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syn-π-Face- and *endo*-selective, inverse electron-demand Diels–Alder reactions of 3,4-di-*tert*-butylthiophene 1-oxide with electron-rich dienophiles

Jun Takayama, Yoshiaki Sugihara, Toshiyuki Takayanagi and Juzo Nakayama*

Department of Chemistry, Faculty of Science, Saitama University, Sakura-ku, Saitama 338-8570, Japan

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Abstract—Diels–Alder reactions of 3,4-di-*tert*-butylthiophene 1-oxide with oxygen (or sulfur)-substituted dienophiles and with simple alkenic dienophiles, which are classified as an inverse electron-demand Diels–Alder reaction on the basis of DFT calculations, took place exclusively at the *syn*-π-face of the diene with respect to the S=O bond to provide the corresponding adducts in high yields.

π-Face-selectivity in Diels–Alder reactions has been attracting much attention from both theoretical and synthetic points of view. It has been investigated most extensively by using C5-substituted cyclopentadienes as the substrate.[1] It is well documented that thiophene 1-oxides, which possess *anti*- and *syn*-π-faces with respect to the S=O bond, act as dienes.[2] 3,4-Di-*tert*-butylthiophene 1-oxide (**1**),[3] which is thermally stable but still extremely reactive, has been shown to serve as an excellent substrate to investigate π-face-selectivity (Fig. 1).[4] It undergoes Diels–Alder reactions, exclusively at its *syn*-π-face with respect to the S=O bond, with a variety of electron-deficient dienophiles to give the corresponding adducts in high yields.[4a] On the other hand, the inverse electron-demand Diels–Alder reaction has not been studied so extensively as has been the normal electron-demand one. Therefore, a little is known about the π-face-selectivity of this reaction.[5] Here, we report that **1** undergoes inverse electron-demand Diels–Alder reactions with a range of electron-rich dienophiles exclusively at its *syn*-π-face to give the corresponding adducts in high yields.

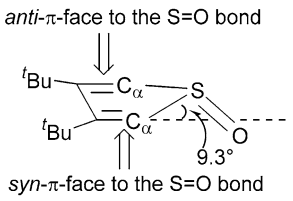

Figure 1. Structure and *syn*- and *anti*-π-face of **1**.

Results of the reactions are summarized in Scheme 1. Both cyclic and acyclic vinyl ethers reacted with **1** to give the corresponding Diels–Alder adducts **2a**–**d** in excellent yields. The reaction with ethyl vinyl ether proceeded at room temperature, while for cyclic vinyl ethers, **1** and an excess of dienophile were heated without solvent. Phenyl vinyl thioether (phenyl vinyl sulfide) also reacted with **1** at room temperature to give the adduct **2e** in 94% yield. Simple cycloalkenic dienophiles such as cyclopentene, cyclohexene, and cyclooctene, reacted with **1** to provide **2f**, **g**, and **h**, respectively, in good yields. The *syn*-addition structure of **2** was determined on the basis of the spectroscopic data, particularly on the basis of a comparison of their NMR data with those of Diels–Alder adducts of **1**, where before the structures had been determined unambiguously.[4a,b] The *endo*-stereoselectivity was determined by examination of coupling constants H_a–H_b and/or $H_{a'}$–$H_{b'}$ (for denotation, see structures **2a** and **c** in Scheme 1).[6] Furthermore, the structures of **2c** and **g** were established by X-ray diffraction analysis (Fig. 2).[7] From the above it can be concluded that the Diels–Alder reactions of **1** with heteroatom-substituted, electron-rich dienophiles and with simple cycloalkenic dienophiles all take place

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Keywords: Thiophene 1-oxide; Exclusive π-face selection; *endo*-Selection; Concerted mechanism; Transition state.

