Inter- and Intramolecular Hetero Diels-Alder Reactions, 40[1]

Effect of High Pressure on the Stereoselectivity of Intermolecular Hetero Diels-Alder Reactions

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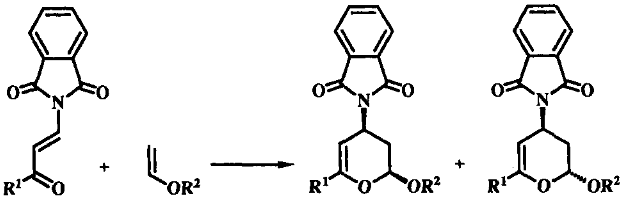
The hetero Diels-Alder reaction of enamino ketone **1** with the vinyl ethers **7** – **11** leading to the dihydropyrans **12a** – **e** and **13a** – **e** is studied in dichloromethane under high pressures up to 7 kbar. The kinetics is measured by on-line FT-IR spectroscopy up to 3 kbar. For the first time individual rate coefficients k_{cis} and k_{trans} have been determined. Pressure-averaged activation volumes, $\overline{\Delta V^{\neq}}$, for the overall reaction leading to the formation of the two diastereomers in dichloromethane solution between –(19.1 ± 1.7) and –(25.4 ± 1.6) cm^3 mol^{-1} are measured. The corresponding activation enthalpies, $\Delta H^{\neq}$, are between (62.2 ± 1.6) and (76.3 ± 3.6) kJ mol^{-1}. The cycloaddition shows a remarkable increase in diastereoselectivity in favour of the *cis* adducts **12a** – **e** toward higher pressure. The pressure-averaged differences in activation volume, $\overline{\Delta\Delta V^{\neq}}$, for the two reaction pathways leading to *cis* and *trans* diastereomers are found to be between –(4.5 ± 0.3) and –(6.9 ± 0.7) cm^3 mol^{-1}. The corresponding differences in activation enthalpy, $\Delta\Delta H^{\neq}$, are between –(4.7 ± 1.4) and –(9.9 ± 1.6) kJ mol^{-1}. Combination of the overall rate coefficient $k = k_{cis} + k_{trans}$ for the reaction leading to the two diastereomers with the measured product ratio, c_{cis}/c_{trans}, which is identified with the ratio of the rate coefficients k_{cis}/k_{trans}, yields the individual coefficients k_{cis} and k_{trans}. The rate coefficient k_{cis} is strongly influenced by the steric demand of the substituents on both diene and dienophile whereas k_{trans} varies to a smaller extent, and the observed changes appear to be mainly due to the electronic properties of the substituents.

Previous investigations of the hetero Diels-Alder reaction of enamino ketones **1** – **3** with ethyl vinyl ether (**4**) have shown that the ratio of the diastereomeric products **5a** – **c** and **6a** – **c** is strongly dependent on pressure[2–4]. In this paper we present data on the kinetics and on the diastereoselectivity of the cycloaddition reaction of enamino ketone **1** with several vinyl ethers **7** – **11** to yield the new dihydropyrans **12a** – **e** and **13a** – **e**. The synthesis of **1** has already been published[5]. The structure of **12a** – **e** and **13a** – **e** has mainly been determined by using ^{1}H-NMR spectroscopy. The data are similar to those obtained for **5a** and **6a**, which have recently been published. The conformation of dihydropyrans similar to **12a** – **e**/**13a** – **e**, being governed by the anomeric and steric effects, has been discussed in detail elsewhere[6].



diene **1 - 3**

dienophile **4, 7 - 11**

***cis* product** **5a - 5c** **12a - 12e**

***trans* product** **6a - 6c** **13a - 13e**

R¹	R²	Starting compounds Diene	Enol ether	Products
CCl$_3$	Et	**1**	**4**	**5a/6a**
CF$_3$	Et	**2**	**4**	**5b/6b**
CO$_2$Me	Et	**3**	**4**	**5c/6c**
CCl$_3$	*i*Bu	**1**	**7**	**12a/13a**
CCl$_3$	*i*Pr	**1**	**8**	**12b/13b**
CCl$_3$	*t*Bu	**1**	**9**	**12c/13c**
CCl$_3$	C$_6$H$_5$CH$_2$	**1**	**10**	**12d/13d**
CCl$_3$	*p*-MeOC$_6$H$_4$	**1**	**11**	**12e/13e**

The cycloadditions have been studied by direct quantitative infrared spectroscopy under high pressures up to 3 kbar. They have also been performed on a preparative scale at ambient pressure (120°C, 24 h, in toluene solution) with good to excellent yields (85 – 99%). The experimental setup including the optical high-pressure cell has already been described[7]. The concentrations of the starting compounds and products are directly derived from the IR spectra[3,6]. As the concentration of the enol ethers **7** – **11** largely exceeds that of the diene, the data can be evaluated by a modified Kezdy-Swinbourne[8] plot for a pseudo first-order reaction. This procedure directly yields rate coefficients k'. Via $k' = k \cdot c_0$, where c_0 is the enol ether concentration in mol per kg solution, second-order rate coefficients k are calculated.

Table 1. Experimental rate coefficients *k* and ratios of diastereomeric products c_{cis}/c_{trans} for the cycloaddition reactions of enamino ketone **1** with the enol ethers **7**–**11** in dichloromethane (A: T [°C]; B: p [bar]; C: k [10^{-5} kg mol s^{-1}]; D: c_{cis}/c_{trans})

Cycloaddition of 1 to 7 in CH_2Cl_2 at 90 °C

B	C	D
250		1.31
350	3.19	1.38
500	3.87	1.45
750	5.61	1.53
1000	6.73	1.67
1250	8.26	1.72
1450		1.76
1500		1.80
1750	12.9	1.86
2000	15.5	1.93
2250	17.7	
2300	19.7	2.00
2500	22.3	2.05
2750	27.8	2.13
2900	29.6	2.20
3000	32.4	2.22

Cycloaddition of 1 to 7 in CH_2Cl_2 at 60 °C

B	D
500	1.87
1000	2.14
1500	2.37
2000	2.54
2500	2.76
3000	3.07
4000	3.44
4500	3.76
5000	3.99
5500	4.09
6000	4.42
6500	4.78
6970	4.91

Cycloaddition of 1 to 7 in CH_2Cl_2 at 1000 bar

A	C	D
49	0.48	
50		2.24
54	0.65	2.15
59		2.04
69	1.76	1.87
79	3.62	1.72
84.5	5.33	
88	6.00	1.67
89	6.73	
99	12.2	1.51
104	16.9	
109	21.1	1.41
119	33.9	1.33

Cycloaddition of 1 to 8 in CH_2Cl_2 at 90 °C

B	D
300	0.762
500	0.792
800	0.857
1000	0.908
1500	1.02
1800	1.09
2000	1.12
2300	1.17
2500	1.23
2750	1.29

Cycloaddition of 1 to 8 in CH_2Cl_2 at 1000 bar

A	D
65	1.20
70	1.06
75	1.02
80	0.983
90	0.908
105	0.844
110	0.816

Cycloaddition of 1 to 9 in CH_2Cl_2 at 90 °C

B	C	D
200	2.95	0.272
400	3.46	0.285
500	3.65	0.289
800	5.48	0.315
1000	6.65	0.337
1500	9.2	0.375
1800	11.6	0.395
2000	12.3	0.443
2200	16.4	0.428
2500	18.7	0.461
2700	23.9	0.452
3000	27.3	

Cycloaddition of 1 to 9 in CH_2Cl_2 at 55 °C

B	D
500	0.353
700	0.340
1000	0.430
1500	0.461
2000	0.501
2500	0.536
3000	0.593
3500	0.620
4000	0.710
4500	0.679
5000	0.731

Cycloaddition of 1 to 9 in CH_2Cl_2 at 1000 bar

A	C	D
55		0.430
60		0.397
65	1.06	0.366
70	1.41	0.425
75	1.99	0.346
80	2.73	0.344
85	4.20	0.339
90	6.65	0.337
95	7.20	0.340
100	9.90	0.355
105	13.0	
110	20.5	
115		0.318

Cycloaddition of 1 to 10 in CH_2Cl_2 at 55 °C

B	D
500	1.79
700	1.83
1000	1.97
1500	2.16
2000	2.29
2500	2.52
3000	2.69
3500	2.95
4000	3.15
4500	3.31
5000	3.49
5500	3.62

Cycloaddition of 1 to 11 in CH_2Cl_2 at 120 °C

B	C	D
500		0.591
600	3.13	
650	3.04	0.614
800	3.44	
1000	4.25	
1300	4.79	0.739
1600	6.36	0.770
1900	6.42	0.831
2000	6.79	
2200	8.41	0.877
2500	9.54	0.916
2600	9.95	
2700	10.6	
2800	11.4	0.952

Cycloaddition of 1 to 11 in CH_2Cl_2 at 1000 bar

A	C	D
100	1.01	0.802
105	1.25	0.770
110	2.06	0.751
120	3.96	
125	4.87	0.662
130	6.51	0.632
140	11.2	0.571
150	18.6	0.495
155	29.4	0.446
160	34.6	

The experimental values for *k* are summarized in Table 1 for the cycloaddition reactions of **1** with **7**, **9**–**11**. They are overall rate coefficients for the cycloaddition leading to both *cis* and *trans* diastereomers. Thus, the pressure and temperature dependence of *k* yields overall activation parameters $\Delta V^{\neq}$ and $\Delta H^{\neq}$, respectively.

