Inter- and Intramolecular Hetero Diels-Alder Reactions, 49[1]

Kinetics and Selectivity of the Intramolecular Hetero Diels-Alder Reaction of 1-Oxa-1,3-butadienes using a Benzylidenebarbituric Acid Derivative Effect of Pressure, Temperature, and Solvent

Michael Buback*[a], Kerstin Gerke[a], Christian Ott[b], and Lutz F. Tietze*[b]

Institut für Physikalische Chemie der Universität Göttingen[a], Tammannstraße 6, D-37077 Göttingen, Germany

Institut für Organische Chemie der Universität Göttingen[b], Tammannstraße 2, D-37077 Göttingen, Germany

Received May 2, 1994

Key Words: Hetero Diels-Alder reactions, intramolecular / High pressure reactions / Regioselectivity / 1-Oxa-1,3-butadienes / Volume profiles / Solvent effects

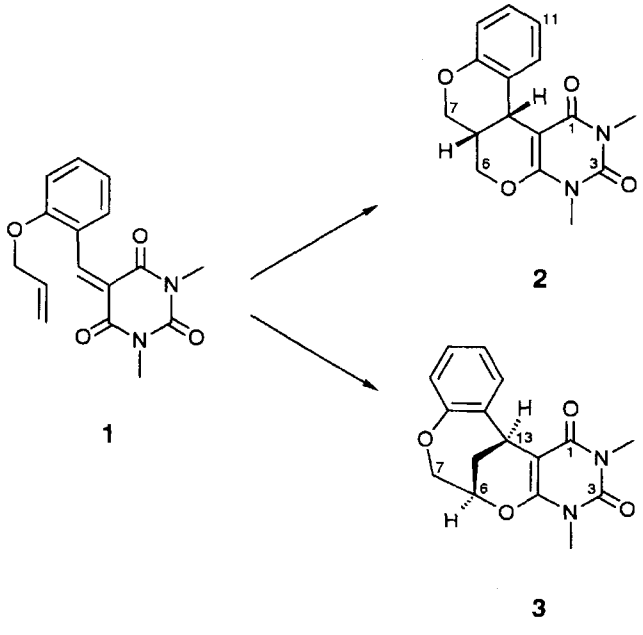
The intramolecular hetero Diels-Alder reaction of the benzylidenebarbituric acid derivative **1** to give the *ortho* and *meta* products **2** and **3** is studied under high pressure up to 6 kbar in various solvents. The kinetics is measured by on-line FT-IR spectroscopy up to 3 kbar. The cycloaddition shows a pressure-dependent increase in regioselectivity in favour of the *ortho* adduct **2**. The activation volumes, $\Delta V^{\neq}$, are determined to be $-(33.1 \pm 1.2)$ and $-(34.2 \pm 1.5)$ cm^3 · mol^{-1} for the reactions in dichloromethane and tetrahydrofuran at 100°C, respectively. For the cycloaddition in toluene and acetonitrile the activation volumes are found to be $-(13.4 \pm 1.5)$ and $-(17.0 \pm 4.1)$ cm^3 · mol^{-1}, respectively. Contrary to the large solvent effect on the activation volume, only a minor effect on the activation volume differences, $\Delta\Delta V^{\neq}$, is observed. Measurement of the molar volumes of **1** and the cycloadducts **2** and **3** show a strong solvent dependency.

The application of high pressure to increase the reaction rate and selectivity has been studied for a wide variety of intermolecular Diels-Alder reactions[2]. The results have been used for mechanistic interpretations by many authors. Investigations into the solvent influence on the transition state were performed by Grieger and McCabe in the early seventies[3]. In particular, they elucidated the solvent effect on the Diels-Alder reaction of maleic anhydride with several dienes finding a change in activation volume with the solvent up to 5 cm^3/mol[3b].

Only very few intramolecular Diels-Alder reactions have been studied under high pressure[4]. The reported values for the activation volume indicate a slightly smaller but still preparatively useful pressure effect on the reaction rate. In the light of this it seemed worthwhile to carry out a detailed study of an intramolecular Diels-Alder reaction over a broad pressure range and in several solvents.