* Corresponding author. Tel.: +81 48 858 3390; fax: +81 48 858 3700; e-mail: nakaj@post.saitama-u.ac.jp

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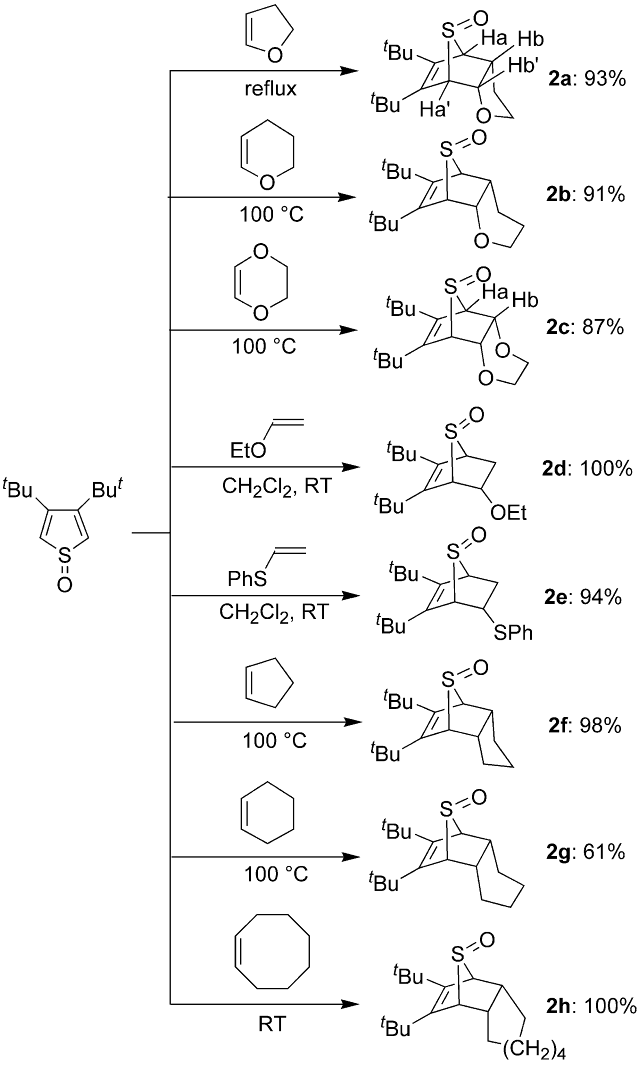


Scheme 1. Diels–Alder reactions of **1** with electron-rich dienophiles.

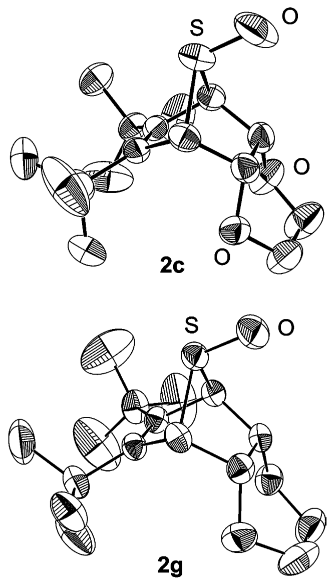
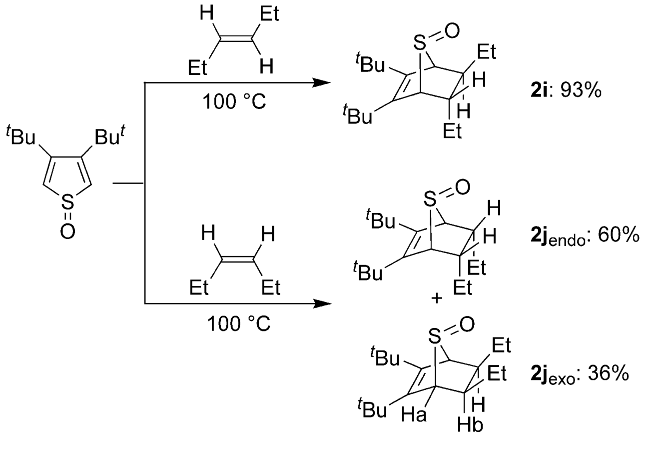


Figure 2. Molecular structures of **2c** and **g**.

exclusively at the *syn*-π-face of **2** with respect to the S=O bond, in addition, exclusively in an *endo*-mode.

