Inter- and Intramolecular Hetero Diels-Alder Reactions, Part XXVI[1)]

Diastereoselectivity and Kinetics of Intermolecular Hetero Diels-Alder Reactions under High Pressure. A Significant Pressure-Induced Increase in Stereoselectivity

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Received January 12, 1989

Key Words: Diastereoselectivity / Hetero Diels-Alder reactions / Enamino ketones / High-pressure kinetics / Pyrans, dihydro-

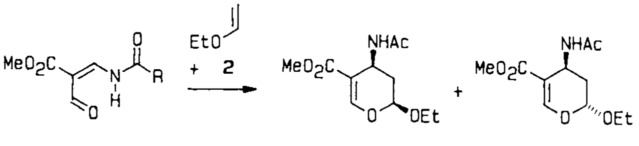
The Hetero Diels-Alder reaction of the enamino ketones 5a – d and ethyl vinyl ether (2) to give the dihydropyrans 6a – d and 7a – d is studied in dichloromethane and in heptane/isodurene under high pressure up to 7 kbar at temperatures between 0.5 and 130°C. The kinetics is measured by on-line FT-IR spectroscopy. The cycloaddition shows a remarkable pressure-dependent increase of diastereoselectivity in favour of the *cis* adducts 6a – c with the largest effect found for the reaction of 5a and the smallest for 5c. The pressure-averaged overall activation volumes $\Delta V^{\neq}$ in dichloromethane are determined to be between $-(23.4 \pm 1.0)$ and $-(24.2 \pm 1.0)$ cm^3/mol. The $\Delta\Delta V^{\neq}$ values for the cycloaddition of 5a, 5b, and 5c are $-(5.9 \pm 0.5)$, $-(3.9 \pm 0.1)$, and $-(2.4 \pm 0.2)$ cm^3/mol, respectively, and the $\Delta\Delta H^{\neq}$ values are $-(8.1 \pm 1.7)$, $-(8.7 \pm 2.7)$, and $-(10.0 \pm 0.9$ kJ/mol, respectively. Because of the favourable $\Delta\Delta V^{\neq}$ and $\Delta\Delta H^{\neq}$, the selectivity of the reaction of 5a to give 6a/7a can be increased from 1.67:1.00 at 90°C and 1 bar to 13.6:1.0 at 0.5°C and 6 kbar. This example shows that a significant and synthetic useful increase of diastereoselectivity in chemical reactions is possible by applying high pressure.

Diastereoselektivität und Kinetik intermolekularer Hetero-Diels-Alder-Reaktionen unter hohem Druck. Eine signifikante druckinduzierte Erhöhung der Stereoselektivität

Die Hetero-Diels-Alder-Reaktion der Enaminoketone **5a – d** mit Ethylvinylether (**2**) in Dichlormethan- und Heptan/Isodurol-Lösung zu den Dihydropyranen **6a – d** and **7a – d** unter hohem Druck bis 7 kbar und 0.5 bis 130°C wird beschrieben. Die Kinetik wurde hierbei durch quantitative FT-IR-Spektroskopie bestimmt. Die Cycloaddition zeigt eine erhebliche druckabhängige Erhöhung der Diastereoselektivität zugunsten der *cis*-Diastereomeren **6a – c** mit dem größten Effekt für die Reaktion von **5a** und dem geringsten für **5c**. Die druckgemittelten Brutto-Aktivierungsvolumina $\Delta V^{\neq}$ liegen zwischen $-(23.4 \pm 1.0)$ und $-(24.2 \pm 1.0)$ cm^3/mol, die $\Delta\Delta V^{\neq}$-Werte für **5a**, **5b** und **5c** wurden zu $-(5.9 \pm 0.5)$, $-(3.9 \pm 0.1)$ bzw. $-(2.4 \pm 0.2)$ cm^3/mol und die $\Delta\Delta H^{\neq}$-Werte zu $-(8.1 \pm 1.7)$, $-(8.7 \pm 2.7)$ bzw. $-(10.0 \pm 0.9)$ kJ/mol bestimmt. Auf Grund der günstigen $\Delta\Delta H^{\neq}$- und $\Delta\Delta V^{\neq}$-Werte konnte bei der Reaktion von **5a** mit **2** zu **6a**/**7a** eine Erhöhung der Selektivität von 1.67:1.00 bei 90°C und Normaldruck auf 13.6:1.0 bei 0.5°C und 6 kbar erreicht werden. Dieses Beispiel zeigt, daß eine signifikante und synthetisch wertvolle Erhöhung der Diastereoselektivität chemischer Reaktionen durch Anwendung von hohem Druck möglich ist.

High pressure has been applied to many transformations in order to increase their rates[2)]. Thus all reactions which display a negative $\Delta V^{\neq}$, can be accelerated under high pressure. Activation volumes of about -25 cm^3/mol have been found for the intramolecular and of -25 to -45 cm^3/mol for intermolecular Diels-Alder reactions[2c)]. Because of the relevance of selective organic synthesis, increasing interest has been addressed to the influence of pressure on relative rates in the formation of stereoisomers. Earlier attempts, however, to induce diastereoselectivity by high pressure[3,4)] were disappointing in that the observed absolute values of $\Delta\Delta V^{\neq}$ did not exceed 1 cm^3/mol. We now show, that a significant and synthetic useful increase in stereoselectivity may be obtained by applying high pressure.

In some recent publications we investigated the hetero Diels-Alder reaction[5)] of enamine carbaldehydes **1** and enamino ketones **5** with vinyl ethers such as **2** leading to 3-amino sugars of the garosamine and daunosamine type[6,7)]. The cycloaddition of **1** and **2** to give the dihydropyrans **3** and **4** was studied by direct quantitative infrared spectroscopy under high pressure, and an activation volume of $-(25.1 \pm 1.7)$ cm^3/mol could be determined in dichloromethane[8)]. This newly developed method allows a detailed study of organic reactions in compressed fluid phase.



