High Pressure Organic Chemistry. III.[1)] Diels-Alder Reaction of Thiophene with Maleic Anhydride

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The Diels-Alder reaction of thiophene with maleic anhydride has been investigated under conditions of very high pressure. The Diels-Alder adduct was obtained in dichloromethane at 100 °C and 15 kbar; above a pressure of 15 kbar the reaction was highly accelerated. From the spectral data and chemical evidence it has been suggested that the adduct has the *exo*-configuration. The reactions in various solvents and with other dienophiles have also been examined.

Recently much attention has been focused on the application of high pressure techniques in the field of synthetic organic chemistry.[2)] In general, the pressure dependence of the rate constant on the reaction may be written as follows:

$$\frac{\delta \ln k}{\delta P} = -\frac{\Delta V^{\neq}}{RT}$$

where $\Delta V^{\neq}$, the activation volume, represents the difference in volume between the reactants and the transition state. If $\Delta V^{\neq}$ is negative, *i.e.*, the volume of the transition state is smaller than the volume of the reactants, the rate k will increase with increasing pressure. The activation volume for a number of organic reactions has been determined and [4+2] cycloaddition reactions, typically the Diels-Alder reaction, are known to have a relatively large activation volume (-25—-50 cm^3/mol)[2,3)] being the most favorable case at high pressure.

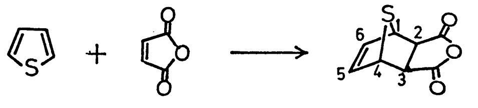
In line with this theory the [4+2] cycloaddition reactions at high pressures have been investigated and it has been shown that the use of high pressure (10—40 kbar) is a very valuable tool for synthetic organic chemistry.[4—6)]

In a preliminary paper it was reported that the Diels-Alder reaction of thiophene with maleic anhydride, which had never undergone reaction under the usual conditions, had effectively proceeded at very high pressures.[1b)] This paper will report a more detailed investigation.

Results and Discussion

Cycloaddition between Thiophene and Maleic Anhydride. It is well documented that thiophene itself does not undergo the Diels-Alder reaction.[7)] Recently, however, there have been reports that some thiophene derivatives do combine with extremely reactive dienophiles such as dicyanoacetylene and dimethyl acetylenedicarboxylate.[8)] The only recorded thiophene derivatives which are able to react with maleic anhydride in a Diels-Alder manner are thiophenc 1,1-dioxide[9)] and 2,5-dimethoxythiophene.[10)]

The authors anticipated that thiophene would react with maleic anhydride if the reaction were performed under high pressure conditions overcoming the high aromatic character.



1 2 3

Initially, the reaction of thiophene with maleic anhydride in dichloromethane at 15 kbar and room temperature was attempted considering the thermal lability of the cycloadduct or the enhancement of the reverse reaction. After 3 days, however, reaction had not occurred and reaction without solvent or with a Lewis acid catalyst (*e.g.* $MgCl_2$) was also fruitless. This demonstrates a striking absence of diene character in thiophene and contrasts remarkably with furan.[4b)] The reaction was examined at higher temperatures at 15 kbar for 3 h in dichloromethane when the reaction did occur (Table 1). Inspection of Table 1 reveals that the most favorable results are obtained at 100 °C. Thus, from the reaction mixture a highly crystalline compound **3**,[11)] mp 159.5—161.5 °C, of molecular formula $C_8H_6O_3S$ (MS, M$^+$ 182) was obtained in yields of 37—47% after recrystallization from ether or chloroform. It is suggested that **3** has an *exo*-configuration from the spectral data and chemical evidence as follows. In the ^{1}H NMR spectra (Table 2), the C_2 and C_3 protons appear at δ 3.63 as a doublet (J=1 Hz) and when the dihedral angle between the protons at C_1 and C_2 (C_3 and C_4) is considered the indication is that **3** has an *exo*-configuration. This assignment is in good agreement with the data of the adducts between furan and maleic anhydride, showing that the *exo*-adduct **6** resembles **3** rather than the *endo*-adduct.[12)]

TABLE 1. TEMPERATURE DEPENDENCE OF THE YIELD[a)] IN THE ADDUCT 3 BETWEEN THIOPHENE AND MALEIC ANHYDRIDE

Room temp	40 °C	80 °C	100 °C	120 °C	150 °C
No reaction	No reaction	8%	37—47%	18%	Decomposition

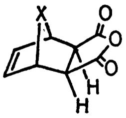
a) The yield based on the isolated materials.