We also investigated the stereochemistry of the Diels–Alder reaction of **1** with *cis*- and *trans*-3-hexenes by heating **1** and an excess of the alkene at 100 °C in a sealed tube. The results, shown in Scheme 2, reveal the following: (1) the relative configuration of the ethyl groups of the alkenes is retained in the Diels–Alder adducts, (2) the Diels–Alder reactions take place at the *syn*-π-face of **1** exclusively, and (3) the reaction with *cis*-3-hexene, which produced the *exo*-adduct $\mathbf{2j}_{exo}$ in 36% yield in addition to the *endo*-adduct $\mathbf{2j}_{endo}$[8] in 60% yield, provides the first instance where both *exo*- and *endo*-products can be found; no thermal isomerization between $\mathbf{2j}_{exo}$ and $\mathbf{2j}_{endo}$ takes place after prolonged heating of each isomer in refluxing toluene. Retention of the configuration of the alkenes indicates a concerted mechanism, while the formation of the *exo*-adduct $\mathbf{2j}_{exo}$ is probably due to steric reasons, not to electronic reasons.

Progress of the reaction of **1** with excess 2,3-dihydrofuran (55 molar amounts) or phenyl vinyl thioether (20 molar amounts) was monitored by ^{1}H NMR. The reactions, at 45, 50, 55, and 60 °C for 2,3-dihydrofuran and at 35, 40, 45, and 50 °C for phenyl vinyl thioether in C_6D_6 and THF-d_8, showed good pseudo-first order kinetics in the diene **1**. The reaction with 2,3-dihydrofuran provided the activation parameters of $\Delta H^{\ddagger}$ = 96.5 kJ mol^{-1} and $\Delta S^{\ddagger}$ = −38.8 J K^{-1} mol^{-1} in C_6D_6 and of $\Delta H^{\ddagger}$ = 94.8 kJ mol^{-1} and $\Delta S^{\ddagger}$ = −45.3 J K^{-1} mol^{-1} in THF-d_8. The reaction with phenyl vinyl thioether gave the activation parameters of $\Delta H^{\ddagger}$ = 37.8 kJ mol^{-1} and $\Delta S^{\ddagger}$ = −193 J K^{-1} mol^{-1} in C_6D_6 and $\Delta H^{\ddagger}$ = 43.7 kJ mol^{-1} and $\Delta S^{\ddagger}$ = −176 J K^{-1} mol^{-1} in THF-d_8. No large solvent effect was observed; the relative rates [$k(C_6D_6)/k(\text{THF-}d_8)$] are 1.17 for 2,3-dihydrofuran and 1.22 for phenyl vinyl thioether (average of four values determined at the different temperatures). The negative $\Delta S^{\ddagger}$ values and small solvent effect indicate that the Diels–Alder reactions of **1** proceed through a concerted mechanism,[1b] even when heteroatom-substituted dienophiles are involved. Next,



Scheme 2. Retention of the configuration of alkenes in Diels–Alder adducts.