The experimental values for the ratio of the concentrations of *cis* and *trans* diastereomers (**12a**–**e** and **13a**–**e**) as determined by HPLC analysis of the crude reaction mixtures are also included in Table 1. The c_{cis}/c_{trans} product ratio clearly increases toward higher pressure and lower temperature.

Table 2. Activation parameters for the cycloaddition reaction of **1** with **7**–**11** leading to the diastereomeric products **12a**–**e** and **13a**–**e** in dichloromethane[a]

Products	$\overline{\Delta V^{\neq}}$ [cm³/mol]	$\Delta V^{\neq}$ [cm³/mol]
12a/13a	$-(25.4 \pm 1.6)$	$-(35.0 \pm 1.8) + (5.8 \pm 0.5)\ p$/kbar
12b/13b	*$-(23.5 \pm 2.6)$*	*$-(32.3 \pm 2.5) + (5.4 \pm 0.5)$* p/kbar
12c/13c	$-(24.2 \pm 1.9)$	$-(29.6 \pm 2.2) + (3.5 \pm 0.3)\ p$/kbar
12e/13e	$-(19.1 \pm 1.7)$	$-(24.4 \pm 1.5) + (3.2 \pm 0.3)\ p$/kbar

Products	$\overline{\Delta\Delta V^{\neq}}$ [cm³/mol]	$\Delta\Delta V^{\neq}$ [cm³/mol]
12a/13a	$-(5.4 \pm 0.6)$	$-(8.9 \pm 0.7) + (2.2 \pm 0.2)\ p$/kbar[b]
		$-(6.0 \pm 0.5) + (0.5 \pm 0.0)\ p$/kbar[c]
12b/13b	*$-(6.5 \pm 0.5)$*	*$-(8.7 \pm 0.6) + (1.5 \pm 0.1)$* p/kbar[b]
12c/13c	$-(6.7 \pm 0.8)$	$-(9.0 \pm 0.7) + (1.4 \pm 0.2)\ p$/kbar[b]
		$-(8.7 \pm 0.7) + (1.6 \pm 0.2)\ p$/kbar[c]
12d/13d	$-(4.5 \pm 0.3)$	$-(5.5 \pm 0.4) + (0.5 \pm 0.0)\ p$/kbar[c]
12e/13e	$-(6.9 \pm 0.7)$	$-(10.9 \pm 0.8) + (2.5 \pm 0.2)\ p$/kbar[b]

Products	$\Delta H^{\neq}$ [kJ/mol]	$\Delta\Delta H^{\neq}$ [kJ/mol]
12a/13a	62.2 ± 1.6	$-(7.8 \pm 0.4)$
12b/13b	*64.5 ± 3.9*	*$-(7.0 \pm 0.7)$*
12c/13c	67.4 ± 4.3	$-(4.7 \pm 1.4)$
12e/13e	76.3 ± 3.6	$-(9.9 \pm 1.6)$

Products	$\Delta S^{\neq}$ [J/molK]	$\Delta\Delta S^{\neq}$ [J/molK]
12a/13a	$-(157 \pm 6)$	$-(17.4 \pm 1.4)$
12b/13b	*$-(147 \pm 9)$*	*$-(18.3 \pm 3.1)$*
12c/13c	$-(143 \pm 15)$	$-(21.4 \pm 6.4)$
12e/13e	$-(138 \pm 10)$	$-(28.2 \pm 5.3)$

[a] $\overline{\Delta V^{\neq}}$: pressure-averaged overall activation volume; $\Delta V^{\neq}$: pressure-dependent overall activation volume; $\overline{\Delta\Delta V^{\neq}}$: pressure-averaged difference in activation volumes, $\overline{\Delta V^{\neq}_{cis}} - \overline{\Delta V^{\neq}_{trans}}$; $\Delta\Delta V^{\neq}$: pressure-dependent difference in activation volumes; $\Delta H^{\neq}$: overall activation enthalpy; $\Delta\Delta H^{\neq}$: difference in activation enthalpy, $\Delta H^{\neq}_{cis} - \Delta H^{\neq}_{trans}$; $\Delta S^{\neq}$: overall activation entropy; $\Delta\Delta S^{\neq}$: difference in activation entropy, $\Delta S^{\neq}_{cis} - \Delta S^{\neq}_{trans}$. The experimental k values for the cycloaddition of **1** to **8** are not given in Table 1 as the reaction mixture contained some impurity which might influence the absolute values of k; it is assumed that relative rate coefficients, and thus c_{cis}/c_{trans}, and also the pressure and temperature dependence of k, characterized by the activation parameters, are not significantly influenced by this impurity; the data for the reaction of **1** with **8** are given in italics. – [b] From experiments up to 3 kbar. – [c] From experiments up to 7 kbar.

The experimental log$k$ versus T^{-1} data closely fit to straight lines (see Figure 1). The slope yields overall activation enthalpies according to Eq. (1).

$$\Delta H^{\neq} = -R(\mathrm{d}\ln k/\mathrm{d}T^{-1})_p - RT \qquad (1)$$

The log$k$ versus p relations are non-linear (see Figure 2). The experimental data are either fitted by a straight line which yields a pressure-averaged activation volume, $\overline{\Delta V^{\neq}}$, (Eq. (2a)) or by a quadratic polynominal ($\ln k = a_0 + a_1 p + a_2 p^2$), which leads to a pressure-dependent activation volume, $\Delta V^{\neq}$, according to Eq. (2b) (Table 2).

$$\overline{\Delta V^{\neq}} = -RT(\mathrm{d}\ln k/\mathrm{d}p)_T \qquad (2a)$$

$$\Delta V^{\neq} = -RT(a_1 + 2a_2 p) \qquad (2b)$$

It is assumed that the cycloaddition proceeds under kinetic control, and therefore c_{cis}/c_{trans} may be identified with the ratio of the individual rate coefficients, k_{cis} and k_{trans}. The pressure and the temperature dependence of $\ln c_{cis}/c_{trans}$ yield the difference in activation volume $\Delta\Delta V^{\neq}$ and the difference in activation enthalpy $\Delta\Delta H^{\neq}$, respectively [Eqs. (3) and (4)]. A curvature is observed on the $\ln c_{cis}/c_{trans}$ versus p plots. For $\Delta\Delta V^{\neq}$ both a pressure-averaged value $\overline{\Delta\Delta V^{\neq}}$ (for data up to 3 kbar) and a pressure-dependent $\Delta\Delta V^{\neq}$ are determined [Eq. (5a) and (5b)].

$$\Delta\Delta V^{\neq} = \Delta V^{\neq}_{cis} - \Delta V^{\neq}_{trans} \qquad (3)$$

$$\Delta\Delta H^{\neq} = \Delta H^{\neq}_{cis} - \Delta H^{\neq}_{trans} \qquad (4)$$

$$\overline{\Delta\Delta V^{\neq}} = -RT(\mathrm{d}\ln c_{cis}/c_{trans}/\mathrm{d}p)_T \qquad (5a)$$

$$\Delta\Delta V^{\neq} = -RT(b_1 + 2b_2 p) \qquad (5b)$$

The b_1 and b_2 coefficients are determined from a fit of the $\ln c_{cis}/c_{trans}$ data by a quadratic polynominal: $\ln c_{cis}/c_{trans} = b_0 + b_1 p + b_2 p^2$.

The difference in activation enthalpy is found according to Eq. (6).

$$\Delta\Delta H^{\neq} = -R(\mathrm{d}\ln(c_{cis}/c_{trans})/\mathrm{d}T^{-1})_p \qquad (6)$$

The overall activation parameters $\Delta V^{\neq}$, $\Delta H^{\neq}$, and $\Delta S^{\neq}$ and the differences in activation parameters $\Delta\Delta V^{\neq}$, $\Delta\Delta H^{\neq}$, and $\Delta\Delta S^{\neq}$ are summarized in Table 2. The entropy values are determined according to Eq. (7) and (8).

$$\Delta S^{\neq} = R\{\ln k - \ln(k_B T/h) - (\mathrm{d}\ln k/\mathrm{d}T^{-1})_p T^{-1} - 1\} \qquad (7)$$

$$\Delta\Delta S^{\neq} = R\{\ln(c_{cis}/c_{trans}) - (\mathrm{d}\ln(c_{cis}/c_{trans})/\mathrm{d}T^{-1})_p T^{-1}\} \qquad (8)$$

The experimental data in Table 1 and 2 refer to cycloaddition reactions in dichloromethane as the solvent. To study the influence of solvent polarity on stereoselectivity, the cycloaddition reaction of **1** with **4** has also been performed in a mixture of heptane and isodurene (2:1)[3,7] and in acetonitrile as solvents. The ratios of c_{cis}/c_{trans} diastereomeric products for the cycloaddition of **1** to **4** in acetonitrile are given in Table 3.