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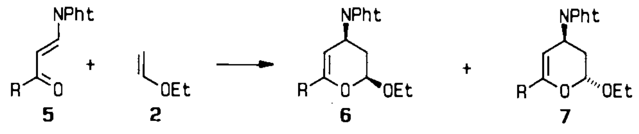
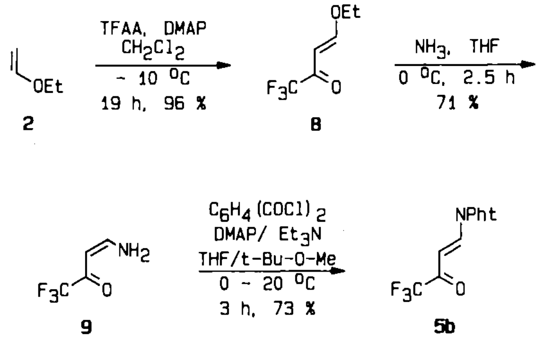
In this paper we describe the kinetics and the diastereoselectivity of the cycloadditions of **5a – d** and ethyl vinyl ether (**2**) to give the dihydropyrans **6a – d** and **7a – d** under high pressure. A part of this work (reaction of **5a** and **2**) has already been published as a communication[9)].

Chem. Ber. **122** (1989) 1179 – 1186 © VCH Verlagsgesellschaft mbH, D-6940 Weinheim, 1989 0009 – 2940/89/0606 – 1179 $ 02.50/0



R		products
CCl_3	**5a**	**6a/7a**
CF_3	**5b**	**6b/7b**
CO_2Me	**5c**	**6c/7c**
CO_2-(+)-menthyl	**5d**	**6d/7d**

The synthesis of the enamino ketones **5a**, **5c**, and **5d** has been described[10]. **5b** was prepared by nucleophilic acylation of ethyl vinyl ether with trifluoroacetic anhydride in a modified "Hojo reaction"[11] followed by treatment with ammonia and subsequent acylation with phthaloyl chloride.



DMAP: Dimethylaminopyridine
TFAA: Trifluoroaceticanhydride

For the pressure-mediated hetero Diels-Alder reaction of **5a**–**d** either an optical high-pressure cell for operation up to 3 kbar[8] equipped with windows from polycrystalline silicon or a 7-kbar autoclave[12] without windows was used. The kinetics of the cycloaddition was studied directly under high pressure by Fourier transform IR spectroscopy up to 3 kbar, mostly in dichloromethane as solvent, with the concentration of the vinyl ether **2** clearly exceeding that of the diene **5**. For the determination of the diastereoselectivity, cycloadditions up to 7 kbar have been performed. The ratio of the obtained diastereomers **6a**–**d**/**7a**–**d** was determined by HPLC of the crude reaction mixture after complete conversion. In order to prevent free-radical polymerisation, 2-*tert*-butyl-4-methylphenol was added in concentrations of about 0.01 mol/kg solution. Each reaction mixture is contained within a closed thin-walled poly(tetrafluoroethylene) (Teflon) bag which, in the spectroscopic experiments, is transmitted by the IR light. This technique avoids the reaction being influenced by the metal walls of the high-pressure cell. IR absorbance spectra for the carbonyl stretching region measured during the cycloaddition of **5a** and **2** in dichloromethane solution at 95°C and 1000 bar are shown in Figure 1. The curves are obtained by subtracting from each of the experimental spectra the first spectrum recorded immediately after the system has reached the reaction temperature and pressure. Positive absorbance in Figure 1 thus refers to the C=O fundamentals of the carbonyl moieties in the phthalimido group of the products **6a**–**c**/**7a**–**c**, whereas negative absorbance refers to those of the substrate **5a**–**c**. The series of spectra in Figure 1 covers a reaction time of about 12 hours which is sufficient to reach almost complete conversion (only one third from a total of 45 spectra measured during the reaction is plotted in Figure 1).

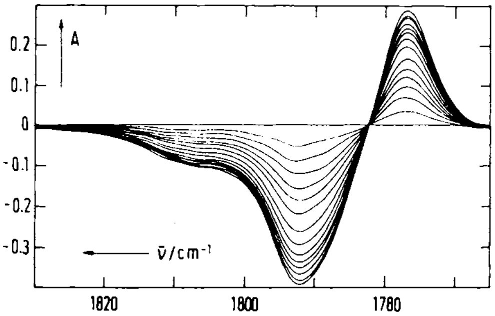


Figure 1. Infrared absorbance in the C=O stretching region measured during the cycloaddition of **5a** and **2** in dichloromethane at 95°C and 1000 bar; the first spectrum recorded at experimental *p* and *T* is subtracted from each experimental absorbance curve; thus positive absorbance refers to products and negative absorbance to substrates

At higher diene concentration or at larger optical path length, the cycloaddition kinetics can also be followed by measuring the absorbance in the first overtone region of C=O stretching modes around 3500 cm^{-1}. This is illustrated by a series of absorbance spectra recorded during the cycloaddition of **5d** and **2** in dichloromethane solution at 50°C and 1000 bar (Figure 2). Again, the absorption for components which do not change during the reaction is eliminated by subtracting the initial spectrum after reaching the experimental temperature and pressure. As before, positive absorbance refers to products and negative to substrates.