Further supporting evidence has been obtained as follows. Adduct **3** was subjected to methanolysis to give the monomethyl ester **4**. As expected **4** did not undergo

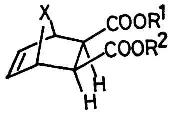
Table 2. ^{1}H NMR spectral data (δ ppm)

Compd	C_1,C_4-H	C_2,C_3-H	C_5,C_6-H		
3[a)]	4.59 (2H, m)	3.63 (2H, d, J=1 Hz)	6.61 (2H, dd, J=2, 3 Hz)		
4[b)]	4.29 (2H, m)	3.15 (1H, d, J=9 Hz)	6.51 (2H, dd, J=2, 2.5 Hz)	-COOMe	3.63
		3.24 (1H, d, J=9 Hz)		-COOH	8.81
5[c)]	4.29 (2H, dd, J=2, 2.5 Hz)	3.16 (2H, s)	6.48 (2H, dd, J=2, 2.5 Hz)	-COOMe	3.68
6[a)]	5.34 (2H, m)	3.26 (2H, s)	6.56 (2H, m)		
	5.34[d)]	3.25[d)]	6.53[d)]		
8[c)]	5.12 (2H, m)	3.43 (2H, dd, J=2, 3 Hz)	6.54 (2H, d, J=1 Hz)	-COOMe	3.63
	5.10[e)]	3.41[e)]	6.52[e)]		3.62[e)]

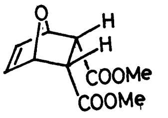
a) $CDCl_3$–DMSO-d_6 (1: 1), b) $CDCl_3$–Acetone-d_6 (2: 1). c) $CDCl_3$. d) Ref. 12. e) Ref. 13.



X=S **3**
X=O **6**



X=S, R^1=Me, R^2=H **4**
X=S, R^1=R^2=Me **5**
X=O, R^1=R^2=H **7**



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iodolactonization (I_2–KI).[13] The corresponding dimethyl ester **5**, which is formally regarded as the Diels-Alder product of thiophene with dimethyl maleate, was prepared from **4** by careful methylation with diazomethane.[14] In the ^{1}H NMR spectra of **5** (Table 2) the C_2 and C_3 protons appeared at δ 3.16 as a singlet. In the ^{1}H NMR spectra of the *exo*-adduct **7** between furan and maleic acid the C_2 and C_3 protons were reported to appear at δ 2.61 as a singlet.[13,15] Moreover, in the case of the *endo*-adduct **8** between furan and dimethyl maleate, which was prepared under similar conditions as reported by Dauben and Krabbenhoft,[4b] the C_2 and C_3 protons appear at δ 3.43 as a doublet of doublets (J=2, 3 Hz)[16] and contrasts remarkably with these results.

The exclusive formation of the *exo*-adduct **3** in the Diels-Alder reaction of thiophene with maleic anhydride is predictable on the basis of the preferential production of the thermodynamically stable adduct at higher temperature.[17] However, it would be premature to say whether **3** represents the kinetic product.

Since the reaction of thiophene with maleic anhydride has been proven efficient in giving an adduct, an investigation of the reactions between thiophene and other dienophiles has been undertaken. However all attempted reactions of thiophene with dimethyl maleate, dimethyl fumarate, methyl acrylate, acrylonitrile, or acrylaldehyde under the same conditions (100 °C, 15 kbar, 3 h, the concentrations of the reactants were 3 M in CH_2Cl_2) were unsuccessful and no adduct formation was observed. At higher temperatures the reaction was too vigorous to give the adduct, thus dimethyl maleate isomerized completely to dimethyl fumarate. Acrylonitrile and acrylaldehyde readily polymerized even in the presence of an inhibitor such as hydroquinone.

