma electron donation into the vacant σ_*^* orbital associated with the incipient bond correctly accounts for axial attack of cyclohexanones[11] and the *syn* approach of a butadiene to 5-fluoroadamantane-2-thione[12] where the electrostatic model fails. Based on related cycloaddition studies[13] and the relative donor properties of the allylic sigma bonds[14] we expect the cycloaddition of cyclopentadienes to display a preference for addition *anti* to the antiperiplanar sigma bond that is the better donor. Thus for thiophene oxides, where the competition is between a lone pair and a sulfoxide oxygen, cycloaddition should be *anti* to the lone pair as has been observed in all cases. As illustrated by
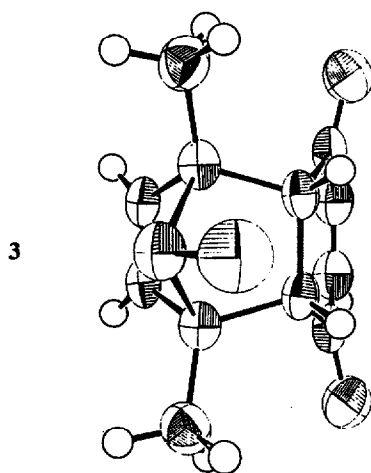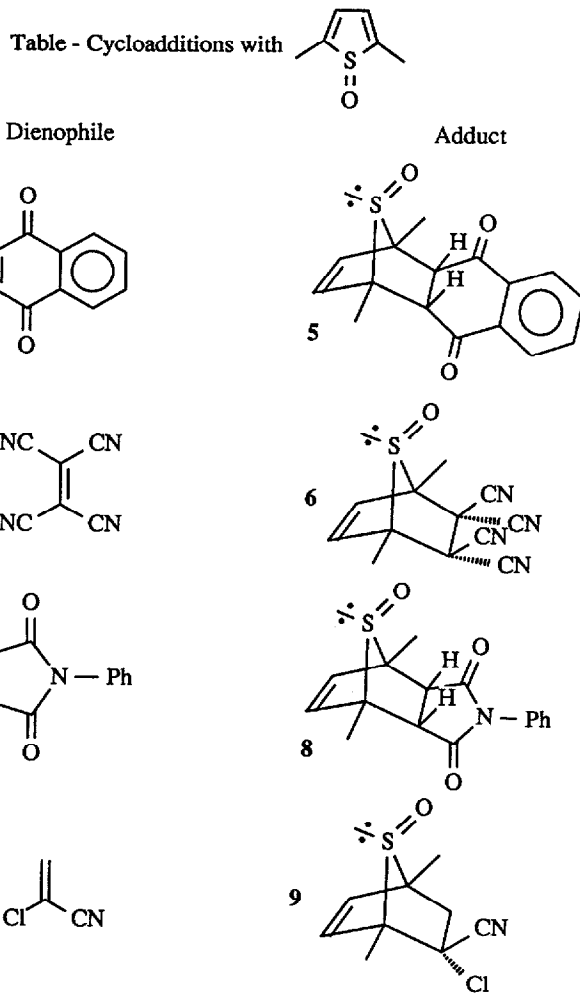
Table - Cycloadditions with

Dienophile

Adduct

5

6

8

9

3

Figure 1

10, the lone pair orbital will interact favourably with the diene HOMO and the developing incipient bonds. Thiophene oxides possess a particularly favourable orbital alignment for these interactions. Thus, in less suitable geometries, one would expect these electronic features to become less important, and steric factors to play a larger role.

In conclusion, the exclusive cycloaddition of dienophiles *syn* to the sulfoxide oxygen has interesting synthetic potential. Thiophene possess a rich chemistry and by increasing the electron density in the resulting thiophene oxides it will be possible to increase their reactivity and employ them as latent butadienes that react with complete facial control. In addition, due to hyperconjugation and the beneficial interaction with the incipient bond(s), one should expect other pericyclic reactions to display a preference for addition *anti* to the antiperiplanar sigma bond that is the better donor.[15]

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