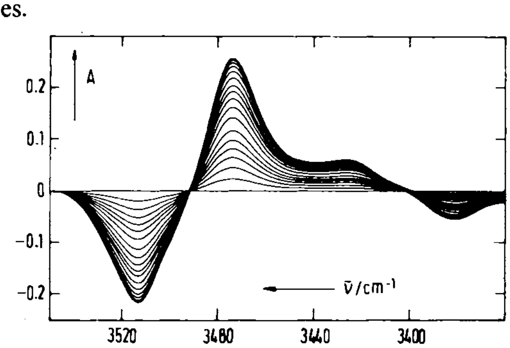


Figure 2. Infrared absorbance in the first overtone region of C=O stretching modes measured during the cycloaddition of **5d** and **2** in dichloromethane at 50°C and 1000 bar; as in Figure 1, the first spectrum is subtracted; positive absorbance refers to products and negative absorbance to substrates

Because of the concentration of vinyl ether **2** largely exceeding that of the hetero dienes **5a**–**c**, the Diels-Alder reactions can be treated by first-order kinetics. From any physical variable x which is linearily related ($x = a \cdot c + b$) to substrate or product concentration, c, the first-order rate constant k^{I} can be obtained from eq. 1 which is a modified Kezdy-Swinbourne expression[13].

$$x(t_2) - x(t_1) =$$
$$x(t_1) \cdot [\exp(-k^{I} \cdot \Delta t) - 1] - x(t \rightarrow \infty) \cdot [\exp(-k^{I} \cdot \Delta t) - 1] \quad (1)$$

$x(t_1)$ and $x(t_2)$ are the values of the variable x at times t_1 and t_2, respectively. Δt is the time interval between t_2 and t_1, and $x(t \rightarrow \infty)$ is the value of x at t approaching infinity. Several quantities from Figures 1 and 2, such as integrated intensities over half bands or total bands, may be identified with x. Plotting $x(t_2) - x(t_1)$ vs. $x(t_1)$, according to eq. 1, should yield a straight line with k^{I} being easily derived from the slope. An evaluation by eq. 1 is illustrated in Figure 3 for the cycloaddition of **5b** and **2** in dichloromethane solution at 45°C and 1000 bar. k^{I} is obtained to be $5.90 \cdot 10^{-5}$ s^{-1} for this reaction.

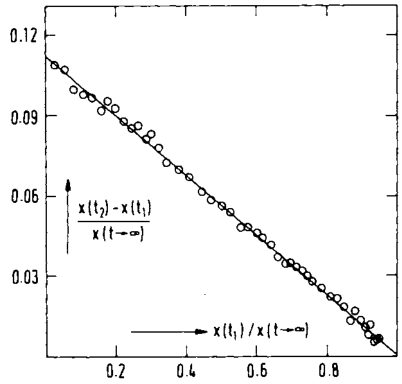


Figure 3. Plot of $x(t_2) - x(t_1)$ vs. $x(t_1)$ for the cycloaddition of **5b** and **2** in dichloromethane at 45°C and 1000 bar; both quantities are reduced by $x(t \rightarrow \infty)$; x is chosen to be the integrated absorbance of the substrates from 1820 to 1798 cm^{-1}

Plots as in Figure 3 are also obtained for the cycloadditions of **5a – d** with ethyl vinyl ether (**2**) at other temperatures and pressures. The resulting first-order rate coefficients k^{I} are related to second-order Diels-Alder rate coefficients k by $k^{I} = k \cdot c_0$ where c_0 is the concentration of the substrate species in large excess. The experimental rate coefficients, in terms of kg solution $\cdot$ $mol^{-1} \cdot s^{-1}$, are presented in Table 1. They should properly be addressed to as overall rate coefficients, because the cycloaddition leads to *cis*/*trans* diastereomers with the ratio of these two components depending on the reaction conditions. It is assumed that the enamino ketones **5a – d** react from the (*E*) configuration forming the *cis* adducts **6a – d** via an *endo* and the *trans* adducts **7a – d** via an *exo* transition state. The ratio of the *cis*/*trans* diastereomers **6a – c**/**7a – c** as obtained by HPLC of the reaction mixture after complete conversion is also shown in Table 1.

The variation of k with pressure for the cycloaddition of **5b** and **2** is presented in Figure 4. The accuracy of experimental data is sufficiently high to establish that the ln k vs. p relation is nonlinear. The data are fitted by a quadratic polynomial from which the pressure-dependent overall activation volume (for the reaction to both diastereomers) is found. The results are summarized in Table 2 for the cycloadditions of **5a – c**.

Table 1. Experimental rate coefficients k and measured product ratios c_{cis}/c_{trans} of *cis* and *trans* diastereomers for the cycloaddition of the hetero dienes **5a – d** and ethyl vinyl ether (**2**) at different pressures and temperatures (A: T [°C], B: p [bar], C: k [10^{-5} kg $\cdot$ $mol^{-1} \cdot s^{-1}$], D: c_{cis}/c_{trans})

Cycloaddition of 5a and 2 in CH_2Cl_2 at 90.0°C

B	C	D
400	3.93	
500	4.87	1.82
600	4.89	1.90
700	5.46	1.93
800	6.17	
1000	7.14	2.06
1100	7.65	
1250	8.71	2.12
1500	10.8	2.27
1750	13.3	2.37
2100	16.6	2.62
2300	19.5	2.66
2500	21.9	2.72
2600	26.0	
2700	28.2	2.78
2750	27.0	2.85
2850	29.6	2.89

Cycloaddition of 5a and 2 in CH_2Cl_2 at 1000 bar

A	C	D
55.0		2.63
60.0	1.06	
65.0	1.55	2.20
70.0	2.07	
75.0	2.98	2.14
80.0	4.19	2.01
95.0	9.81	
95.0	10.2	1.84
105.0	18.4	1.70
110.0	24.9	
115.0	30.8	
120.0	36.8	1.60
125.0	49.7	1.44
130.0	60.2	

Cycloaddition of 5a and 2 in CH_2Cl_2 at 60.0°C

B	D
500	2.36
500	2.34
980	2.65
980	2.65
1500	2.91
2000	3.27
2500	3.40
2990	3.79
3500	4.08
4000	4.39
4500	4.78
5000	4.95
5490	5.38
6000	5.79
6500	6.11
6000[a]	13.6

[a] 0.5°C.

