Regiocontrol of Diels-Alder Reaction of Conjugate 1-Trienol Ether in Chiral Tropilidene with TCNE

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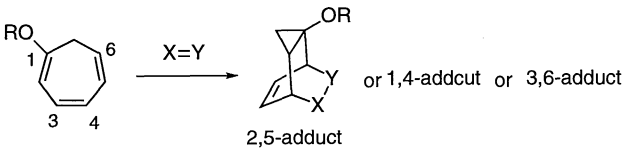
The Diels-Alder reaction of tetracyanoethylene (TCNE) with a 1-trienol unit in the tropilidenes at the 1,4-position was a quick and reversible process, whereas the 3,6-addition only proceeded in polar solvent and was irreversible.

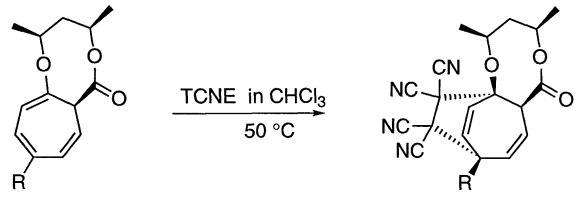
Cycloheptatrienes (tropilidene) are useful synthons for a variety of cycloadditions that produce bicyclic and tricyclic compounds.[1] Recently, we reported a simple and handy method to prepare optically active tropilidenes under complete regio- and diastereo-control in high yield.[2] Although all known Diels-Alder reactions of tropilidenes with tetracyanoethylene (TCNE) yielded the 2,5-adduct through the norcaradiene tautomers,[3] TCNE addition to the chiral tropilidenes, **1** and **2**, obtained by our process, afforded **3** and **4** of the 1,4-adducts in quantitative yields (in chloroform at 50 °C, 15–50 h). The MO calculation



and the NOE study on the ^{1}H NMR of **1** indicated the ester carbonyl having an axial conformation and a relatively planar triene unit, the structure of which reasonably explains the unique reactivities of **1** and **2**. The calculated MO also suggested the higher reactivity at the 1,4-position versus the 3,6-position. However, the same reactions except for the use of acetonitrile as a solvent afforded isomers as minor products, which were determined to be the 3,6-adducts, **5** and **6**. The regiocontrol factors of the conjugate 1-trienol ether in the Diels-Alder reaction have not yet been clarified because of the lack of a good model compound having a 2,3-*s*-*cis* and 4,5-*s*-*cis* conformation. By using **1** and **2** as model compounds of the 1-trienol ether, the regiocontrol factor and its control method for the Diels-Alder reaction were investigated.

First, the reaction of **1** and TCNE in acetonitrile was carefully monitored by TLC analysis. Since the amount of **5** increased after the conversion of **1** to **3**, it was assumed that **5** was the secondary product. As a matter of fact, the reaction of **1** in acetonitrile at the shorter reaction time (50 °C, 5 h) produced only **3** in quantitative yield. The regioisomer of **5** could be produced through two possible ways; one is the rearrangement of **3**, and the other is a side-reaction of **1** if the formation of **3** is a reversible process. The 1,4-adducts, **3** and **4**, were stable crystals, but these solutions gradually became mixtures of the adducts and the tropilidenes, which indicated that the 1,4-additions were reversible processes.

The reaction rates for the 1,4-addition and the reverse process were determined by heating dilute solutions of **3** and **4** (4.6 mM for **3** and 5.0 mM for **4**). The solution in $CDCl_3$ or CD_3CN was heated in an NMR tube at 50 °C, and the ratio of the 1,4-adduct and the tropilidene was determined by ^{1}H NMR peak integration. The reactions were monitored at 1 hour intervals and continued long enough to determine the equilibration constants (30 h), where the 3,6-adducts and the other products were not detected. The obtained retro-Diels-Alder reaction rates (k'), equilibration constants ($K = k/k'$), and addition rates (k) calculated from k' and K are summarized in Table 1. Although both k and k' were somewhat changed by the solvent used, the equilibration step is clearly not responsible for the fact that the 3,6-adduct formed in acetonitrile but not in chloroform.



1. R = H
2. R = Me

3. R = H
4. R = Me

Scheme 1.

