High Pressure Organic Chemistry. V.[1] Diels-Alder Reactions of Furan with Acrylic and Maleic Esters

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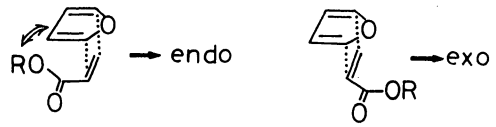
A series of Diels-Alder reactions of furan with acrylic and maleic esters has been investigated under conditions of high pressure. The approximate *endo/exo* ratios of the adducts with acrylic and maleic esters were 6 : 4 and 8 : 2 respectively. The observed isomer distributions are ascribed to the kinetic control.

In a previous paper we reported the successful Diels-Alder reaction of thiophene with maleic anhydride at 15 kbar and 100 °C, which afforded stereoselectively the *exo*-adduct.[2] In the pioneering work of Dauben and Krabbenhoft on the cycloaddition reactions of furan, it has been reported that both *endo* and *exo* isomers are obtained in approximate ratios of 1 : 1 with acrylic esters and only the *endo* isomer with dimethyl maleate.[3]

As a continuation of our investigation in this area, we were particularly interested in the stereochemical outcome of the Diels-Alder reaction at very high pressure.

Generally, steric factors play a significant role in determining the reactivity of dienophiles for high pressure reactions.[3,4] We presumed that in the Diels-Alder reaction of furan with acrylic and maleic esters, the *endo/exo* ratio would change with the variation o alkoxyl in the ester group, since the volume of the transition state for the *endo* addition is expected to be increased by crowding of R function, as shown in the Scheme 1 for the reaction of the acrylic esters. Based on this assumption, we have examined the Diels-Alder reaction of furan with several acrylic and maleic esters at very high pressure.



Scheme 1.

TABLE 1. DIELS-ALDER REACTION OF FURAN WITH MALEIC ESTERS

R	Temp °C	Time h	*P* kbar	Yield %[a]	*endo/exo* ratio[b]
	27	8	20	94	81 : 19
	27	8	15	90	81 : 19
a Me	27	8	10	60	82 : 18
	27	16	15	95	82 : 18
	16	6	15	46	82 : 18
	27	8	20	88	80 : 20
	27	8	15	87	81 : 19
b Et	27	8	10	58	81 : 19
	16	6	15	40	80 : 20
	27	8	20	96	84 : 16
	27	8	15	88	83 : 17
c *n*-Bu	27	8	10	43	83 : 17
	16	6	15	37	83 : 17

a) Crude yields determined from ^{1}H NMR integrals. The values are the average of three or more runs. b) The ratios were determined from ^{1}H NMR integrals.

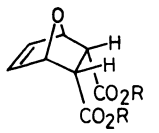
Results and Discussion

The results are summarized in Tables 1 and 2. The

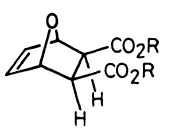
TABLE 2. DIELS-ALDER REACTION OF FURAN WITH ACRYLIC ESTERS (27 °C, 4 h)

	R	*P* kbar	Yield %[a]	*endo/exo* ratio[b]
		20	83	
a	H[c,d]	15	63	6 : 4
		10	43	
		20	79	
b	Me[d]	15	95[e]	6 : 4
		15	62	
		10	20	
		20	82	
c	Et[d]	15	58	6 : 4
		10	23	
		20	65	
d	*n*-Bu	15	55	6 : 4
		10	17	
e	CH_2CCl_3	15	75	6 : 4
f	*i*-Bu	15	55	6 : 4
g	C_6H_5	15	40	6 : 4

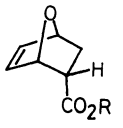
a) Crude yields by ^{1}H NMR except as noted. The values are the average of three or more runs. b) The ratios were determined from ^{1}H NMR integrals. c) Isolated after esterification with diazomethane. d) Isolated after evaporation. e) 60 °C, 6 h.