Cycloaddition of 5a and 2 in heptane/isodurene at 110°C

B	C	D
250	3.81	0.827
350	3.96	0.846
500	4.64	0.848
700	5.50	0.913
900	6.53	0.911
950	6.77	0.971
1000	6.87	
1250	8.36	0.985
1500	10.2	1.05
1750	11.9	1.09
2200	16.3	1.21
2400	18.0	1.20
2500	18.9	1.24
2600	20.7	1.21
2900	25.2	1.30
3000	25.5	1.28

Cycloaddition of 5b and 2 in CH_2Cl_2 at 45°C

B	C	D
200	2.66	6.79
300	3.09	6.94
500	3.91	7.10
700	4.90	7.38
800	5.30	7.45
1000	6.85	
1200	8.05	7.89
1300	8.76	8.10
1500	10.6	8.15
1800	14.1	8.61
2000	15.8	8.86
2300	20.8	9.25
2500	23.7	9.62
2700	26.7	9.81
2800	30.2	
2900	33.1	10.1
3000	35.2	10.1
3100	35.8	10.4

Cycloaddition of 5c and 2 in CH_2Cl_2 at 70°C

B	C	D
300	4.62	8.92
400	5.05	9.16
500	5.56	
600	6.37	9.17
800	7.78	9.36
1000	9.70	9.51
1200	11.5	9.83
1500	14.9	9.86
1800	19.2	10.3
2000	22.2	
2300	35.8	10.7
2500	30.7	10.9
2600	34.9	10.8
2800	38.3	11.2
2900	41.9	11.1
3000	47.5	11.1
3100	47.6	11.1

Table 1. *(Continued)*

Cycloaddition of 5b and 2 in CH_2Cl_2 at 45°C

B	C	D
200	2.66	6.79
300	3.09	6.94
500	3.91	7.10
700	4.90	7.38
800	5.30	7.45
1000	6.85	
1200	8.05	7.89
1300	8.76	8.10
1500	10.6	8.15
1800	14.1	8.61
2000	15.8	8.86
2300	20.8	9.25
2500	23.7	9.62
2700	26.7	9.81
2800	30.2	
2900	33.1	10.1
3000	35.2	10.1
3100	35.8	10.4

Cycloaddition of 5c and 2 in CH_2Cl_2 at 70°C

B	C	D
300	4.62	8.92
400	5.05	9.16
500	5.56	
600	6.37	9.17
800	7.78	9.36
1000	9.70	9.51
1200	11.5	9.83
1500	14.9	9.86
1800	19.2	10.3
2000	22.2	
2300	35.8	10.7
2500	30.7	10.9
2600	34.9	10.8
2800	38.3	11.2
2900	41.9	11.1
3000	47.5	11.1
3100	47.6	11.1

Cycloaddition of 5b and 2 in CH_2Cl_2 at 1000 bar

A	C	D
30.0	2.31	9.33
35.0	3.31	7.88
60.0	16.9	
70.0	30.3	5.93
80.0	52.4	5.28
90.0	88.0	5.14

Cycloaddition of 5c and 2 in CH_2Cl_2 at 1000 bar

A	C	D
30.0	0.771	15.5
40.0	1.57	12.5
50.0	3.13	11.6
60.0	5.62	10.6
80.0	17.5	8.76
90.0	28.5	7.80
100.0	48.6	6.97
105.0	58.6	6.77
110.0	72.5	

Cycloaddition of 5c and 2 in CH_2Cl_2 at 40°C

B	D
500	12.0
700	12.6
1000	12.7
1500	13.4
2000	14.1
2500	14.3
3000	14.6
3500	14.8
4000	15.8
4500	15.9
5000	16.7
5500	16.8
5600	16.5
6100	17.4
6200	17.0
6600	17.9
6950	17.5

Cycloaddition of 5d and 2 in CH_2Cl_2

A	B	D
70.0	300	2.56
70.0	2500	19.6
50.0	250	1.04
50.0	1000	1.73
50.0	2000	4.14
50.0	2500	5.43

Table 2. Pressure-dependent overall activation volumes for the cycloaddition of the hetero dienes **5a**–**c** with ethyl vinyl ether (**2**)

hetero diene	$\Delta V^{\ddagger}$ [cm^3/mol]
5a	$(-28.0 \pm 5.0) \pm (3.8 \pm 2.0)\ p/\text{kbar}$[a]
5b	$(-31.8 \pm 1.3) \pm (5.0 \pm 0.8)\ p/\text{kbar}$[b]
5c	$(-32.5 \pm 1.5) \pm (5.1 \pm 0.6)\ p/\text{kbar}$[b]

[a] In heptane/isodurene. – [b] In CH_2Cl_2.

For the cycloaddition of **5d**, the number and the accuracy of data points is not sufficient to precisely measure a curvature on the ln k vs. p relation. Thus a pressure-averaged activation volume, $\overline{\Delta V^{\ddagger}}$, has been determined for the pressure range up to 3 kbar. This value is given together with the corresponding $\overline{\Delta V^{\ddagger}}$ data for the cycloadditions of **5a**–**c** in Table 3.