Table 3. Product ratios c_{cis}/c_{trans} for the cycloaddition of **1** to **4** in acetonitrile (B: p [bar]; D: c_{cis}/c_{trans}) at 60 °C

Cycloaddition of 1 to 4 in acetonitrile at 60 °C	
B	D
500	2.56
1000	2.87
1500	3.13
2000	3.43
2500	3.78
3000	4.06
3500	4.34
4000	4.64
4500	4.94
5000	5.26
5500	5.28
6000	5.85
6500	6.05
6970	6.45

Table 4. Difference in activation volumes, $\overline{\Delta\Delta V^{\neq}}$, for the cycloaddition of **1** to **4** in dichloromethane, heptane/isodurene, and acetonitrile

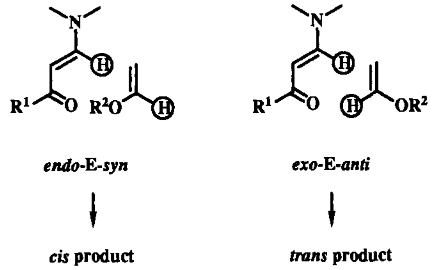
Solvent	$\overline{\Delta\Delta V^{\neq}}$ [cm^3/mol]
Dichloromethane	$-(5.8 \pm 0.4)$
Heptane/isodurene	$-(5.3 \pm 0.4)$
Acetonitrile	$-(5.8 \pm 0.4)$

The pressure-averaged $\overline{\Delta\Delta V^{\neq}}$ values for the cycloaddition of **1** to **4** in dichloromethane[2,3,7], heptane/isodurene[3,7], and acetonitrile are presented in Table 4.

Results and Discussion

The development of new synthetic methods in organic chemistry is directed toward inducing or improving stereoselectivity. It has appeared rewarding to explore the potential of the application of high pressures in influencing reactivity and selectivity of chemical transformations. The hetero Diels-Alder reaction of enamino ketones with vinyl ethers yielding 4-aminodihydropyrans is taken as an example. These reactions provide an important access to 3-amino sugars[6].

Recently, we have shown that the diastereoselectivity of the hetero Diels-Alder reaction of the enamino ketones **1**–**3** with ethyl vinyl ether (**4**) is strongly pressure-dependent[3,4]. The *cis*/*trans* product ratio is significantly enhanced with increasing pressure. The *cis* products are presumably formed via an *endo-(E)-syn* transition state and the *trans* products via an *exo-(E)-anti* transition state in a kinetically controlled reaction. We assume that the formation of both *cis* and *trans* adducts occurs in a concerted reaction.



The $\Delta\Delta V^{\neq}$ value depends on the nature of the group R^1 on the oxadiene moiety in **1**–**3**. For the reaction of **1** with **4** the highest pressure-induced selectivity [$\overline{\Delta\Delta V^{\neq}} = -(5.8 \pm 0.4)$ cm^3 mol^{-1}] is found while the absolute value of selectivity is lowest. On the other hand, in the cycloaddition of **3** to **4**, the absolute value for *cis*/*trans* selectivity is highest, and $\Delta\Delta V^{\neq}$ is relatively small [$-(2.3 \pm 0.2)$ cm^3 mol^{-1}]. These observations are explained by assuming that the difference in the activation volume, $\Delta\Delta V^{\neq}$, increases with the steric hindrance due to the substituent R^1 on the hetero diene.

The diastereoselectivity also increases at lower temperatures. Thus, **5a** and **6a** are formed at 60°C and 6 kbar in a 5.79:1 ratio, whereas at 0.5°C and 6 kbar a 13.6:1 ratio is obtained. High selectivities are thus achieved in reactions at high pressure and low temperature[3,4].

After having studied the influence of different substituents R^1 on the diene[3,4] it has appeared interesting to investigate whether and to which extent the substituent R^2 on the vinyl ethers affects reactivity and stereoselectivity. Figure 1 shows the temperature dependence of the experimental overall rate coefficients k for the cycloaddition reactions of enamino ketone **1** with the enol ethers **4**, **7**, **9**, and **11** in dichloromethane solution at 1000 bar.

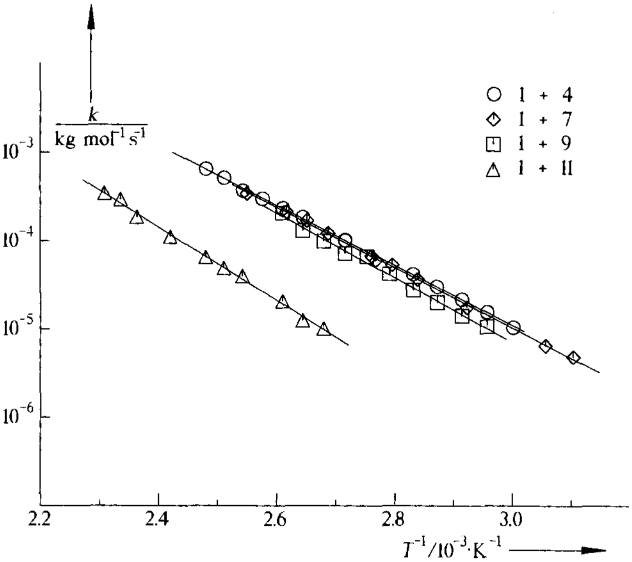


Figure 1. Temperature dependence of the overall rate coefficients k for the cycloaddition reactions of enamino ketone **1** with the enol ethers **4**, **7**, **9**, and **11** in dichloromethane solution at 1000 bar

For the aliphatic vinyl ethers **4**, **7**, and **9** with R^2 = ethyl, isobutyl, and *tert*-butyl almost identical k values are observed. The aromatic enol ether **11** is by ca. one order of magnitude less reactive than the alkyl vinyl ethers. The $\Delta H^{\neq}$ values for the cycloaddition reactions of **1** with **4**, **7**, and **9** are rather similar (Table 1) and by ca. 10 kJ mol^{-1} below the activation enthalpy for the reaction of **1** with **11** ($\Delta H^{\neq} = 76.3 \pm 3.6$ kJ mol^{-1}).

The pressure dependence of k for the reactions of enamino ketone **1** with the vinyl ethers **4**, **7**, **9** and with **11** in dichloromethane is illustrated in Figure 2. The data points in Figure 2, via the individual values for $\Delta H^{\neq}$ (Table 2), are calculated (Eq. (2)) from the experimental data, which are determined between 90°C and 120°C, for a common temperature of 90°C.

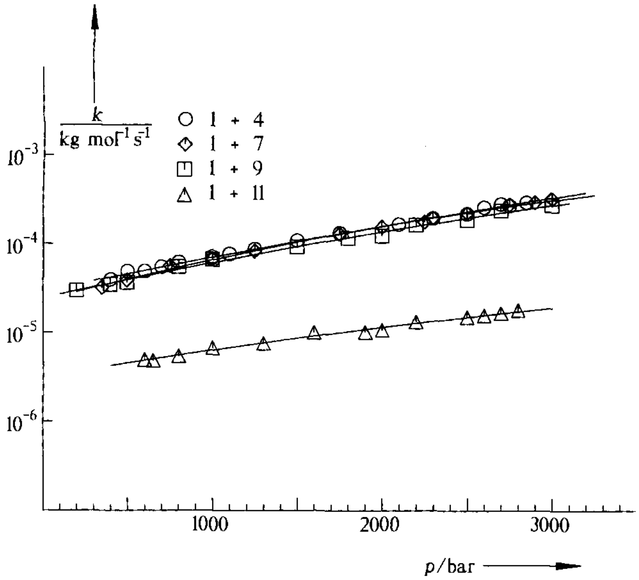


Figure 2. Pressure dependence of the overall rate coefficients k for the cycloaddition reactions of enamino ketone **1** with the enol ethers **4**, **7**, **9**, and **11** in dichloromethane solution at 90°C

The k values for the cycloaddition reactions of **1** with the alkyl vinyl ethers **4**, **7**, and **9** are rather similar in the absolute value and also in the pressure dependence, which yields pressure-averaged activation volumes between $-(24.2 \pm 0.8)$ and $-(25.4 \pm 1.6)$ cm^3 mol^{-1}. The k value for the cycloaddition of **1** to **11** is smaller than the corresponding data for the reactions of **1** with **4**, **7**, and **9**, and the activation volume is found to be $\overline{\Delta V^{\neq}} = -(19.1 \pm 1.7)$ cm^3 mol^{-1}. The difference in the $\overline{\Delta V^{\neq}}$ values for the cycloaddition reactions of **1** with **4**, **7**, and **9**, however, appears to be not sufficiently large as to provide clear evidence for a different reaction mechanism[9]. It should be noted that all the $\overline{\Delta V^{\neq}}$ values in Table 2 are relatively low in comparison with typical values for intermolecular Diels-Alder reactions[10].