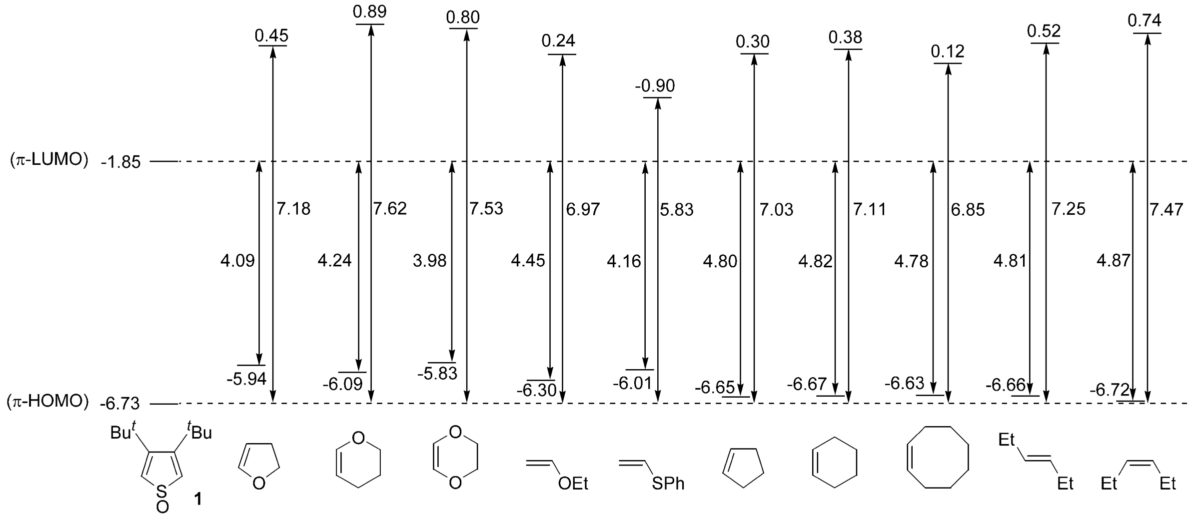


Figure 3. π-LUMO and π-HOMO energy levels of **1** and the dienophiles in electron volts.

energy levels of the π-HOMO and π-LUMO of **1** and the dienophiles were calculated by DFT calculations at the B3LYP/6-311 + G(3df,2p) level (Fig. 3).[9] Calculated π-HOMO and π-LUMO of **1** are -6.73 and -1.85 eV, respectively, and π-HOMOs and π-LUMOs of the dienophiles range between -5.83 and -6.72 and between -0.90 and 0.89 eV, respectively. Thus, differences between the π-LUMO of **1** and the π-HOMOs of the dienophiles are in the range 3.98–4.87 eV and are smaller than differences between the π-HOMO of **1** and the π-LUMOs of the dienophiles which are in the range 5.83–7.62 eV. Therefore, all the present reactions are classified as an inverse electron-demand Diels–Alder reaction;[10] even for the least inverse electron-demand case, the reaction with phenyl vinyl thioether, (π-LUMO$_{\text{dienophile}}$–π-HOMO$_1$) – (π-LUMO$_1$–π-HOMO$_{\text{dienophile}}$) is 1.67 eV.

How can we rationalize the exclusive *syn*-π-face-selectivity in both normal and inverse electron-demand Diels–Alder reactions of **1**? π-Face-selective additions have been explained in many ways,[11] including non-equivalent orbital extension.[11o–s] The DFT calculations predicted that the π-HOMO lobe of **1** at the α-position is slightly greater for the *syn*-π-face than for the *anti*-π-face, whereas the situation becomes reversed for the π-LUMO. Thus, the *syn*-π-face-selectivity[4a] of the normal electron-demand Diels–Alder reactions is in harmony with the non-equivalent orbital extension of the π-HOMO of **1**, whereas the *syn*-π-face-selectivity of the inverse electron-demand Diels–Alder reactions cannot be explained by the orbital extension of the π-LUMO of **1**. Therefore, other crucial factor that governs the π-face-selectivity must be operative. We therefore calculated the transition state structures of the reaction of the parent thiophene 1-oxide with ethylene and that of **1** with ethylene at both HF and B3LYP levels with the 6-31G(d) basis set.[9] Here are given the results obtained by the B3LYP/6-31G(d) level calculations (for the HF level calculations, see Supplementary data). Figure 4 shows the computer-visualized transition states that lead to the *syn*-π-face adducts (left) and the *anti*-π-face adducts (right). The calculations predict that the transition state leading to the *syn*-π-face adduct is 7.46 (7.17)[12] kcal mol^{-1} more favorable than that leading to the *anti*-π-face adduct for the reaction of the parent thiophene 1-oxide, and is 7.05 (6.90)[12] kcal mol^{-1} more favorable for the reaction of **1**.[13] Figure 4 clearly shows that greater conformational change of thiophene 1-oxides is required for the *anti*-π-face addition to reach the transition states, where inversion at the α-carbons of the thiophene ring occurs. On the other hand, for the *syn*-π-face addition, the transition state is easily reached with smaller conformational change of thiophene 1-oxides.[13] In other words, if **1** keeps the conformation shown in Figure 1 in solution with a tilt angle of 9.3°, the *anti*-π-face transition state will encounter about 18.6° (9.3° × 2) larger change in bond angle around the two C_α carbons than will the *syn*-π-face transition state