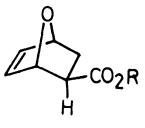
1a R=Me
b R=Et
c R=n-Bu



2a R=Me
b R=Et
c R=n-Bu



3a R=H
b R=Me
c R=Et
d R=n-Bu



4a R=H
b R=Me
c R=Et
d R=n-Bu

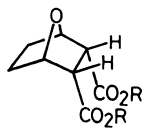
Table 3. Spectral data of Diels-Alder adducts and their dihydro derivatives

Compound	IR ν_{co}/cm^{-1}	NMR δ C_1,C_4–H	C_2,C_3–H	C_5,C_6–H	Others
1a	1740	4.97 (2H, m)	3.27 (2H, dd, J=2, 3 Hz)	6.42 (2H, br s)	3.55 (6H, s)
2a[a]	1740[b]	5.24 (2H, br s)	2.80 (2H, s)	6.47 (2H, br s)	3.68 (6H, s)
1b	1735	4.95 (2H, m)	3.24 (2H, br d, J=2 Hz)	6.39 (2H, br s)	3.98 (4H, q, J=6 Hz) 1.20 (6H, t, J=6 Hz)
1c	1740	4.95 (2H, m)	3.26 (2H, dd, J=2, 3 Hz)	6.40 (2H, br s)	3.94 (4H, t, J=6 Hz) 1.7—1.1 (8H) 0.95 (6H, t, J=6 Hz)
5a	1735	4.57 (2H, m)	3.08 (2H, m)	2.1—1.5 (4H, m)	3.60 (6H, s)
5b	1735	4.57 (2H, m)	3.06 (2H, m)	2.1—1.5 (4H, m)	4.06 (4H, q, J=7 Hz) 1.23 (6H, t, J=7 Hz)
5c	1735	4.55 (2H, m)	3.06 (2H, m)	2.1—1.1	3.97 (4H, t, J=6 Hz) 2.1—1.1 (12H) 0.94 (6H, t, J=6.5 Hz)
3b	1735	5.01 (1H, br d, J=5 Hz) 4.89(1H, br d, J=5 Hz)	2.96 (1H, quintet, J=4.5 Hz) 2.00 (1H, ddd, J=11.5, 10, 5 Hz) 1.50 (1H, dd, J=11.5, 4 Hz)	6.35 (1H, dd, J=6, 1.5 Hz) 6.13 (1H, dd, J=6, 1.5 Hz)	3.56 (3H, s)
4b	1735	5.06 (1H, br s) 4.94 (1H, d, J=4 Hz)	2.20 (1H, dd, J=8, 4 Hz) 2.09 (1H, dt, J=11, 4 Hz) 1.43 (1H, dd, J=11, 8 Hz)	6.30 (2H, br s)	3.64 (3H, s)
3c	1735	5.02 (1H, br d, J=5 Hz) 4.89 (1H, dd, J=5, 2 Hz)	2.96 (1H, quintet, J=4.5 Hz) 1.99 (1H, ddd, J=11.5, 9.5, 5 Hz) 1.51 (1H, dd, J=11.5, 4 Hz)	6.35 (1H, dd, J=6, 2 Hz) 6.13 (1H, br d, J=6 Hz)	4.01 (2H, q, J=7 Hz) 1.22 (3H, t, J=7 Hz)
4c	1735	5.02 (1H, br s) 4.91 (1H, d, J=4 Hz)	2.27 (1H, dd, J=8, 4 Hz) 2.12 (1H, dt, J=10.5, 4 Hz) 1.41 (1H, dd, J=10.5, 8 Hz)	6.26 (2H, br s)	4.10 (2H, q, J=7 Hz) 1.28 (3H, t, J=7 Hz)
3d	1735	4.97 (1H, d J=5 Hz) 4.85 (1H, dd, J=5, 2 Hz)	2.93 (1H, quintet, J=4.5 Hz) 1.96 (1H, ddd, J=11.5, 10, 5 Hz)	6.31 (1H, dd, J=6, 2 Hz) 6.08 (1H, dd, J=6, 1.5 Hz)	3.93 (2H, t, J=6 Hz) 1.7—1.2 (5H) 0.94 (3H, t, J=7 Hz)
4d	1735	5.04 (1H, br s) 4.93 (1H, d, J=4 Hz)	2.28 (1H, dd, J=8, 4 Hz) 2.10 (1H, dt, J=11, 4 Hz)	6.30 (2H, br s)	4.06(2H, t, J=6 Hz) 1.8—1.2 (5H) 0.96 (3H, t, J=7 Hz)
6b	1735	4.5 (2H, br m)	2.90 (1H, br q, J=7 Hz) 1.9—1.4	1.9—1.4 (6H)	3.57 (3H, s)
7b	1735	4.69 (1H, m) 4.53 (1H, br dd, J=5, 3 Hz)	2.46 (1H, dd, J=10, 5 Hz) 2.2—1.3	2.2—1.3 (6H)	3.63 (3H, s)