The influence of temperature on the ratio of diastereomeric product concentrations, c_{cis}/c_{trans}, is depicted in Figure 3 for the cycloadditon reactions of enamino ketone **1** with enol ethers **4**, **7**–**9**, and **11** in dichloromethane at 1000 bar. With the exception of the **1** + **11** cycloaddition, the c_{cis}/c_{trans} data are adequately represented by linear Arrhenius plots. In the **1** + **11** cycloaddition side reactions or additional reaction pathways may become important at high temperatures. For this reason the **1** + **11** reaction will not be further considered in the subsequent discussion.

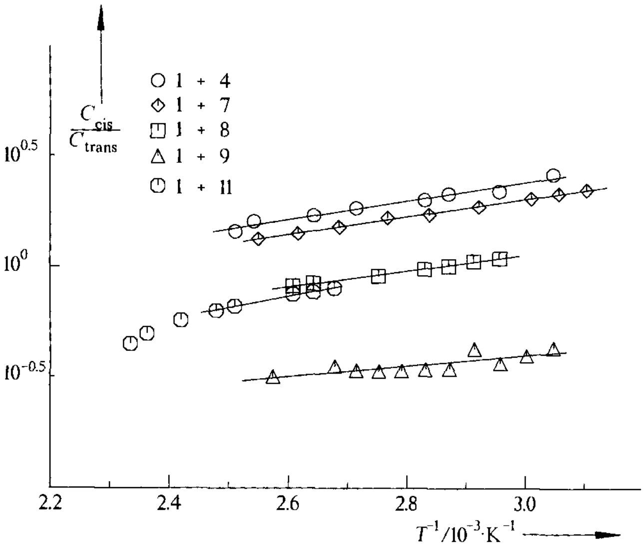


Figure 3. Temperature dependence of the product ratio of *cis*/*trans* diastereomers for the cycloadditon reactions of enamino ketone **1** with enol ethers **4**, **7**–**9**, and **11** in dichloromethane solution at 1000 bar

At identical pressure and temperature, the product ratio, c_{cis}/c_{trans}, increases in the order R^2 = *tert*-butyl (**9**) < *p*-$MeOC_6H_4$ (**11**) ≈ isopropyl (**8**) < isobutyl (**7**) < ethyl (**4**). For example, at 1000 bar and 80°C, the product ratios are 0.34:1 (25% *cis* product) for R^2 = *tert*-butyl, 0.98:1 (49% *cis* product) for R^2 = isopropyl, 1.72:1 (63% *cis* product) for R^2 = isobutyl, and 2.01:1 (67% *cis* product) for R^2 = ethyl. The $\Delta\Delta H^{\neq}$ values are found to be between $-(4.7 \pm$

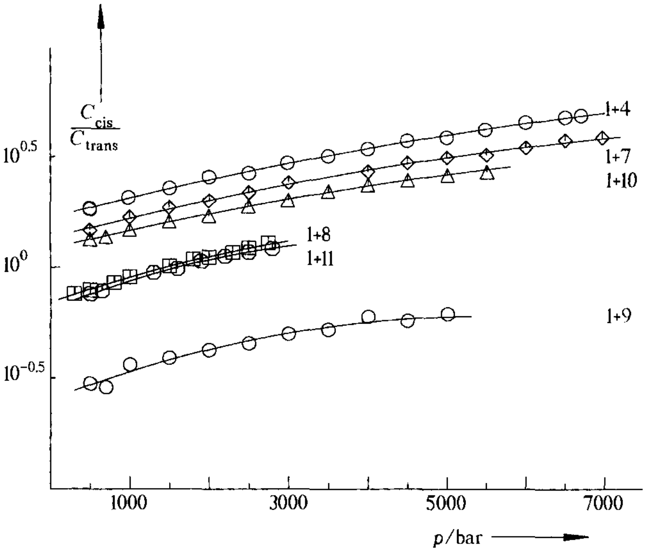


Figure 4. Pressure dependence of the product ratio of *cis*/*trans* diastereomers for the cycloaddition reactions of enamino ketone **1** with enol ethers **4** and **7**–**11** in dichloromethane solution at 90°C

1.4) kJ/mol for R^2 = *tert*-butyl (**9**) and −(9.9 ± 1.6) kJ mol^{-1} for R^2 = *p*-$MeOC_6H_4$ (**11**).

Figure 4 illustrates the pressure dependence of c_{cis}/c_{trans} for the cycloaddition reactions of enamino ketone **1** with enol ethers **4** and **7**−**11**. The data points are calculated for 90°C from the experimental values at different temperatures by using Eq. (6) and the individual ΔH^{+} values in Table 2.

The c_{cis}/c_{trans} ratio clearly increases with pressure, e.g. for R^2 = *tert*-butyl (**9**) at 90°C from 0.32:1 (24% *cis* product) at ambient pressure up to 0.90:1 (47% *cis* product) at 7000 bar. The corresponding increase for the reaction of **1** with **4** is from 2.2:1 (69% *cis* product) (1 bar) to 6.3:1 (86% *cis* product) (7000 bar). The comparison of selectivities for the vinyl ethers with ethyl (**4**) and with *tert*-butyl (**9**) substituents indicates (Figures 3 and 4) that increasing steric demand lowers the c_{cis}/c_{trans} product ratio. The alkyl vinyl ethers **7** and **8** satisfactorily fit into this scheme if it is assumed that the steric demand is primarily determined by the character of the carbon atom adjacent to the oxygen atom. CH_2 groups in this position as in **4** and **7** and also in benzyl vinyl ether (**10**) lead to relatively high *cis* selectivity. The c_{cis}/c_{trans} ratio is smaller for a $CH(CH_3)_2$ group, as in **8**, and the lowest selectivity is found in **9** where a tertiary carbon atom is next to the ether oxygen atom.

The preceding discussion of the c_{cis}/c_{trans} product ratios is based on the assumption that the diastereomeric species are produced under kinetic control which states that the c_{cis}/c_{trans} ratio equals the ratio of the corresponding rate coefficients [Eq. (9)].

$$c_{cis}/c_{trans} = k_{cis}/k_{trans} \tag{9}$$

The overall rate coefficient k for the parallel reactions is given Eq. (10).

$$k = k_{cis} + k_{trans} \tag{10}$$

Via Eqs. (9) and (10), k_{cis} and k_{trans} are easily and directly obtained from the primary experimental quantities k and c_{cis}/c_{trans} given in Table 1 and for the cycloaddition reactions of **1**−**3** with **4** (in Table 1 of Ref.[3]).

The temperature dependence of k_{trans}, with the transformation presumably occurring through an *exo*-(*E*)-*anti* transition state, is given for the cycloaddition reactions of **1** with **4**, **7**, and **9** as well as of **2** and **3** with **4** in Figure 5. All data refer to 1000 bar. The corresponding values for k_{cis}, where the reaction is assumed to occur via an *endo*-(*E*)-*syn* transition state, are plotted in Figure 6.

The data in Figures 5 and 6 clearly show that substitution on the diene and on the dienophile has a much stronger effect on k_{cis} than on k_{trans} which provides strong support for the postulated reaction pathways proceeding via *endo* and *exo* transition states, respectively.

It is to be expected that k_{cis} and k_{trans} are influenced by both electronic and steric effects of the substituents. Changing the alkyl substituent on the vinyl ether (**4**, **7**, **9**), in cycloadditions with the same diene (**1**), should enhance the reaction rate coefficient from ethyl (**4**) to *tert*-butyl (**9**) due to an increasing +*I* effect whereas due to the increasing steric hindrance within the same sequence – ethyl (**4**) ⩽ isobutyl (**7**) < *tert*-butyl (**9**) – the rate coefficient should be lowered. Inspection of the data in Figure 5 and 6 for the different vinyl ethers reacting with **1** suggests that the electronic effect determines k_{trans} as k_{trans}(**1** + **9**) is slightly, but significantly above k_{trans}(**1** + **4**) and k_{trans}(**1** + **7**). The steric argument, as is to be expected, is dominant for the reaction proceeding via the *endo* transition state (Figure 6), and k_{cis}(**1** + **9**) is well below k_{cis}(**1** + **4**) and k_{cis}(**1** + **7**) which are identical within the limits of experimental accuracy.