Thus sole criterion of high pressure is insufficient to bring about the reaction of thiophene with dienophiles less reactive than maleic anhydride.

Effect of Solvent. It is usually recognized that the conventional Diels-Alder reaction is little affected by the solvent.[17] However, under high pressure conditions the choice of solvent becomes important and there have been various studies on the kinetic solvent effects in Diels-Alder reactions.[3,18] Unfortunately these studies have been limited to relatively low pressures (*ca.* 2 kbar max.), and little information is available in the pressure range from 10 to 20 kbar. Consequently an investigation of the solvent effect in the Diels-Alder reaction of thiophene with maleic anhydride has been undertaken and the results are summarized in Table 3. In a previous paper the low yield in benzene (Run 11) was assumed to be due to the freezing of the reaction medium at 15 kbar.[1b] According to the Simon equation the freezing temperature of substances is dependent on pressure.[19] The estimated freezing point of benzene at 4 kbar is *ca.* 100 °C, so that freezing of the reaction medium appears to be probable. The interpretation based on freezing temperature of solvent is plausible in the cases of dichloromethane, chloroform, and carbon tetrachloride (Runs

Table 3. Solvent dependence of the yield in the adduct **3** (100 °C, 3 h)

Run	Solvent	Pressure(kbar)	Yield(%)[a)]	
1	CH_2Cl_2	10	6	22 kbar[b)]
2		15	43	
3		20	47	
4	$CHCl_3$	10	3	12 kbar[b)]
5		15	42	
6		20	42	
7	CCl_4	10	No reaction	4 kbar[b)]
8		15	12	
9		20	21	
10	$CHCl_2CHCl_2$	15	47	
11	C_6H_6	15	7	
12	$C_6H_5CH_3$	15	Trace[c)]	
13	C_6H_5Cl	15	20	
14	C_6H_5Br	15	5	
15	C_6H_5CN	15	29	
16	$C_6H_5COCH_3$	15	Trace[c),d)]	
17	CH_3CN	15	39	
18	AcOEt	15	17	
19	Et_2O	15	Trace[c)]	
20	CH_3COCH_3	15	No reaction[d)]	

a) The values are the average of two or more runs. b) The estimated freezing point is 100 °C at this pressure. See Ref. 19. c) Only trace amounts of adduct were detected by TLC. d) A considerable amount of polymeric substances was obtained.

1—9). In this connection it can be seen that *at pressures above 15 kbar the reaction is highly accelerated !* The fact that at 20 kbar, a respectable increase of product yield was observed in carbon tetrachloride (Run 9) leads to the assumption that the reaction proceeds to some extent in the frozen state,[20)] although further experiments were necessary. In addition the results in Table 3 suggest that the adduct formation should increase in aromatic solvents having an electron withdrawing substituent (Runs 13 and 15) rather than ones having an electron donating substituent (Runs 11 and 12). This may be explained in terms of the specific solute-solvent interactions such as the charge transfer complex formation between maleic anhydride and benzene or toluene which would become significant at high pressure.[21),22)]

The very low yield of product in ether, acetone, and acetophenone can not be explained.

Experimental

Apparatus. Figure 1 shows a schematic version of the high pressure apparatus used which consists essentially of a press frame, the upper and bottom drive cylinders, an induction heater and a sample cylinder. The sample cylinder, shown in Fig. 2, has been fabricated from a SUS-27 multiplex cylinder subject to autofrettage and a hardened S-3 tool steel cylinder or sintered tungsten carbide cylinder (80 mm long and 50 mm diameter). The piston made from hardened S-3 tool steel or sintered tungsten carbide has a diameter of 12 mm. The reaction vessel has been made from Teflon which is a good container for most organic substrates and pressure transmitter at elevated temperatures (below 300 °C). Talc and stainless steel disks have been used to prevent leakage from the Teflon vessel. The pressure generated in the reaction vessel can not be directly read on the pressure gauge and so has been calibrated using the change in volume of $AgNO_3$ (9.8 kbar) and KBr (17.9 kbar) and the resistivity of Bi I–II (25.3 kbar) at room temperature. The leakage from the Teflon vessel containing the reactants and solvent has been checked and appears to be negligible.