In this paper we present data on the kinetics and selectivity of the intramolecular hetero Diels-Alder reaction of the benzylidenebarbituric acid derivative **1** leading to the *ortho* and *meta* addition products **2** and **3** (see Scheme 1). We consider the effects of pressure, temperature, and solvent; we also present data on the molar volumes of the substrate and of the products in dichloromethane, 1-chlorobutane, tetrahydrofuran, acetonitrile, and toluene which allow us to perform calculations of the molar volume of transition structures and of the reaction volumes.

Scheme 1



The cycloaddition has been studied by direct quantitative infrared spectroscopy under high pressure up to 3 kbar. Spectral series in the region of the C=C and C=O fundamentals were measured during each experiment at constant pressure and temperature. As the molecular surrounding is

  0009–2940/94/1111–2241 $ 10.00+.25/0

not varied during the reaction in solution, Lambert-Beer's law holds, and changes in concentration are directly obtained from the measured changes in integrated absorbance. From the time dependence of starting compound and product concentrations, the overall rate coefficient k for the reaction to both *ortho* and *meta* products is derived using the modified Kezdy-Swinbourne procedure for a pseudo first-order reaction[5a,b,d]. Cycloadditions have also been performed on a preparative scale at ambient pressure (xylene, reflux) with satisfactory yields.

The ratios of *ortho* and *meta* product concentrations, c_{ortho}/c_{meta}, have been determined by HPLC analysis of the crude reaction mixtures. The products are formed under kinetic control, which has been verified by isomerization studies in dichloromethane. It is assumed that this is true also for the reaction in the other solvents. Thus, the c_{ortho}/c_{meta} ratio equals the ratio of the corresponding rate coefficients:

$$c_{ortho}/c_{meta} = k_{ortho}/k_{meta} \quad (1)$$

The overall rate coefficients k for the parallel reactions is given by

$$k = k_{ortho} + k_{meta} \quad (2)$$

With the help of Eqs. (1) and (2) the individual rate coefficients k_{ortho} and k_{meta} are easily obtained from the primary experimental quantities k and c_{ortho}/c_{meta}.

Hetero Diels-Alder Reaction of 1

The synthesis of the substrate **1** is performed by Knoevenagel condensation of 2-(2-propenyloxy)benzaldehyde and 1,3-dimethylbarbituric acid in 94% yield. For the intramolecular Diels-Alder reaction at ambient pressure, **1** is heated in xylene for 92 h under reflux to give the *ortho* and the *meta* product **2** and **3** in approximately 70% yield and a ratio of about 4.5:1. These two adducts are separated by chromatography on silica gel. Their structure is elucidated by ^{1}H- and ^{13}C-NMR spectroscopy. Characteristic resonance signals for **2** are found at δ = 4.32 and 4.39 as doublets of doublets with J = 11.5 and 2.0 Hz for 6-H_{ax} and 6-H_{eq} as well as at δ = 4.33 and 4.58 as a doublet of doublets and a doublet of doublets of doublets with J = 12.0 and 11.0 Hz and J = 11.0, 4.5, and 2.0 Hz for 7-H_{ax} and 7-H_{eq}, respectively. Proof for structure **3** is provided by signals at δ = 2.17 as a doublet of triplets with J = 14.0 and 1.5 Hz and at δ = 2.42 as a doublet of triplets of doublets with J = 14.0, 5.5, and 2.0 Hz for the two hydrogen atoms of the methano bridge. The coupling of J = 2.0 Hz can be traced back to a long-range coupling with 7-H_{eq}. In the ^{13}C-NMR spectra using an APT pulse sequence C-6 in **2** resonates at δ = 67.86 indicating a secondary carbon, whereas for the bridge head carbon C-6 in **3** a signal at δ = 76.54 indicates a tertiary carbon.

Determination of Kinetic Parameters

The experimental values for k of the intramolecular Diels-Alder reaction of **1**, as directly obtained from the spectral series, are presented in Tables 1–5. The measured product ratios and the individual rate coefficients, k_{ortho} and k_{meta}, calculated from k and c_{ortho}/c_{meta} using Eqs. (1) and (2), are also included.