Changing the substituent on the hetero diene (**1**−**3**), in cycloaddition reactions with the same dienophile (**4**), should enhance the rate coefficient due to an increasing electron

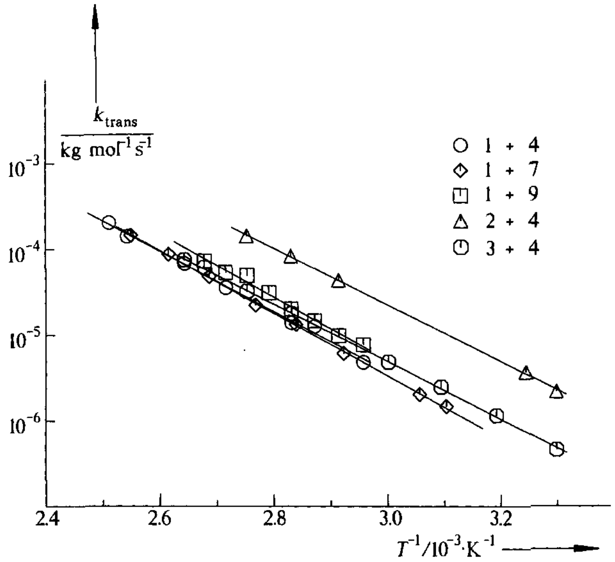


Figure 5. Temperature dependence of the individual rate coefficients k_{trans} for the cycloaddition reactions of enamino ketone **1** with enol ethers **4**, **7**, and **9** and of enamino ketones **2** and **3** with enol ether **4** in dichloromethane solution at 1000 bar

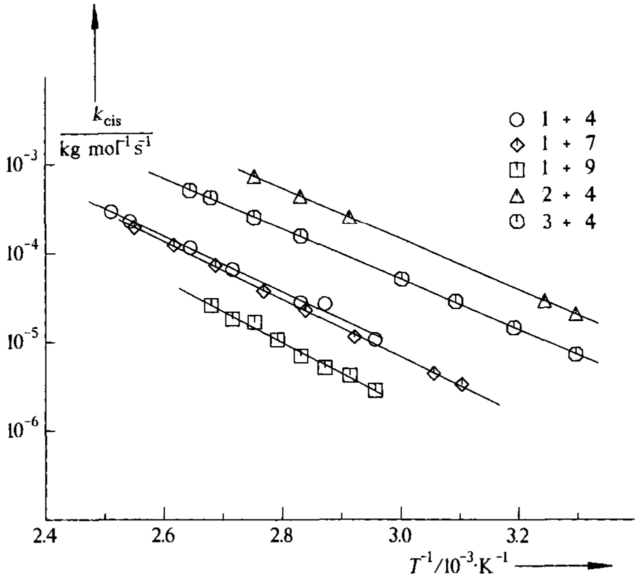


Figure 6. Temperature dependence of the individual rate coefficients k_{cis} for the cycloaddition reactions of enamino ketone **1** with enol ethers **4**, **7**, and **9** and of enamino ketones **2** and **3** with enol ether **4** in dichloromethane solution at 1000 bar

withdrawing effect in the sequence CO_2Me (**3**) $\leqslant$ CCl_3 (**1**) < CF_3 (**2**). The steric hindrance should lead to an increase of the cycloaddition rate coefficient in the sequence CCl_3 (**1**) < CF_3 (**2**) $\leqslant$ CO_2Me (**3**). Inspection of the experimental data in Figures 5 and 6 indicates again that k_{trans} is essentially determined by the electronic effect: k_{trans}(**3** + **4**) $\leqslant$ k_{trans}(**1** + **4**) < k_{trans}(**2** + **4**). As is to be expected, the steric contributions are important for the *endo* transition state. Thus, k_{cis}(**3** + **4**) is well above k_{cis}(**1** + **4**). Although the steric hindrance by the CF_3 (**2**) substituent may be slightly higher than by CO_2Me (**3**), k_{cis}(**2** + **4**) is largest because of the electronic effect.

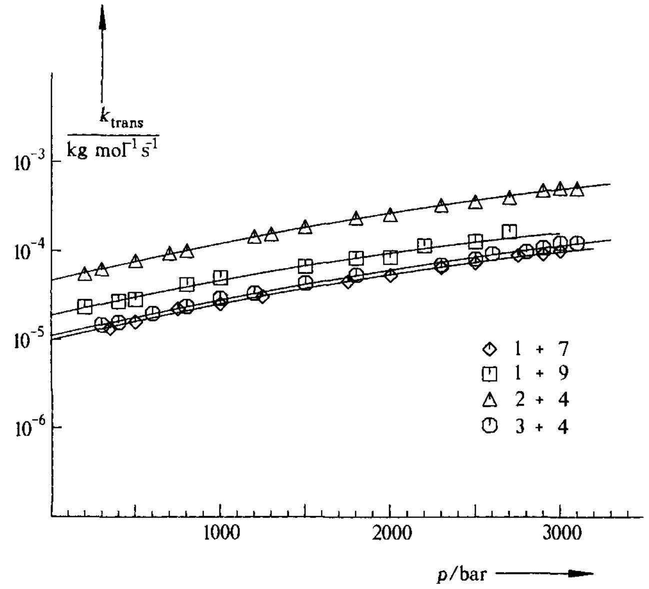


Figure 7. Pressure dependence of the individual rate coefficients k_{trans} for the cycloaddition reactions of enamino ketone **1** with enol ethers **7** and **9** and of enamino ketones **2** and **3** with enol ether **4** in dichloromethane solution at 90°C

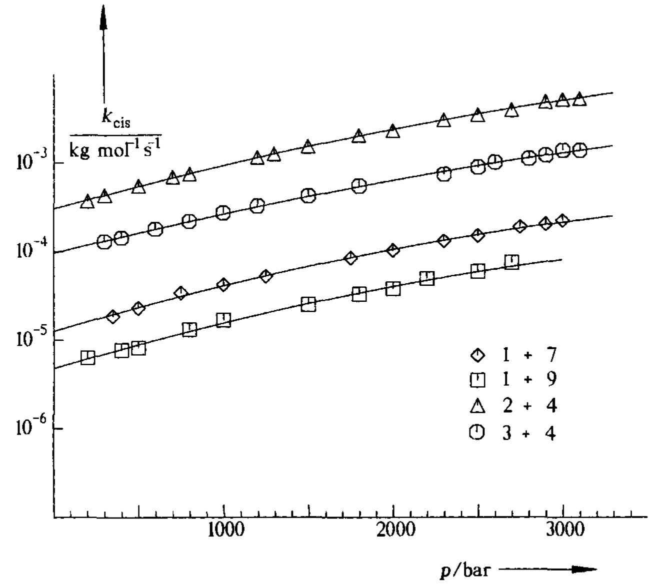


Figure 8. Pressure dependence of the individual rate coefficients k_{cis} for the cycloaddition reactions of enamino ketone **1** with enol ethers **7** and **9** and of enamino ketones **2** and **3** with enol ether **4** in dichloromethane solution at 90°C

The pressure dependence of individual cycloadditon rate coefficients, k_{trans} and k_{cis}, is shown in Figures 7 and 8. The data refer to a common temperature of 90°C. As has also been found from Figures 5 and 6, the change in the rate coefficient with a substituent on the diene and the dienophile is larger for k_{cis} than for k_{trans}.

It appears especially interesting to compare the kinetic data for the systems **1** + **4** or **1** + **7** (both have almost identical rate coefficients) with **1** + **9** and with **3** + **4**. The rate coefficients k_{trans} for the cycloadditions are very similar (Figure 5) with k_{trans}(**1** + **9**) being slightly above the corresponding values for **1** + **4**, **1** + **7**, and **3** + **4** (Figures 5 and 7). The data suggest that the electronic effects of CCl_3 and CO_2Me substituents on the diene are close to one another and that steric effects are less important for those *exo* transition states. It is presumably because of the $+I$ effect that k_{trans} for **1** + **9** slightly exceeds the k_{trans} values in the **1** + **4** and **1** + **7** cycloadditions.

On the other hand, steric contributions clearly influence the *endo* transition states leading to the *cis* diastereomers. With k_{cis} for the cycloadditions of **1** + **4** taken as a reference (Figure 6), the bulky *tert*-butyl substituent on the dienophile (**1** + **9**) leads to an appreciable decrease of k_{cis}, and the smaller ester substituent on the diene (**3** + **4**) gives rise to a pronounced increase in k_{cis}.