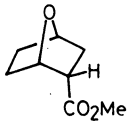
a) Measured in $CDCl_3$. b) Measured in $CHCl_3$.

isomer distributions of the reactions were analyzed by means of NMR (Table 3).[5]

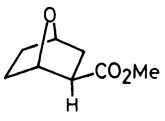
The observed *endo*/*exo* ratios of the adducts with acrylic and maleic esters were approximately 6 : 4 and 8 : 2 respectively. The *endo*/*exo* ratios were not substantially affected by the change of pressure up to 20 kbar[6] nor by the variation of the alkoxyl in the ester group in the reactions with either acrylic or maleic esters.[7] To examine the possibility of equilibrium between the stereoisomers, the isolated *endo* and *exo* products with methyl acrylate and dimethyl maleate were each kept at 15 kbar for 15 h. However, no isomerization was observed by NMR measurements. These results are in accordance with the restricted retro-Diels-Alder reaction under high pressure conditions.[8] Therefore, the obtained *endo*/*exo* isomer distributions would be the results of kinetic control rather than the type of kinetic and thermodynamic pattern mentioned for the furan-



5a R = Me
b R = Et
c R = n-Butyl



6b



7b

Table 4. Relative rates in the Diels-Alder reactions of furan with maleic and acrylic esters at 15 kbar and 27 °C in dichloromethane

No.	Dienophile		Relative rate[a]
1		R=Me	2.76
2		Et	2.06
3		*n*-Bu	2.25
4		R=H	1.05
5		Me	1.00
6		Et	0.85
7		*n*-Bu	0.75
8		CH_2CCl_3	1.84
9		*i*-Bu	0.75
10		C_6H_5	0.41

a) Rate relative to that of reaction 5 ($k=3.77\times10^{-5}$ l mol^{-1} s^{-1}). The values are the average of three or more runs.

maleic anhydride reaction.[9] The high *endo* selectivity of maleic esters is probably due to large secondary orbital interactions.[10]

The steric effects of an alkoxyl group on the reactivity of these dienophiles were explored by a kinetic approach. All the reactions were clearly second-order at 15 kbar. The rate constant (k_2) for the reaction of furan with methyl acrylate was 3.77×10^{-5} l mol^{-1} s^{-1} at 27 °C. The relative rates are shown in Table 4. These show that the reactivity of both acrylic and maleic esters was slightly decreased by increasing the bulkiness of the alkoxyl in the ester group. The most notable decrease is in the reaction with phenyl acrylate (No. 10). The steric factors, such as expected from "rule of six,"[11] might affect the reactivity of these dienophiles. For the usual Diels-Alder reactions, *e.g.*, the reactions of cyclopentadiene with acrylic esters at atmospheric pressure, no such effects due to the variation of an alkoxyl group were observed.[12] Our findings suggest the steric effects must be more serious for high pressure reactions.

Experimental

General Methods. All boiling points and melting points are uncorrected. ^{1}H NMR spectra were obtained on a JEOL-MH-100 spectrometer using solutions in carbon tetrachloride with TMS as the internal standard; the IR spectra were recorded as films on a JASCO IRA-1, unless otherwise stated.

Table 5. Physical constants of Diels-Alder adducts and their dihydro derivatives

Compound	Mp θ_m/°C or Bp θ_b/°C(mmHg[a])	Found (Calcd) (%) C	H
2a	120—121.5	56.70 (56.60	5.75 5.70)
5a	135—140 (14)	55.75 (56.07	6.55 6.59)
5b	170—175 (15)	59.27 (59.49	7.46 7.49)
5c	148—15 (21)	64.20 (64.40	8.68 8.78)
6b	130 (23)	61.55 (61.52	7.69 7.75)
7b	130 (18)	61.64 (61.52	7.68 7.75)

a) Bath temperature. 1 mmHg=133.322 Pa.

All high pressure reactions were performed at a concentration of 3 M† of the reactants in dry dichloromethane. For a description of our high pressure equipment and of the general procedure for high pressure reactions, see Ref. 2.

Since the direct distillation of oily adducts gave a complete decomposition,[3] the elemental analyses were performed after hydrogenation and are expressed as their dihydro derivatives.