Table 1. Experimental rate coefficients k, measured product ratios c_{ortho}/c_{meta}, and individual rate coefficients k_{ortho} and k_{meta} for the intramolecular cycloaddition of **1** in dichloromethane

T = 110 °C

p [bar]	φ [bar]	k [10^{-5} s^{-1}]	$\frac{c_{ortho}}{c_{meta}}$	k_{meta} [10^{-5} s^{-1}]	k_{ortho} [10^{-5} s^{-1}]
750	627	1.46	4.15	0.284	1.18
1000	806	1.68	4.21	0.322	1.36
1200	943	2.19	4.26	0.416	1.77
1500	1139	2.76	4.29	0.522	2.24
1750	1326	3.20	4.35	0.598	2.60
2000	1446	3.83	4.36	0.715	3.12
2500	1734	4.93	4.40	0.913	4.02
2800	1900	5.20	4.42	0.959	4.24
4000			4.60		
6000			4.76		

p = 1500 bar

T [K]	k [10^{-5} s^{-1}]	$\frac{c_{ortho}}{c_{meta}}$	k_{meta} [10^{-5} s^{-1}]	k_{ortho} [10^{-5} s^{-1}]
363.15	.500	4.50	0.091	0.409
373.15	1.18	4.34	0.221	0.959
383.15	2.76	4.29	0.522	2.24
393.15	5.60	4.17	1.08	4.52
403.15	13.0	4.11	2.54	10.5
413.15	23.9	3.99	4.79	19.1

The temperature dependence of the individual rate coefficients yields activation enthalpies according to Eq. (3).

$$\Delta H^{\neq} = -R\,(\mathrm{d}\ln k/\mathrm{d}\,T^{-1})_p - RT \quad (3)$$

Activation volumes are obtained from ln k versus pressure data by the method described by El'yanov et al.[6] using the following expressions:

$$\ln k_p = \ln k_0 - \Delta V^{\neq}/RT \cdot \varphi \quad (4)$$

with

$$\varphi = [(1+\alpha)p - (\alpha/\beta)(1+\beta p)\ln(1+\beta p)] \quad (5)$$

The coefficients α and β have been determined empirically from the study of 56 Diels-Alder reactions to be α = 0.170 and $\beta = 4.94 \cdot 10^{-3}$ bar^{-1} [6]. By this El'yanov procedure the ln k vs. pressure plots in general are curved and may be represented by linear ln k vs. φ plots in most cases[5d]. The slope of these straight lines directly yields the activation volume at zero pressure [Eq. (4)].

According to Eq. (1), the pressure and temperature dependence of ln (c_{ortho}/c_{meta}) yield the difference in activation

Table 2. Experimental rate coefficients k, measured product ratios c_{ortho}/c_{meta}, and individual rate coefficients k_{ortho} and k_{meta} for the intramolecular cycloaddition of **1** in 1-chlorobutane

T = 110 °C

p [bar]	φ [bar]	k [10^{-5} s^{-1}]	$\frac{c_{ortho}}{c_{meta}}$	k_{meta} [10^{-5} s^{-1}]	k_{ortho} [10^{-5} s^{-1}]
500	436	.97	4.16	0.189	0.785
1250	976	1.26	4.28	0.239	1.02
1500	1139	1.77	4.58	0.318	1.45
1750	1295	1.57	4.67	0.277	1.29
2000	1446	2.02	4.45	0.371	1.65
2500	1734	3.54	4.47	0.646	2.89
4000			4.55		
5000			4.70		
6000			4.82		

p = 1500 bar

T [K]	k [10^{-5} s^{-1}]	$\frac{c_{ortho}}{c_{meta}}$	k_{meta} [10^{-5} s^{-1}]	k_{ortho} [10^{-5} s^{-1}]
368.15	.360	4.47	0.066	0.29
373.15	.560	5.05	0.093	0.47
383.15	1.05	4.58	0.188	0.86
415.15	14.0	4.00	2.80	11.20

Table 3. Experimental rate coefficients k, measured product ratios c_{ortho}/c_{meta}, and individual rate coefficients k_{ortho} and k_{meta} for the intramolecular cycloaddition of **1** in tetrahydrofuran