The influence of substituents may also be studied by the individual activation parameters derived from the pressure and temperature dependence of k_{cis} and k_{trans}. Activation volumes and activation enthalpies for some of the cycloaddition reactions from Figures 5–8 are presented in Table 5. The values for the pressure-averaged activation volume $\overline{\Delta V^{\ddagger}_{trans}}$ are almost identical. The values of $\overline{\Delta V^{\ddagger}_{cis}}$ are clearly more negative which is consistent with the well-established rule that high pressure favours sterically hindered processes, such as these *endo* transitions, stating that the corresponding activation volumes are smaller. It is to be expected, that the steric hindrance is smallest for the ethyl substituent on the dienophile (**4**) and the CO_2R group on the diene (**3**). This

Table 5. Activation volumes and activation enthalpies determined from the individual rate coefficients for several hetero Diels-Alder reactions (A: $\overline{\Delta V^{\ddagger}_{cis}}$ [$cm^3\ mol^{-1}$]; B: $\overline{\Delta V^{\ddagger}_{trans}}$ [$cm^3\ mol^{-1}$]; C: $\overline{\Delta\Delta V^{\ddagger}}$ [$cm^3\ mol^{-1}$]; D: $\Delta H^{\ddagger}_{cis}$ [$kJ\ mol^{-1}$]; E: $\Delta H^{\ddagger}_{trans}$ [$kJ\ mol^{-1}$]; F: $\Delta\Delta H^{\ddagger}$ [$kJ\ mol^{-1}$])

System	A[a]	B[a]	C
3 + **4**	−25.1	−22.7	−2.4
2 + **4**	−27.2	−22.9	−4.3
1 + **7**	−27.3	−22.2	−5.1
1 + **9**	−29.6	−22.8	−6.8

System	D[b]	E[b]	F
3 + **4**	51.3	61.3	−10.0
2 + **4**	51.6	60.3	−8.7
1 + **4**	56.5	64.2	−7.7
1 + **7**	59.1	66.9	−7.8
1 + **9**	64.0	67.6	−3.6

[a] 90°C. – [b] 1000 bar.

assumption is supported by the particularly small value for the difference in activation volume, $\Delta\Delta V^{+}$. The observation that the pressure-induced *cis* diastereoselectivity is larger in systems where the selectivity at ambient pressure is lower due to steric reasons may also be easily understood from the data in Table 5. The strongest steric hindrance (reaction **1** + **9**) is accompanied by both the lowest value of k_{cis} and the largest negative value for $\Delta\Delta V^{+}$.

As can be seen from the ΔH^{+} values in Table 5, the activation enthalpy of the sterically hindered transition state for the **1** + **9** cycloaddition is fairly high and rather similar to the activation enthalpies of the *exo* transition states (ΔH^{+}_{trans}). The ΔH^{+}_{trans} values for the different cycloadditions are rather similar and well above the ΔH^{+}_{cis} values for the reactions of **2** + **4** and **3** + **4**. The low activation barrier for these two processes is responsible for the appreciably high *cis* diastereoselectivity of these reactions even at ambient pressure.

The description of cycloaddition reactions in terms of individual rate coefficients, k_{cis} and k_{trans}, and of their temperature and pressure dependence, which have been measured by us for the first time, provides an adequate understanding of the stereocontrol in these systems. The values are of special interest with respect to model calculations of rate coefficients and activation energies. Moreover, they may be used to predict which substituents on the diene or on the dienophile might further increase selectivity.

A higher stereoselectivity can also be reached by reaction in an appropriate solvent. In Figure 9, the pressure dependence of the product ratio, c_{cis}/c_{trans}, at 90°C is plotted for the reaction of **1** with **4** in different solvents: acetonitrile (data from Table 3), dichloromethane[2,3,7], and a 2:1 mixture of heptane/isodurene[3,7]. The *cis* diastereoselectivity increases with the polarity of the solvent. At ambient pressure, the product ratios are 0.90:1 (47% *cis* product) in heptane/isodurene, 1.7:1 (63% *cis* product) in dichloromethane, and 1.8:1 (64% *cis* product) in acetonitrile.

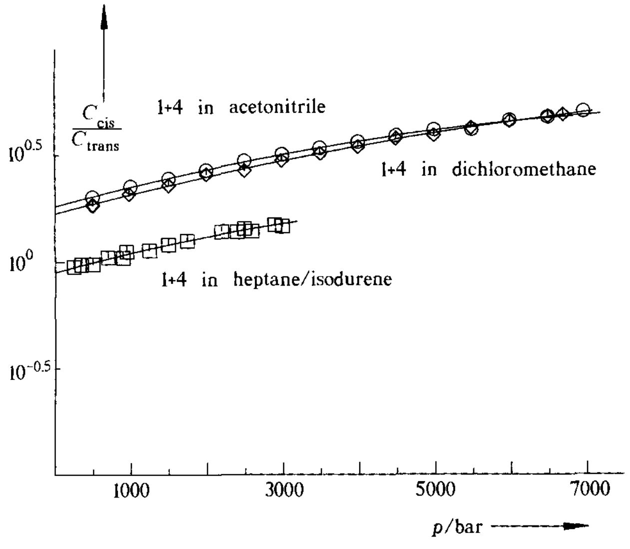


Figure 9. Pressure dependence of the product ratio of *cis*/*trans* diastereomers for the cycloaddition reaction of enamino ketone **1** with enol ether **4** at 90°C in acetonitrile, in dichloromethane, and in a 2:1 mixture of heptane/isodurene

As precise overall rate coefficients k could not yet be determined from IR spectra taken during the cycloadditions in acetonitrile and in heptane/isodurene, the question to which extent individual rate coefficients k_{cis} and k_{trans} vary with the solvent may not be answered at the moment. The pressure dependence of c_{cis}/c_{trans}, corresponding to $\Delta\Delta V^{+}$, within the limits of experimental accuracy is the same for the **1** + **4** cycloadditions in these three solvents (see Table 4).

The kinetic analysis demonstrates that high *cis* diastereoselectivity can be achieved in the hetero Diels-Alder reaction of phthalimidobutenones with vinyl ethers by appropriate choice of the substituents on the diene and dienophile, based on the study of individual rate coefficients at temperatures as low as possible, at pressures as high as possible, and in highly polar solvents.

Generous support of this work by the *Deutsche Forschungsgemeinschaft* (SFB 93 "Photochemie mit Lasern") and by the *Fonds der Chemischen Industrie* is gratefully acknowledged. We thank Dr. *R. Seele*, BASF, for his gifts of several enol ethers and Dr. *H. P. Vögele* for his valuable support in completing this work.

Experimental

The high-pressure cells and details about the experimental setup and procedures have been described[2,3]. The experimental pressures were determined to better than ±10 bar. The uncertainty in temperature was below ±0.5°C. HPLC parameters: detection wavelength: λ = 240 nm; **5a**/**6a**: column Nucleosil 7C18, 250 mm, 7 µm, eluent acetonitrile/water (40:60), flow 0.9 ml/min, t_R(**5a**) = 21 min, t_R(**6a**) = 26 min; **12a**/**13a**: column LiChrospher 100 RP-18, 250 mm, 5 µm, eluent acetonitrile/water (55:45), flow 1.5 ml/min, t_R(**12a**) = 33 min, t_R(**13a**) = 39 min; **12b**/**13b**: column LiChrospher 100 RP-18, 250 mm, 5 µm, eluent acetontrile/water (65:35), flow 1.5 ml/min, t_R(**12b**) = 15 min, t_R(**13b**) = 17 min; **12c**/**13c**: column Nucleosil 100C18, 500 mm, 5 µm, eluent acetonitrile/water (75:25), flow = 3.0 ml/min, t_R(**12c**) = 19 min, t_R(**13c**) = 22 min; **12d**/**13d**: column 2 sequel connected LiChrospher 100 RP-18, 250 mm, 5 µm, eluent acetonitrile/water (65:35), flow = 1.0 ml/min, t_R(**12d**) = 48 min, t_R(**13d**) = 54 min. Knauer HPLC system using a Merck-Hitachi Integrator D-2500. Acetonitrile was purchased from commercial sources, water was bidistilled in quartz vessels. The solvents were automatically mixed and filtered through a membrane filter (0.2 µm) prior to use. — ^{1}H and ^{13}C NMR: Varian XL-200 and VXR-200, multiplets were determined with the APT pulse sequence. — IR: Bruker IFS 25 and Perkin-Elmer 297. — UV: Varian Cary 219. — MS: Varian MAT 311 A. — Elemental analyses were carried out in the analytical laboratory of the university. — All solvents were distilled prior to use.