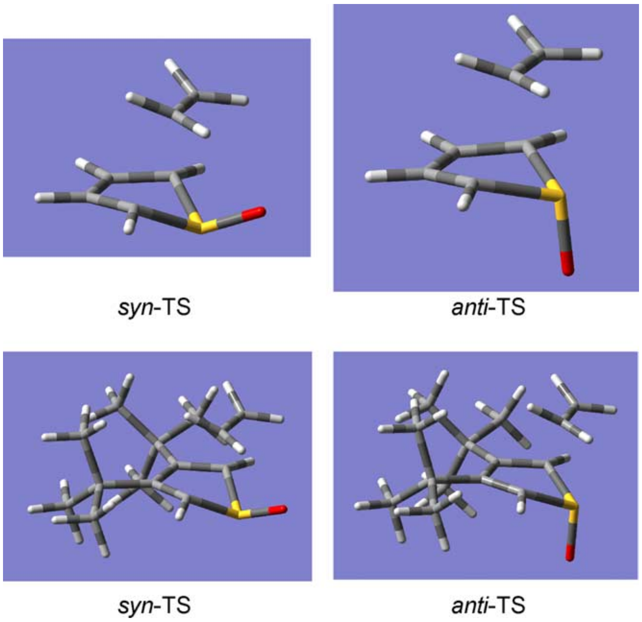


Figure 4. Transition states of the reactions of ethylene with the parent thiophene 1-oxide (top) and with **1** (bottom).

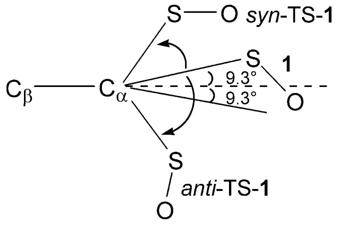


Figure 5. Difference of the conformational change of **1** in the *anti*- and *syn*-addition transition states.

(Fig. 5). Accordingly, the activation energy of the reaction will be smaller for the *syn*-π-face addition than for the *anti*-π-face addition, thus making the former addition more favorable. We therefore conclude that the conformational change, which is required to reach the transition state, is the crucial factor that governs the π-face- selectivity for the present Diels–Alder reactions.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version at doi:10.1016/j.tetlet.2005.04.070.

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7. Crystal data for **2c** and **g** were recorded on a Bruker SMART APEX CCD area detector by using 0.30°-wide ω scans and graphite-monochromated Mo-$K\alpha$ radiation ($\lambda = 0.71073$ Å). Frame data (20 s, 0.30°-wide ω scans) were collected using the Bruker SMART software package. Peak integration was performed by the Bruker SAINT-Plus software package. Absorption correction was made by the software SADABS. Space group determination was done by the software XPREP. All calculations were performed by the Bruker SHELXTL 5.1 software package. The structure was solved by direct methods and refined with full-matrix least-squares by all independent reflections. The non-hydrogen atoms were refined anisotropically, and hydrogen atoms were placed at calculated positions. **2c**: $C_{16}H_{26}O_3S$, $M_w = 298.43$, monoclinic, space group $P2_1/c$; $a = 9.0260(7)$, $b = 9.1531(8)$, $c = 19.6033(19)$ Å, $\beta = 96.508(2)°$; $Z = 4$; $V = 1609.1(2)$ Å^3, $D_c = 1.232$ g/cm^3; unique reflections 3529, observed reflections 2841 [$I > 2\sigma(I)$], $R = 0.0514$, $R_w = 0.1558$, GOF = 1.051. **2g**: $C_{18}H_{30}OS$, $M_w = 294.48$, triclinic, space group P-1; $a = 8.8198(6)$, $b = 8.9383(6)$, $c = 12.2923(10)$ Å; $\alpha = 100.8560(10)$, $\beta = 102.2780(10)$, $\gamma = 111.4800(10)°$; $Z = 2$, $V = 842.51(10)$ Å^3, $D_c = 1.161$ g/cm^3; unique reflections 3996, observed reflections 3359 [$I > 2\sigma(I)$], $R = 0.0480$, $R_w = 0.1453$, GOF = 1.038.
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12. The values in parenthesis are those obtained by zero point energy corrections.

13. HF/6-31G(d) level calculations predicted that the transition state leading to the *syn*-π-face adduct is more favorable by 8.95 (8.79) kcal mol^{-1} than that leading to the *anti*-π-face adduct for the reaction of the parent thiophene 1-oxide, and by 17.96 (17.07) kcal mol^{-1} for the reaction of **1**.