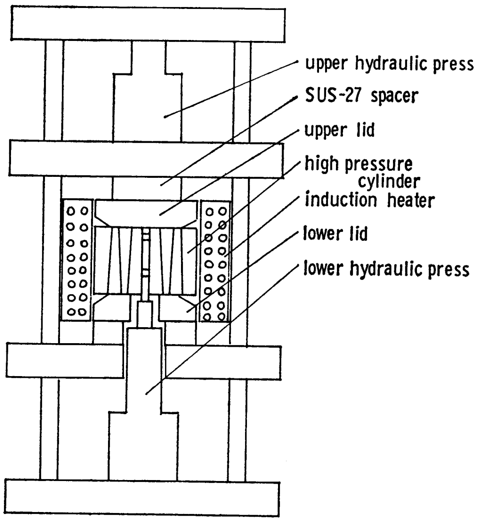

Fig. 1. Schematic version of high pressure apparatus.

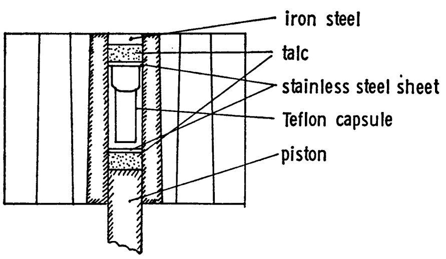

Fig. 2. Detailed schematic version of the sample cylinder.

The procedure for a high pressure reaction is as follows. The reaction vessel (*ca.* 0.85 ml capacity) is filled completely with the reactants dissolved in an appropriate solvent and covered with Teflon lid. The reaction vessel and the piston are forced into the bore of a sample cylinder by synchronously raising the upper and bottom drive cylinders hydraulically until the desired pressure is attained. To conduct a reaction at elevated temperatures, the sample cylinder system is inserted into the induction heater and heated to the desired temperature measured by an alumel-chromel thermocouple. After the experiment the sample cylinder is cooled to room temperature by a fan and the pressure released. A representative temperature-pressure diagram is shown in Fig. 3 in the experiment at 150 °C and 15 kbar for 3.5 h.

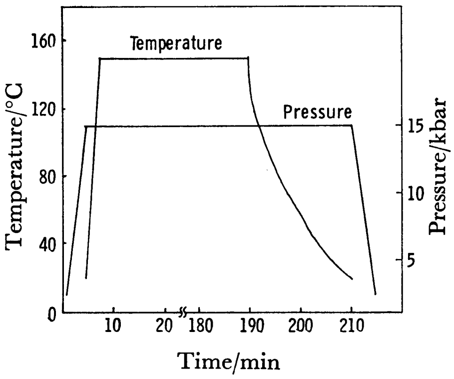

Fig. 3. Representative temperature-pressure diagram at 150 °C and 15 kbar for 3.5 h.

All high pressure reactions were performed at a concentration of 3 M of the reactants in the dried solvents.

General. All melting points are uncorrected. ^1H NMR spectra were obtained on a JEOL-MH-100 spectrometer using TMS as the internal standard. ^{13}C NMR spectra were obtained at 25.05 MHz on a JEOL-FX-100 spectrometer. The IR spectra were measured with a JASCO infrared spectrophotometer Model IRA-1 and the mass spectra on a Hitachi Model M-52 spectrometer.

TLC was conducted using Merck's precoated Kieselgel 60 (5721) and for column chromatography, Wakogel C-200 (74—149 μ) was employed.