(2SR,4SR)- and (2SR,4RS)-2-Isobutyloxy-4-phthalimido-6-trichloromethyl-3,4-dihydro-2H-pyran (**12a** and **13a**): A solution of **1** (110 mg, 0.35 mmol), 2-*tert*-butyl-4-methylphenol (2 mg) and isobutyl vinyl ether (**7**) (2 ml) in 6 ml of toluene was heated at 120°C for 24 h in a pressure flask. After removal of the solvent in vacuo, the residue was purified by column chromatography on silica gel [diethyl ether/petroleum ether (1:1)]. — Yield 134 mg (91%) of **12a**/**13a** in a ratio of 1.5:1 (HPLC). — R_f = 0.54 [diethyl ether/petroleum ether (1:1)]. — IR (KBr): $\tilde{\nu}$ = 2956 cm^{-1} (C—H), 1716 (C=O). — UV (CH$_3$CN): λ_{max} (lg ε) = 220 nm (4.666), 292 (3.413). — ^{1}H NMR (200 MHz, CDCl$_3$): δ = 0.86—0.97 [m, 6H,

$CH(C\mathit{H}_3)_2$], 1.81 – 2.00 [m, 1 H, $C\mathit{H}(CH_3)_2$], 2.03 – 2.16 (m, 0.6 H, 3-H_{eq}), 2.19 (dddd, *J* = 1.5, 2.0, 6.5, 13 Hz, 0.4 H, 3-H_{eq}), 2.53 – 2.72 (m, 1 H, 3-H_{ax}), 3.31 – 3.46 [m, 1 H, $OC\mathit{H}_2CH(CH_3)_2$], 3.76 – 3.88 [m, 1 H, $OC\mathit{H}_2CH(CH_3)_2$], 5.13 – 5.38 (m, 1.4 H, 2-, 4-H), 5.46 (t, *J* = 3.0 Hz, 0.6 H, 2-H), 5.73 (m_c, 1 H, 5-H), 7.69 – 7.89 (m, 4 H, phthaloyl-H). – ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 19.15, 19.24, 19.28, 19.32 [$OCH_2CH(\mathit{C}H_3)_2$]; 28.33 [$OCH_2\mathit{C}H(CH_3)_2$]; 29.28, 30.93 (C-3); 40.55, 42.96 (C-4); 75.62, 76.46 [$O\mathit{C}H_2CH(CH_3)_2$]; 92.50 (CCl_3), 99.03, 100.1 (C-2); 101.3, 101.6 (C-5); 123.3, 123.4 (phthaloyl C-2); 131.8 (phthaloyl C-1); 134.2 (phthaloyl C-3); 149.0, 150.7 (C-6); 167.3, 167.6 (C=O). – MS (70 eV), *m/z* (%): 419 (3) [M^+], 417 (3) [M^+], 381 (3) [M^+ – Cl], 344 (2) [M^+ – $HOCH_2CH(CH_3)$ or – 2 Cl], 318 (3) [M^+ – $CH_2{=}CHOCH_2CH(CH_3)_2$], 307 (14) [M^+ – Cl, – $(CH_3)_2CHCH_2OH$], 200 (25) [M^+ – CCl_3, – $CH_2{=}CHOCH_2CH(CH_3)_2$], 100 (79) [$CH_2{=}CHOCH_2CH(CH_3)_2^+$].

$C_{18}H_{18}Cl_3NO_4$ (418.7) Calcd. C 51.64 H 4.33
Found C 51.76 H 4.50

(2SR,4SR)- and (2SR,4RS)-2-Isopropyloxy-4-phthalimido-6-trichloromethyl-3,4-dihydro-2H-pyran (**12b** and **13b**): A solution of **1** (111 mg, 0.35 mmol), 2-*tert*-butyl-4-methylphenol (2 mg) and isopropyl vinyl ether (**8**) (2 ml) in 6 ml of toluene was heated at 120°C for 24 h in a pressure flask. After removal of the solvent in vacuo, the residue was purified by column chromatography [diethyl ether/petroleum ether (1 : 1)]. – Yield 129 mg (91%) of **12b/13b** in a ratio of 0.4 : 1 (HPLC). – R_f = 0.47 [diethyl ether/petroleum ether (1 : 1)]. – IR (KBr): $\tilde{\nu}$ = 2978 cm^{-1} (C–H), 1716 (C=O). – UV (CH_3CN): λ_{max} (lg ε) = 221 nm (4.674), 292 (3.332). – ^1H NMR (200 MHz, $CDCl_3$): δ = 1.10 – 1.38 [4 d, *J* = 6.5 Hz, 6 H, $CH(C\mathit{H}_3)_2$], 2.05 (dddd, *J* = 1.0, 3.0, 6.5, 12 Hz, 0.6 H, 3-H_{eq}), 2.16 (dddd, *J* = 1.2, 3.0, 7.0, 13 Hz, 0.4 H, 3-H_{eq}), 2.60 (ddd, *J* = 3.0, 11, 13 Hz, 0.6 H, 3-H_{ax}), 2.61 (ddd, *J* = 9.0, 10, 13 Hz, 0.4 H, 3-H_{ax}), 4.20 [sept, *J* = 6.5 Hz, 0.4 H, $C\mathit{H}(CH_3)_2$], 4.28 [sept, *J* = 6.5 Hz, 0.6 H, $C\mathit{H}(CH_3)_2$], 5.16 – 5.40 (m, 1.4 H, 2-, 4-H), 5.62 (t, *J* = 3.0 Hz, 0.6 H, 2-H), 5.72 (m_c, 1 H, 5-H), 7.70 – 7.88 (m, 4 H, phthaloyl-H). – ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 21.15, 21.73, 23.20, 23.29 [$OCH(\mathit{C}H_3)_2$]; 29.82, 31.26 (C-3); 40.58, 43.05 (C-4); 69.92, 72.01 [$O\mathit{C}H(CH_3)_2$]; 92.47 (CCl_3); 96.49, 99.87 (C-2); 100.1, 101.1 (C-5); 123.3 (phthaloyl C-2); 131.8 (phthaloyl C-1); 134.2 (phthaloyl C-3); 149.1, 150.8 (C-6); 167.3, 167.6 (C=O). – MS (70 eV), *m/z* (%): 328 (0.5) [M^+ – Cl, – C_3H_7], 318 (2) [M^+ – $C_3H_7OCH{=}CH_2$], 310 (4), 308 (6) [M^+ – Cl, – C_3H_7OH], 200 (12) [M^+ – CCl_3, – $C_3H_7OCH{=}CH_2$].

$C_{17}H_{16}Cl_3NO_4$ (404.7) Calcd. C 50.45 H 3.99
Found C 50.60 H 3.92

(2SR,4SR)- and (2SR,4RS)-2-tert-Butyloxy-4-phthalimido-6-trichloromethyl-3,4-dihydro-2H-pyran (**12c** and **13c**): A solution of **1** (100 mg, 0.33 mmol), 2-*tert*-butyl-4-methylphenol (2 mg), and *tert*-butyl vinyl ether (**9**) (2 ml) in 6 ml of toluene was heated at 120°C for 24 h in a pressure flask. The solvent was removed in vacuo and the residue purified by column chromatography [$CHCl_3$/petroleum ether (1 : 2)]. – Yield 120 mg (87%) of **12c/13c** in a ratio of 0.2 : 1 (HPLC). – R_f = 0.35 [$CHCl_3$/petroleum ether (1 : 2)]. – IR (KBr): $\tilde{\nu}$ = 3030 cm^{-1} (=C–H), 2980 (C–H), 1712 (C=O). – UV (CH_3CN): λ_{max} (lg ε) = 220 nm (4.656), 292 (2.314). – ^1H NMR (200 MHz, $CDCl_3$): δ = 1.35 [s, 9 H, $C(C\mathit{H}_3)_3$], 2.05 (dddd, *J* = 1.0, 5.0, 7.0, 13 Hz, 1 H, 3-H_{eq}), 2.45 (ddd, *J* = 3.0, 9.0, 13 Hz, 1 H, 3-H_{ax}), 5.27 (m_c, 1 H, 4-H), 5.44 (dd, *J* = 2.0, 9.0 Hz, 0.2 H, 2-H), 5.63 (dd, *J* = 1.5, 3.0 Hz, 0.2 H, 5-H), 5.69 (dd, *J* = 1.0, 3.0 Hz, 0.8 H, 5-H), 5.81 (dd, *J* = 2.0, 5.0 Hz, 0.8 H, 2-H), 7.80 (m_c, 4 H, phthaloyl-H). – ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 28.67 [$OC(\mathit{C}H_3)_3$]; 31.84, 31.94 (C-3); 40.93, 43.47 (C-4); 76.36, 76.90 [$O\mathit{C}(CH_3)_3$]; 92.43 (CCl_3); 94.20, 96.88 (C-2); 99.86, 100.0 (C-5); 123.3 (phthaloyl C-2); 131.8 (phthaloyl C-1); 134.2 (phthaloyl C-3); 150.0 (C-6); 167.7 (C=O). – MS (70 eV), *m/z* (%): 345 (4) [M^+ – C_4H_9OH], 328 (54) [M^+ – C_4H_9, – Cl], 326 (85) [M^+ – C_4H_9, – Cl], 198 (30) [M^+ – CCl_3, – C_4H_9OH].