Table 3. Pressure-averaged activation volumes $\overline{\Delta V^{\ddagger}}$ for the cycloaddition of the hetero dienes **5a**–**d** with ethyl vinyl ether (**2**) studied up to 3 kbar

hetero diene	solvent	$\overline{\Delta V^{\ddagger}}$ [cm^3/mol]
5a	CH_2Cl_2	-24.2 ± 0.8
5a	heptane/ isodurene	-22.3 ± 0.8
5b	CH_2Cl_2	-23.4 ± 1.0
5c	CH_2Cl_2	-23.9 ± 1.0
5d	CH_2Cl_2	-20 ± 4

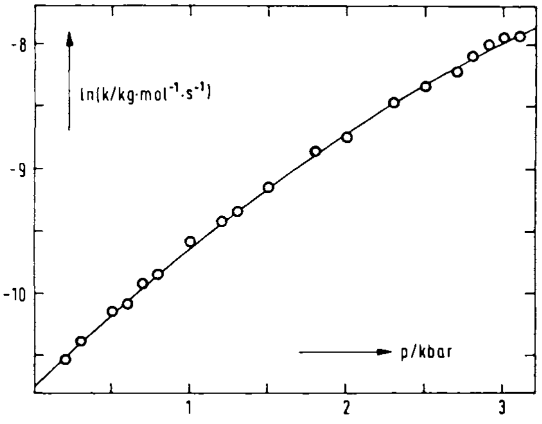


Figure 4. Pressure dependence of rate coefficient k for the cycloaddition of **5b** and **2** in dichloromethane at 45°C

In order to evaluate the influence of the solvent polarity on $\Delta V^{\ddagger}$, the cycloaddition of **5a** and **2** has been performed additionally in a mixture of heptane and isodurene. The data are also given in Table 3.

The temperature dependence of k for the cycloaddition of **5a** and **2** in dichloromethane at 1000 bar is shown in Figure 5. The straight-line slope m yields the activation energy $E = -R \cdot m$ which leads to the activation enthalpy $\Delta H^{\ddagger} = E - R \cdot T$ where R is the gas constant. The $\Delta H^{\ddagger}$

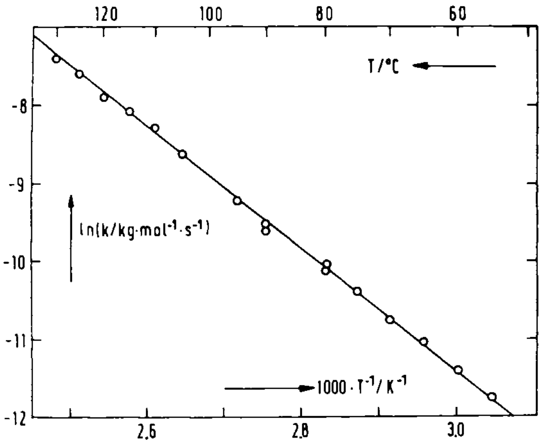


Figure 5. Temperature dependence of rate coefficient k for the cycloaddition of **5a** and **2** in dichloromethane at 1000 bar

Table 4. Activation enthalpies ΔH^+ for the cycloaddition of the hetero dienes **5a**–**c** with ethyl vinyl ether (**2**) in CH_2Cl_2 solution

hetero diene	ΔH^+ [kJ/mol]
5a	62.7 ± 2.3
5b	52.7 ± 0.8
5c	52.1 ± 0.6

values for the cycloadditions of **5a**–**c** and **2** are given in Table 4.

The pressure and the temperature dependence of the *cis/trans* ratios (Table 1) lead to differences in activation volume, $\Delta\Delta V^+$, and in activation enthalpy, $\Delta\Delta H^+$, respectively. Both dependences are illustrated in Figure 6 and 7 for the reaction of **5c** and **2** in dichloromethane.

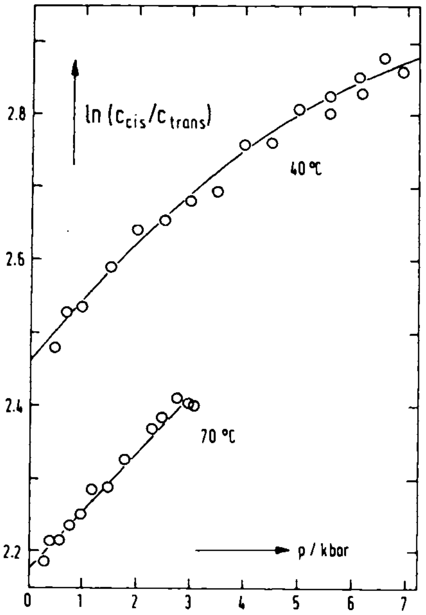


Figure 6. Pressure dependence of the product concentration ratio of *cis/trans* diastereomers for the cycloaddition of **5c** and **2** in dichloromethane at 40 and 70°C

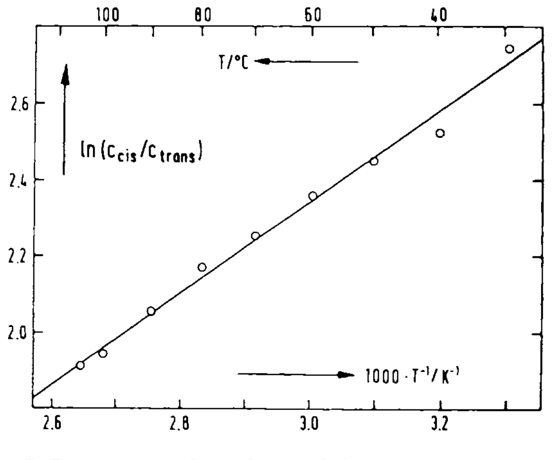


Figure 7. Temperature dependence of the product concentration ratio of *cis/trans* diastereomers for the cycloaddition of **5c** and **2** in dichloromethane at 1000 bar

In the hetero Diels-Alder reaction of **5a**–**c** and **2** the selectivity toward the *cis* diastereomers **6a**–**c** is clearly enhanced with increasing pressure and with decreasing temperature. From the pressure and from the temperature dependence of the *cis/trans* ratios, the difference in activation volume, $\Delta\Delta V^+ = \Delta V^+_{cis} - \Delta V^+_{trans}$, and the difference in activation enthalpy, $\Delta\Delta H^+ = \Delta H^+_{cis} - \Delta H^+_{trans}$, respectively, are derived. The $\Delta\Delta V^+$ and $\Delta\Delta H^+$ values are summarized in Table 5.