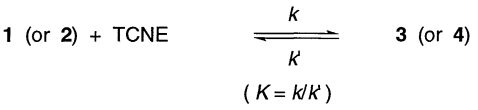
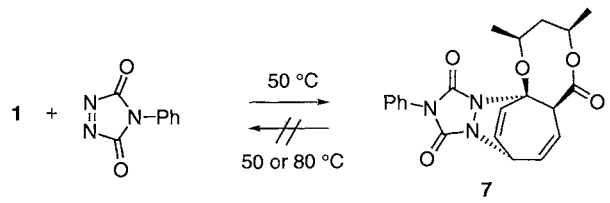


Table 1. 1,4-Addition and elimination rates of TCNE to **1** and **2** at 50 °C[a]

1,4-adduct	Solvent	k /M^{-1}s^{-1}	k' /s^{-1}	K /M^{-1}
3	chloroform-d_1	1.3×10^{-2}	2.2×10^{-5}	6.0×10^{2}
3	acetonitrile-d_3	1.9×10^{-2}	3.6×10^{-5}	5.3×10^{2}
4	chloroform-d_1	1.1×10^{-2}	5.2×10^{-5}	2.1×10^{2}
4	acetonitrile-d_3	5.6×10^{-3}	1.3×10^{-4}	4.2x10

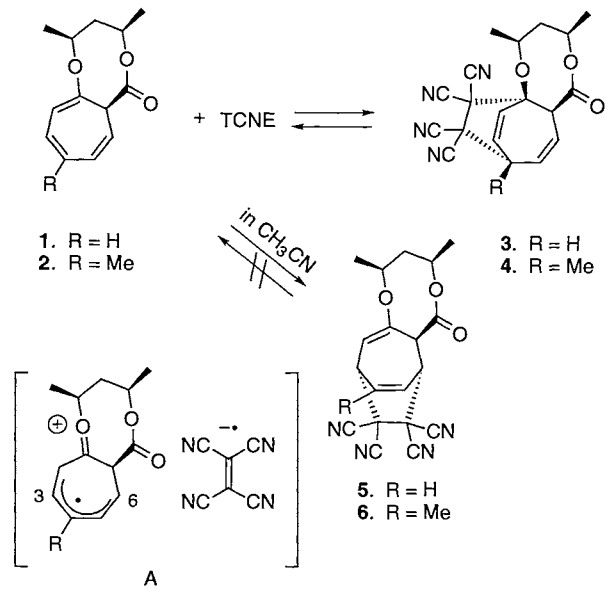
[a] The retro-Diels-Alder rates (k') and equilibration constants ($K = k/k'$) were determined by ^{1}H NMRpeak integration. The adducts **3** (4.6 mM) and **4** (5.0 mM) was heated in an NMR tube at 50 °C and measured every 1 h. The addition rates (k) were calculated from k' and K.

The highly regio- and diastereo-differentiating 1,4-addition was also possible using 4-phenyl-1,2,4-triazol-3,5-dione[5] as the dienophile. The addition to **1** at 50 °C proceeds faster than that with TCNE and predominantly resulted in the 1,4-adduct **7**. In this case, **7** in dilute solution (4.6 mM in acetonitrile or chloroform) did not result in any reverse reaction even at 80 °C (100% recovery). Thus, the quick retro-Diels-Alder reaction was not a characteristic process for the 1-trienol ether.



Scheme 2.

By heating a solution of **1** and TCNE in acetonitrile (70 mM each) at 80 °C for 48 h, the predominant formation of the 3,6-adduct **5** was achieved. Under these conditions, the 1,4-adduct **3** was immediately produced and gradually changed to **5** without any detectable side-reaction. The same reaction in THF also produced **5**, but the conversion rate was much slower (**3**/**5** = 20/1 after 24 h). On the other hand, the reactions in benzene and chloroform did not give **5**, but afforded only **3** in good yield. The conversion of **2** to **6** in acetonitrile in quantitative yield was also possible at 80 °C. In THF, **4** also became undetectable after 24 h, and the produced **6** then gradually decomposed. The reaction of **2** in benzene or chloroform at this temperature did not give **6**, but resulted in a complex mixture after 24 h. The retro-Diels-Alder reactions during the 3,6-additions should be very slow, because **5** and **6** were completely recovered in the dilute solution (4.6 mM) of both acetonitrile and chloroform at 80 °C after 48 h.



Scheme 3.

The reaction of the tropilidenes and TCNE can be concluded as shown in Scheme 3. The 1,4-addition was the kinetically predominant process in both polar and non-polar solvents, and was reversible at the same temperature as the addition. It should be noted that the diastereomer of the 1,4-adduct was not detected even at the higher temperature (80 °C in chloroform for 48 h), and thus, the diastereoface differentiation of the 1,4-addition should be very high. The 3,6-addition was a slower process than the 1,4-addition, and occurred only in a polar solvent. Since the 3,6-addition was irreversible, the adducts could be obtained as the sole product at the higher temperature (80 °C in acetonitrile). The solvent effect on the 3,6-addition rate can be explained by the charge transfer character[6] of the collision complex of the tropilidene and TCNE (**A**). Complex **A** was stabilized in a polar solvent and the radical distribution at the 2-, 4- and 6-positions in **A** made it possible to proceed with the 3,6-addition.

In this communication, we determined the regiocontrol mechanism for the Diels-Alder addition of 1-trienol ether and TCNE, and found the conditions to selectively obtain both regioisomers. Since the obtained bicyclo[3.2.2]nonanes were optically pure in both regioisomers, they are considered to be useful chiral synthons.

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