$C_{18}H_{18}Cl_3NO_4$ (418.7) Calcd. C 51.64 H 4.33
Found C 51.84 H 4.44

(2SR,4SR)- and (2SR,4RS)-2-Benzyloxy-4-phthalimido-6-trichloromethyl-3,4-dihydro-2-H-pyran (**12d** and **13d**): A solution of **1** (105 mg, 0.33 mmol), 2-*tert*-butyl-4-methylphenol (2 mg) and benzyl vinyl ether (**10**) (2 ml) in 6 ml of toluene was heated at 120°C for 24 h in a pressure flask. The solvent was removed in vacuo and the residue purified by column chromatogryaphy [diethyl ether/petroleum ether (1 : 1)] to give 148 mg (99%) of **12d/13d** in a ratio of 1.5 : 1 (HPLC). – R_f = 0.48 [diethyl ether/petroleum ether (1 : 1)]. – IR (Film): $\tilde{\nu}$ = 3032 cm^{-1} (=C–H), 2946 (C–H), 1716 (C=O). – UV (CH_3CN): λ_{max} (lg ε) = 220 nm (4.636), 289 (3.407). – ^1H NMR (200 MHz, $CDCl_3$): δ = 2.06 – 2.25 (m, 1 H, 3-H_{eq}), 2.58 – 2.74 (m, 1 H, 3-H_{ax}), 4.73 (d, *J* = 4.5 Hz, 0.4 H, $C\mathit{H}_2Ph$), 4.79 (d, *J* = 4.5 Hz, 0.6 H, $C\mathit{H}_2Ph$), 5.01 (d, *J* = 4.5 Hz, 0.6 H, $C\mathit{H}_2Ph$), 5.07 (d, *J* = 4.5 Hz, 0.4 H, $C\mathit{H}_2Ph$), 5.16 (ddd, *J* = 3.0, 7.0, 10 Hz, 0.6 H, 4-H), 5.27 (dd, *J* = 2.0, 8.5 Hz, 0.4 H, 2-H), 5.36 (dddd, *J* = 0.5, 2.5, 6.5, 11 Hz, 0.4 H, 4-H), 5.55 (t, *J* = 3.5 Hz, 0.6 H, 2-H), 5.73 – 5.79 (m, 1 H, 5-H), 7.28 – 7.41 (m, 5 H, Ph-H), 7.68 – 7.88 (m, 4 H, phthaloyl-H). – ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 29.04, 30.84 (C-3); 40.45, 42.79 (C-4); 70.24, 70.62 ($O\mathit{C}H_2Ph$); 92.06, 92.47 (CCl_3); 99.03, 100.1 (C-2); 100.4, 101.7 (C-5), 123.3, 123.4 (phthaloyl C-2), 127.6, 127.7 (Ph C-*o*); 128.1, 128.4 (Ph C-*p*); 128.4, 128.5 (Ph C-*m*), 131.7, 131.8 (phthaloyl C-1); 134.1, 134.2 (phthaloyl C-3); 136.4, 136.8 (Ph C-*i*); 148.9, 150.6 (C-6); 167.3, 167.5 (C=O). – MS (70 eV), *m/z* (%): 453 (0.5) [M^+], 451 (0.5) [M^+], 416 (7) [M^+ – Cl], 362 (32) [M^+ – C_7H_7], 308 (26) [M^+ – Cl, – $C_6H_5CH_2OH$], 200 (62) [M^+ – CCl_3, – $CH_2{=}CHOCH_2C_6H_5$], 91 (100) [$C_7H_7^+$].

$C_{21}H_{16}Cl_3NO_4$ (452.7) Calcd. C 56.71 H 3.56
Found C 56.75 H 3.70

(2SR,4SR)- and (2SR,4RS)-2-p-Methoxyphenyl-4-phthalimido-6-trichloromethyl-3,4-dihydro-2H-pyran (**12e** and **13e**): A solution of **1** (223 mg, 0.70 mmol), 2-*tert*-butyl-4-methylphenol (2 mg), and *p*-methoxyphenyl vinyl ether (**11**) (4 ml) in 12 ml of toluene was heated at 120°C for 44 h in a pressure flask. The solvent was removed in vacuo and the residue purified by column chromatography [*tert*-butyl methyl ether/petroleum ether (1 : 1)]. – Yield 280 mg (85%) of **12e/13e** in a ratio of 0.2 : 1 (HPLC). – R_f = 0.51 [*tert*-butyl methyl ether/petroleum ether (1 : 1)]. – IR (KBr): $\tilde{\nu}$ = 3058 cm^{-1} (=C–H), 2954 (C–H), 1716 (C=O). – UV (CH_3CN): λ_{max} (lg ε) = 222 nm (4.772), 286 (3.651). – ^1H NMR (200 MHz, $CDCl_3$): δ = 2.26 – 2.45 (m, 1 H, 3-H_{eq}), 2.67 – 2.91 (m, 1 H, 3-H_{ax}), 3.79 (s, 3 H, OCH_3), 5.28 (ddd, *J* = 3.0, 6.5, 9.5 Hz, 0.3 H, 4-H), 5.50 (ddd, *J* = 2.5, 6.5, 10 Hz, 0.7 H, 4-H), 5.74 (dd, *J* = 2.0, 9.0 Hz, 0.3 H, 2-H), 5.83 (dd, *J* = 1.0, 2.5 Hz, 1 H, 5-H), 6.02 (t, *J* = 3.0 Hz, 0.7 H, 2-H), 6.77 – 7.21 (m, 4 H, $MeOC_6\mathit{H}_4$), 7.71 – 7.95 (m, 4 H, phthaloyl-H). – ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 29.58, 30.92 (C-3); 40.37, 42.70 (C-4); 55.59, 55.73 (OCH_3); 91.94 (CCl_3); 97.78, 99.80 (C-2); 100.6, 101.4 (C-5); 114.5, 114.8 ($MeOC_6H_4$, C-*o*); 118.2, 118.5 $MeOC_6H_4$, C-*m*); 123.4, 123.7 (phthaloyl C-2); 131.4, 131.8 (phthaloyl C-1); 134.3, 134.5 (phthaloyl C-3); 149.1 ($MeOC_6H_4$, C-*p*); 150.6, 150.5 (C-6); 155.3, 155.5 ($MeOC_6H_4$, C-*i*); 167.3, 167.6 (C=O). – MS (70 eV), *m/z* (%): 469 (2) [M^+], 467 (2) [M^+], 432 (2) [M^+ – Cl], 344 (40) [M^+ – CCl_3 or – $OC_6H_4OCH_3$], 308 (38) [M^+ – $OC_6H_4OCH_3$, – Cl], 197 (100) [M^+ – CCl_3, – $CH_2{=}CHOC_6H_4OCH_3$], 124 (100) [$HOC_6H_4OCH_3^+$].

$C_{21}H_{16}Cl_3NO_5$ (468.7) Calcd. C 53.81 H 3.44
Found C 53.96 H 3.55

[1] Part 39: L. F. Tietze, J. Fennen, J. Wichmann, *Chem. Ber.* **1992**, *125*, 1507–1511.

[2] L. F. Tietze, T. Hübsch, E. Voß, M. Buback, W. Tost, *J. Am. Chem. Soc.* **1988**, *110*, 4065–4066.

[3] M. Buback, W. Tost, T. Hübsch, E. Voß, L. F. Tietze, *Chem. Ber.* **1989**, *122*, 1179–1186.

[4] L. F. Tietze, T. Hübsch, M. Buback, W. Tost, *High Press. Res.* **1990**, *5*, 638–640.

[5] [5a] L. F. Tietze, E. Voß, *Tetrahedron Lett.* **1986**, *27*, 6181–6184. – [5b] L. F. Tietze, A. Bergmann, G. Brill, K. Brüggemann, U. Hartfiel, E. Voß, *Chem. Ber.* **1989**, *122*, 83–94.

[6] [6a] L. F. Tietze, U. Hartfiel, T. Hübsch, E. Voß, J. Wichmann, *Chem. Ber.* **1991**, *124*, 881–888. – [6b] L. F. Tietze, U. Hartfiel, T. Hübsch, E. Voß, K. Bogdanowicz-Szwed, J. Wichmann, *Liebigs Ann. Chem.* **1991**, 275–281.

[7] W. Tost, Thesis, Göttingen, **1988**.

[8] [8a] F. J. Kezdy, J. Jaz, A. Bruylants, *Bull. Soc. Chim. Belg.* **1958**, *67*, 687–706. – [8b] E. S. Swinbourne, *J. Chem. Soc.* **1960**, 2371–2372.

[9] F. G. Klärner, *Chem. Unserer Zeit* **1989**, *23*, 53–63.

[10] [10a] T. Asano, W. J. le Noble, *Chem. Rev.* **1978**, *78*, 407–489. – [10b] K. Matsumoto, A. Sera, *Synthesis* **1985**, 999–1027. – [10c] R. van Eldik, T. Asano, W. J. le Noble, *Chem. Rev.* **1989**, *89*, 549–688.

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