Table 5. Difference in activation volume, $\Delta\Delta V^+$, and difference in activation enthalpy, $\Delta\Delta H^+$, for the cycloadditions of **5a**–**c** with **2** leading to the diastereomers **6a**–**c** and **7a**–**c**

hetero diene	solvent	$\Delta\Delta V^+$ [cm³/mol]	$\Delta\Delta H^+$ [kJ/mol]
5a	CH_2Cl_2	$(-5.9 \pm 0.5) + (0.44 \pm 0.04)\ p$/kbar	-8.1 ± 1.7
5a	*n*-heptane/ isodurene	(-5.3 ± 0.4)	
5b	CH_2Cl_2	(-3.85 ± 0.08)	-8.7 ± 2.7
5c	CH_2Cl_2	$(-2.4 \pm 0.2) + (0.22 \pm 0.02)\ p$/kbar	-10.0 ± 0.9

The influence of reaction temperature and pressure on the ratio of the diastereoselectivity of the hetero Diels-Alder reaction (in dichloromethane) of **5a** and **2** to give **6a** and **7a** is shown in Figure 8. Experimental data (●) have been determined for 60°C and 90°C. In addition, one measurement has been performed at 0.5°C. The dashed lines are selectivities as calculated with the activation parameters in Table 5. The dotted lines indicate reaction half-lives [15 minutes (lower line) and 6 days (upper line)], referring to the substrate concentrations chosen within our experiments.

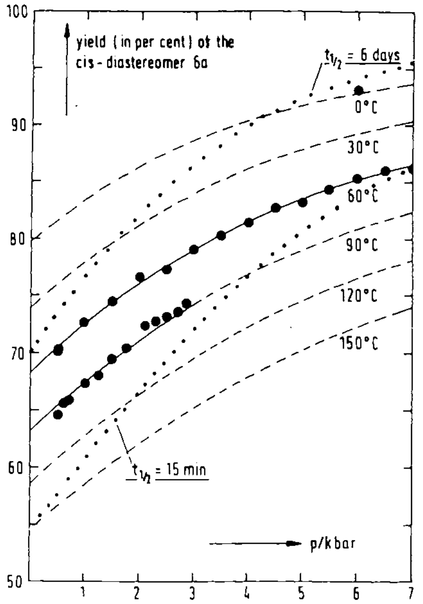


Figure 8. Pressure dependence of the yield in *cis* diastereomer **6a** for the cycloaddition of **5a** and **2** in dichloromethane at various temperatures; (●) experimental data points, (----) yields calculated from $\Delta\Delta V^+$ and $\Delta\Delta H^+$, (•••) curves of constant reaction half-life (for the selected initial concentrations) as determined from the measured rate coefficients; the figure allows the simultaneous consideration of selectivity and kinetics; the area between the two dotted lines encompasses a region of "reasonable" reaction rate half-lives between 15 min and 6 d

Curves as in Figure 8 can be constructed also for the cycloadditions of **5b** and **5c** with **2** from the corresponding numbers in Tables 1, 2, 4, and 5.

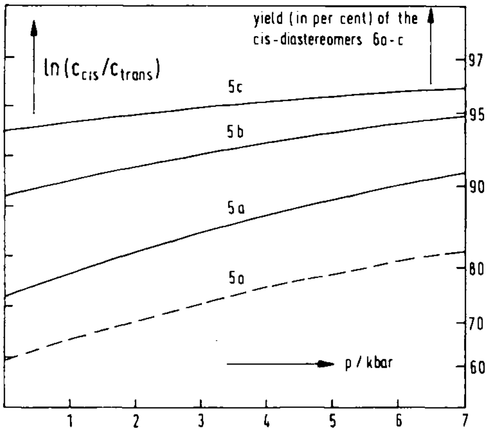


Figure 9. Pressure dependence of diastereoselectivity for the cycloaddition of **5a**–**c** with **2**; full lines refer to experiments in dichloromethane; the dashed line comes from experiments in *n*-heptane/isodurene solution; all data refer to 25°C

A comparison of diastereoselectivities within an extended pressure range for the cycloadditions of **5a**–**c** with **2** in dichloromethane is given in Figure 9. The reference temperature is chosen to be 25°C.

Results and Discussion

The hetero Diels-Alder reaction of enamino carbaldehydes and enaminones with ethyl vinyl ether is an excellent entry to 3-amino sugars$^{6)}$. As we have shown by introducing an electron-withdrawing group at position 2 or 3, a strong increase in reactivity can be obtained$^{14)}$. Thus, the cycloaddition of the enamino ketones **5a**–**d** and ethyl vinyl ether (**2**) leads to the dihydropyrans **6a**–**d** and **7a**–**d** as a mixture of diastereomers in very good yield. The reactivity of **5** increases in the order **5a** < **5c** < **5b** according to the strength of the electron-withdrawing group at position 2. With increasing pressure a strong enhancement of the reaction rate and also of diastereoselectivity is found. Quantitative analysis of the data reveals to a pressure-dependent activation volume and a difference in activation volume, $\Delta\Delta V^{+}$, for the formation of the *cis* and *trans* diastereomers. In all cases the formation of the *cis* adduct presumably formed via an *endo-E-syn* transition state is favoured. The selectivity could also be enhanced by lowering the reaction temperature because of a favourable $\Delta\Delta H^{+}$, but trying to increase diastereoselectivity only by decreasing the reaction temperature is not recommendable as the reaction time would become intolerably large. Thus the reaction half-life for the cycloaddition of **5a** and **2** at 0°C and ambient pressure to give a 4:1 mixture of **6a** and **7a** (Figure 8), at identical initial concentrations, is about 1.5 years. At high pressure, however, because of the negative activation volume, the reaction can be run with a reasonable rate even at low temperature.