Diels-Alder Reaction of Furan with Maleic Esters. The general procedure is as follows. A CH_2Cl_2 solution (1 ml) of furan (3 mmol) and dimethyl maleate (3 mmol) was subjected to 15 kbar hydrostatic pressure for 8 h at 27 °C. After the run, the solution was concentrated to a clear, colorless liquid whose NMR spectrum indicated that the cycloadduct was obtained in a 90% yield and in an *endo*/*exo* ratio of 8 : 2. By chromatographic separation on neutral alumina (elution with hexane–ether), a pure *endo* isomer was obtained as a colorless liquid.[13] An analytical sample was obtained as a colorless liquid after hydrogenation in AcOEt on 10% Pd/C and bulb-to-bulb distillation.[3]

For a large scale preparation of the *exo* isomer, a mixture of 1 g (7 mmol) of dimethyl maleate and 0.48 g (7 mmol) of furan was subjected to 15 kbar pressure at 60 °C for 16 h *without solvent*.[14] The crude product was purified by column chromatography on neutral alumina using hexane–dichloromethane (1 : 1) as the eluent to give the *endo*-adduct **1a** (232 mg; 15.7%). Further elution with dichloromethane gave the *exo*-adduct **2a** (345 mg; 23.4%), which was recrystallized from ether or hexane–dichloromethane.

The spectral data and physical constants are given in Tables 3 and 5.

Diels-Alder Reaction of Furan with Acrylic Esters. The reaction of furan with methyl acrylate was performed as described above. A pure sample of each *endo* and *exo* isomer was obtained after column chromatography on neutral alumina (with hexane–ether, *endo* isomer was obtained from earlier fractions).[13] Analytical samples **6b** and **7b** were obtained as in the case of dimethyl maleate after hydrogenation and distillation.[3] The spectral data and physical constants are given in Tables 3 and 5.

Equilibrium Experiments. A pure sample of each *endo* and *exo*-adduct with methyl acrylate or dimethyl maleate was kept at 15 kbar and 27 °C for 15 h in dichloromethane (*ca.* 1.5 M solution). After the treatments all equilibrium mixtures were checked by NMR.

† 1 M = 1 mol dm^{-3}.

Kinetic Experiments. Kinetic measurements were made using a piston-cylinder type high pressure apparatus[2] in teh same manner as was used for the other high pressure reactions. Each kinetic solution of a diene and a dienophile in dichloromethane was transferred into a Teflon cell (0.8 cm^3) and subjected to pressure. The amount ratio of dienophile and adduct were measured by NMR at appropriate time intervals for 16 h.

Each reaction studied was clearly second-order and gave a mixture of *end-exo* isomeric products. The second-order rate constants were calculated by the usual second-order rate expression.

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References

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5) For the literature of NMR data, see a) W. L. Nelson and D. R. Allen, *J. Heterocycl. Chem.*, **9**, 561 (1972); b) T. A. Eggelte, H. de Koning, and H. O. Huisman, *Tetrahedron*, **29**, 2491 (1973); c) S. Iwase, T. Maeda, S. Hamanaka, and M. Ogawa, *Nippon Kagaku Kaishi*, **1975**, 1934. The isomer distributions could be also determined by GLC (OV-101) of hydrogenated samples.

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7) The temperature effect was briefly examined and the *endo/exo* ratio of the adduct with methyl acrylate was 6 : 4 at 60 °C for 6 h (96% yield).

8) *Cf.* S. D. Hamann, "Physico-Chemical Effects of Pressure," Butterworths, London (1957), Chap. 9; G. Jenner, *Angew. Chem.*, **87**, 186 (1975); J. Osugi *et al.*, *Kagaku Sosetsu*, **22**, Chap. 7 (1979).

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10) *Cf.* K. Seguchi, A. Sera, Y. Otsuki, and K. Maruyama, *Bull. Chem. Soc. Jpn.*, **48**, 3641 (1975); J. Rimmelin, G. Jenner, and P. Rimmelin, *Bull. Soc. Chim. Fr.*, **1978**, II, 461; T. Asano and W. J. le Noble, *Chem. Rev.*, **78**, 407 (1978).

11) "Steric Effects in Organic Chemistry," ed by M. S. Newman, Wiley, New York (1956), Chap. 4.

12) J. M. Mellor and C. F. Webb, *J. Chem. Soc., Perkin Trans. 2*, **1974**, 17.

13) Column or preparative thin layer chromatography on silica gel resulted in a considerable decomposition of the products. Both the *endo* and the *exo* products from maleic or acrylic esters were simply separated by using alumina columns. For the use of silica gel–$AgNO_3$, see Ref. 5a.

14) Considerable amounts of unidentified by-products were also obtained, as well as *ca.* 20% of recovered dimethyl maleate.