Diels-Alder Reaction of Thiophene with Maleic Anhydride. The general procedure is as follows. A CH_2Cl_2 solution (1 ml) of thiophene (3 mmol) and maleic anhydride (3 mmol) was injected into the Teflon reaction vessel. The reaction vessel was heated to 100 °C at 15 kbar for 3 h. After cooling of the reaction mixture and the release of pressure, the solvent was evaporated and the product recrystallized from ether or chloroform to give pure **3** in 37—47% yield: mp 159.5—161.5 °C (from $CHCl_3$), 159—160 °C (from Et_2O); IR (Nujol) 1850, 1795, 1085, 943, and 920 cm^{-1}; ^1H NMR spectrum (Table 2); ^{13}C NMR spectrum (Table 4); MS (20 eV), *m/e* (rel intensity),

Table 4. ^{13}C NMR spectral data of **3** and **5** (in $CDCl_3$)[a]

	3	**5**
C-1, C-4	54.2(d)	54.0(d)
C-2, C-3	52.0(d)	50.2(d)
C-5, C-6	139.8(d)	139.8(d)
C=O	169.2(s)	171.8(s)
CH_3		52.2(q)

a) Chemical shifts are expressed in ppm downfield from the ^{13}C NMR of TMS.

182 (36, M^+), 110 (27), 84 (44), 78 (100), 66 (25), 45 (12).

Found: C, 52.80; H, 3.32%. Calcd for $C_8H_6O_3S$: C, 52.74; H, 3.32%.

Methanolysis of Adduct 3. Two ml of an absolute MeOH solution of adduct **3** (200 mg) was stirred at 40 °C for 5 days under a N_2 atmosphere.[23] After removal of excess MeOH the crude product, which still contained a small amount of starting anhydride (R_f 0.61, 4: 1 C_6H_6–AcOEt) on TLC, was obtained as a viscous oil. A pure sample of the monomethyl ester **4** was obtained in crystalline form after column chromatography on silica gel: mp 123—124 °C (from Et_2O); IR (Nujol) 3200—2600, 1740, 1710, 1245, 1210, and 1185 cm^{-1}; ^1H NMR spectrum (Table 2); MS (30 eV), *m/e*, 214 (M^+).

Found: C, 50.42; H, 4.66%. Calcd for $C_9H_{10}O_4S$: C, 50.46; H, 4.70%.

Methylation of the Monomethyl Ester 4. The monomethyl ester **4** (123 mg) was treated conventionally with a small excess of diazomethane. After the renewed addition of diazomethane succeeded in producing a pale yellow coloration (*ca.* 1 min on standing at 0 °C), the excess of reagent was instantly decomposed with the minimum amount of AcOH and the solution evaporated *in vacuo* (below 45 °C).[14] The crude product with an unpleasant odor was purified by column chromatography on silica gel (eluted with $CHCl_3$) and 100 mg of dimethyl ester **5** was obtained as a colorless and odorless oil which crystallized on standing in the refrigerator: mp 73—73.5 °C (from Et_2O-petroleum ether); IR (Nujol) 1745, 1585, 1335, 1225, 1215, 1160, and 1035 cm^{-1}; ^1H NMR spectrum (Table 2); ^{13}C NMR spectrum (Table 4); MS (70 eV), *m/e*, 228 (M^+).

Found: C, 52.67; H, 5.28%. Calcd for $C_{10}H_{12}O_4S$: C, 52.62; H, 5.30%.

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14) With an excess of reagent and/or a long time the 1,3-dipolar cycloaddition to the C–C_6 double bond easily occurred.

15) The hydrolysis of adduct **3** failed to give the dicarboxylic acid derivative. Adduct **3** was slightly hydrolyzed in refluxing water and with this treatment the reaction product became contaminated with a considerable amount of unidentified impurities. See also Ref. 23.

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23) A significant amount of the starting material (*ca.* 20%) remained unchanged on ^{1}H NMR even after refluxing for 2 days under a N_2 atmosphere. In this case the reaction mixture was colored yellow and difficult to purify.