The activation volume, ΔV^{+}, was found to be similar for all reactions performed in the same solvent within the limits of experimental accuracy. For the hetero Diels-Alder reaction of **5a**–**c** in dichloromethane the pressure-averaged $\overline{\Delta V^{+}}$ is between $-(23.4 \pm 1.0)$ and $-(24.2 \pm 1.0)$ cm^3/mol (Table 3) and around -32 cm^3/mol, if ΔV^{+} is obtained from an extrapolation toward ambient pressure. In unpolar solvents such as heptane/isodurene, a slightly reduced (negative) activation volume is observed. The data are relatively low in comparison with ΔV^{+} values of common intermolecular Diels-Alder reactions$^{2)}$. They are, however, close to the ΔV^{+} values found for the reaction of **1** and **2** in dichloromethane$^{8)}$.

The most important result in this work is the finding that the cycloadditions of enamino ketones **5a**–**c** and **2** show a significant pressure-induced increase in selectivity which corresponds to a favourable $\Delta\Delta V^{+}$ to give the *cis* adducts **6a**–**c**. Interestingly, the $\Delta\Delta V^{+}$ value strongly depends on the nature of the electron-withdrawing group at position 2 of the oxadiene moiety in **5a**–**c**. Thus for the reaction of **5a**, where the largest pressure-induced selectivity [$\Delta\Delta V^{+} = -(5.9 \pm 0.5)$ cm^3/mol] is found (Figure 9), the selectivity at ambient pressure is lowest. The situation is reversed for the cycloaddition of **5c** and **2** [$\Delta\Delta V^{+} = -(2.4 \pm 0.2)$ cm^3/mol]. These observations could be explained by assuming that the difference in activation volume, $\Delta\Delta V^{+}$, increases with steric hindrance due to the substituent at position 2 of the hetero diene. Thus, we believe that the formation of both *cis* and the *trans* adducts occurs by a concerted reaction$^{15)}$. A pressure-dependent change in diastereoselectivity, however, would also be observed, if the obtained diastereomers are formed by different mechanisms$^{16)}$. In the nonpolar solvent system heptane/isodurene, diastereoselectivity is clearly decreased whereas the strong pressure dependence of selectivity remains almost unchanged (Figure 9).

The great synthetic utility of the pressure-induced increase in selectivity is shown by the hetero Diels-Alder reaction of **5a** and **2**, where at 0.5°C and 6 kbar the two adducts **6a** and **7a** were obtained in a 13.6:1.0 ratio compared to 1.67:1.00 at ambient pressure and 90°C. In order to reach even larger diastereoselectivity in high-pressure syntheses, the cycloaddition should be studied in highly polar solvent systems, such as acetonitrile. First experiments of this kind are under way.

Generous support of this work by the *Deutsche Forschungsgemeinschaft* (SFB 93: "Photochemie mit Lasern") and by the *Fonds der Chemischen Industrie* is gratefully acknowledged.

Experimental

The optical high-pressure cell for operation up to 3 kbar and some details about the experimental setup and procedures using small bags prepared from 0.1 mm poly(tetrafluoroethylene) (Teflon) have already been described$^{8)}$. The initial diene concentrations were: **5a** 0.003–0.030 mol/kg solution, **5b** 0.01 mol/kg solution, **5c** 0.001 mol/kg solution, and **5d** 0.3 mol/kg solution. The concentration of **2** was close to 1.0 mol/kg solution in all experiments. Spectra during the reaction are recorded on a Bruker IFS 88 infrared spectrometer. The 7-kbar cell$^{12)}$ is made from stainless steel (RGT 601, W.-Nr.

2.4668, Arbed Saarstahl). The experimental pressures are determined to better than ±10 bar. The uncertainty in temperature is below ±0.5°C. The rate coefficients given in Table 1 are accurate within ±9%. The Teflon bags containing the reaction mixtures are stored in liquid nitrogen before and after the cyclisation to prevent any further reaction. For HPLC analysis, the solvent is removed under reduced pressure, and a solution of the residues in acetonitrile is prepared (concentration 1–2 mg/ml solvent). HPLC parameters: detection wavelength 240 nm; **6a**/**7a**: column Nucleosil 7 C 18, eluent acetonitrile/water (50:50), flow 0.9 ml/min, t_R(**6a**) = 36 min, t_R(**7a**) = 44 min; **6b**/**7b**: column LiChrospher 100 C18, 5 µm, eluent acetonitrile/water (40:60), flow 1.5 ml/min, t_R(**6b**) = 16 min, t_R(**7b**) = 21 min; **6c**/**7c**: column Nucleosil 7 C 18, eluent acetonitrile/water (40:60) flow 0.9 ml/min, t_R(**6c**) = 11 min, t_R(**7c**) = 12 min. Knauer HPLC system using a Merck-Hitachi Integrator D-2000. Acetonitrile for HPLC was purchased from Riedel-de Haen AG, water was bidistilled in quartz vessels. The solvents were manually mixed and filtered through a membrane filter (0.2 µm) prior to use. – ^{1}H and ^{13}C NMR: Varian XL-200 and FT-80A, multiplicities are determined with the APT pulse sequence. – IR: Bruker IFS 25 and Perkin-Elmer 297. – UV: Varian Cary 219. – MS: Varian MAT 311A. – Melting points (corrected values): Kofler melting point apparatus. – Elemental analyses were carried out in the analytical laboratory of the university. – All solvents were distilled prior to use. – Ethyl vinyl ether (**2**) (Fluka, purum) is of 99% purity. The enamino ketones **5a**, **5c**, and **5d** are prepared according to ref.[10].

Synthesis of Trifluoromethylenamino Ketone **5b**

4-Ethoxy-1,1,1-trifluoro-3-buten-2-one (**8**): To a solution of 4-dimethylaminopyridine (2.16 g, 2.40 mmol) in trifluoroacetic acid (100 ml, 0.72 mol) was added dropwise at −10°C ethyl vinyl ether (**2**) (65.5 ml, 0.63 mol). After stirring the mixture for 19 h at 0°C, the solvent was removed i. vac. Distillation of the residue afforded 110 g (96%) of **8**, b.p. 44–45°C/12.5 Torr. – IR (film): $\tilde{\nu}$ = 2992 cm^{-1} (CH), 1710 (C=O), 1600 (C=C), 1200 (CF). – UV (acetonitrile): λ_{max} (lgε) = 271 nm (3.728). – ^{1}H NMR (CDCl$_3$): δ = 1.35 (t, J = 7 Hz, 3H, $\mathrm{OCH_2C}H_3$), 4.20 (q, J = 7.0 Hz, 2H, $\mathrm{O}C\mathrm{H_2CH_3}$), 5.78 (d, J = 13.0 Hz, 1H, 3-H), 7.83 (d, J = 13.0 Hz, 1H, 4-H). – ^{13}C NMR (CDCl$_3$): δ = 14.41 ($\mathrm{OCH_2}C\mathrm{H_3}$), 69.12 ($\mathrm{O}C\mathrm{H_2CH_3}$), 98.04 (C-4), 116.6 (q, J = 290.4 Hz, C-1), 168.1 (q, J = 1.3 Hz, C-3), 180.1 (q, J = 35.2 Hz, C-2). – MS (70 eV): m/z (%) = 168 (10.6) [M$^+$], 99 (54.5) [M$^+$ − CF$_3$], 71 (100) [M$^+$ − CF$_3$ − CO].

$C_6H_7F_3O_2$ (168.1) Calcd. C 42.87 H 4.20 F 33.9
Found C 42.67 H 4.34 F 34.1

4-Amino-1,1,1-trifluoro-3-buten-2-one (**9**): An excess of ammonia was introduced to a stirred solution of **8** (86.8 g, 0.52 mol) in dry tetrahydrofuran (200 ml) at 0°C within 2.5 h. The mixture was concentrated i. vac. and the residue distilled (53°C/0.4 Torr) to give 50.9 g (71%) of **9**. – IR (film): $\tilde{\nu}$ = 3370, 3220 cm^{-1} (NH), 1660 (C=O), 1198 (CF). – UV (acetonitrile): λ_{max} (lgε) = 306 (4.167). – ^{1}H NMR (CDCl$_3$): δ = 5.43 (d, J = 8.0 Hz, 0.95 H, 3-H), 5.60 (d, J = 12.0 Hz, 0.05 H, 3-H), 6.65 (br., 1H, NH), 7.25 (dt, J = 8.0, 16.0 Hz, 0.95 H, 4-H), 7.90 (q, J = 12.0 Hz, 0.05 H, 4-H), 9.85 (br., 1H, NH chelated). – ^{13}C NMR (CDCl$_3$): δ = 88.47 (q, J = 1.2 Hz, C-3), 117.3 (q, J = 289 Hz, C-1), 157.3 (C-4), 179.3 (q, J = 34.0 Hz, C-2). – MS (70 eV): m/z (%) = 139 (80.1), [M$^+$], 70 (100) [M$^+$ − CF$_3$], 42 (30.8) [M$^+$ − CF$_3$ − CO].

$C_4H_4F_3NO$ (139.1) Calcd. C 34.54 H 2.90 N 10.07
Found C 34.57 H 3.00 N 10.06

1,1,1-Trifluoro-4-phthalimido-3-buten-2-one (**5b**): To a stirred solution of **9** (1.42 g, 10.2 mmol), 4-dimethylaminopyridine (0.2 g, 1.6 mmol), and triethylamine (2.42 g, 24.0 mmol) in a mixture of anhydrous tetrahydrofuran and *tert*-butyl methyl ether (1:1, 40 ml) was added phthaloyl chloride (2.68 g, 13.2 mmol) at 0°C. The mixture was allowed to warm up to room temp. and stirred for 3 h. After evaporation of the solvent i. vac., the residue was purified by flash chromatography [ether/petroleum ether (2:1)] and crystallised from *tert*-butyl methyl ether to give 2.01 g (73%) of **5b**, m.p. 99°C. (*tert*-butyl methyl ether). – IR (KBr): $\tilde{\nu}$ = 1730 cm^{-1} (C=O), 1615 (C=C), 1210 (CF). – UV (acetonitrilc): λ_{max} (lgε) = 285 (4.433), 218 (4.380). – ^{1}H NMR (CDCl$_3$): δ = 7.64 (dq, J = 1.0, 14.5 Hz, 1H, 3-H), 8.00 (m, 4H, Ph-H), 8.25 (d, J = 1.0, 14.5 Hz, 1H, 4-H). – ^{13}C NMR (CDCl$_3$): 106.1 (C-3), 117.3 (q, J = 290 Hz, CF$_3$), 125.4 (2-Ph), 132.2 (1-Ph), 136.4 (C-4), 137.0 (3-Ph) 166.1 (CO), 181.5 (q, J = 35.3 Hz, C-2). – MS (70 eV): m/z (%) = 269 (11.4) [M$^+$], 200 (100) [M$^+$ − CF$_3$], 172 (25.3) [M$^+$ − CF$_3$ − CO].

$C_{12}H_6F_3NO_3$ (269.2) Calcd. C 53.54 H 2.25 F 21.2 N 5.20
Found C 53.73 H 2.24 F 21.0 N 5.20

CAS Registry Numbers

2: 109-92-2 / **5a**: 110945-43-2 / **5b**: 120417-46-1 / **5c**: 120417-47-2 / **5d**: 120520-85-6 / **6a**: 120417-48-3 / **6b**: 120417-49-4 / **6c**: 120417-50-7 / **6d**: 120417-51-8 / **7a**: 120417-52-9 / **7b**: 120417-53-0 / **7c**: 120417-54-1 / **8**: 59938-06-6 / **9**: 120417-45-0 / phthaloyl chloride: 88-95-9

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