T = 110 °C

p [bar]	φ [bar]	k [10^{-5} s^{-1}]	$\frac{c_{ortho}}{c_{meta}}$	k_{meta} [10^{-5} s^{-1}]	k_{ortho} [10^{-5} s^{-1}]
750	627	3.80	3.79	0.793	3.01
1000	806	4.38	3.90	0.894	3.49
1500	1139	5.97	3.97	1.20	4.77
2000	1446	9.59	4.03	1.91	7.68
2500	1734	13.6	4.10	2.67	10.9
3000	2007	15.0	4.17	2.90	12.1

p = 1500 bar

T [K]	k [10^{-5} s^{-1}]	$\frac{c_{ortho}}{c_{meta}}$	k_{meta} [10^{-5} s^{-1}]	k_{ortho} [10^{-5} s^{-1}]
353.15	.560	4.23	0.110	0.45
383.15	5.97	3.97	1.20	4.77
393.15	16.0	3.89	3.27	12.7
403.15	37.5	3.88	7.68	29.8

volumes, $\Delta\Delta V^{\neq}$, and in activation enthalpies, $\Delta\Delta H^{\neq}$, respectively [Eqs. (6) and (7)].

$$\Delta\Delta V^{\neq} = \Delta V^{\neq}_{ortho} - \Delta V^{\neq}_{meta} \quad (6)$$

$$\Delta\Delta H^{\neq} = \Delta H^{\neq}_{ortho} - \Delta H^{\neq}_{meta} \quad (7)$$

Table 4. Experimental rate coefficients k, measured product ratios c_{ortho}/c_{meta}, and individual rate coefficients k_{ortho} and k_{meta} for the intramolecular cycloaddition of **1** in acetonitrile

T = 110 °C

p [bar]	φ [bar]	k [10^{-5} s^{-1}]	$\frac{c_{ortho}}{c_{meta}}$	k_{meta} [10^{-5} s^{-1}]	k_{ortho} [10^{-5} s^{-1}]
500	436	1.53	5.40	0.240	1.29
1000	806	2.77	5.54	0.424	2.35
1250	976	3.15	5.62	0.476	2.67
1500	1139	2.16	5.64	0.325	1.83
2000	1446	3.31	5.90	0.480	2.83
3000	2007	4.09	5.95	0.588	3.50
4000			6.33		

Table 5. Experimental rate coefficients k, measured product ratios c_{ortho}/c_{meta}, and individual rate coefficients k_{ortho} and k_{meta} for the intramolecular cycloaddition of **1** in toluene

T = 110 °C

p [bar]	φ [bar]	k [10^{-5} s^{-1}]	$\frac{c_{ortho}}{c_{meta}}$	k_{meta} [10^{-5} s^{-1}]	k_{ortho} [10^{-5} s^{-1}]
1000	806	9.27	3.85	1.91	7.36
1500	1139	9.84	3.87	2.02	7.82
1750	1295	10.2	3.96	2.06	8.14
3000	2007	14.9	4.04	2.96	11.9
4000			4.06		
5000			4.22		
6000			4.27		

p = 1500 bar

T [K]	k [10^{-5} s^{-1}]	$\frac{c_{ortho}}{c_{meta}}$	k_{meta} [10^{-5} s^{-1}]	k_{ortho} [10^{-5} s^{-1}]
363.15	2.49	4.05	0.49	2.00
383.15	9.80	3.87	2.01	7.79
393.15	21.0	3.80	4.38	16.6

$\Delta\Delta V^{\neq}$ is determined from the slope of the ln (c_{ortho}/c_{meta})-against-pressure plots according to Eq. (8).

$$\Delta\Delta V^{\neq} = -RT\,(\mathrm{d}\ln(c_{ortho}/c_{meta})/\mathrm{d}\,p)_T \quad (8)$$

$\Delta\Delta H^{\neq}$ is found according to Eq. (9).

$$\Delta\Delta H^{\neq} = -R\,(\mathrm{d}\ln(c_{ortho}/c_{meta})/\mathrm{d}\,T^{-1})_p \quad (9)$$

The activation parameters $\Delta V^{\neq}$ and $\Delta H^{\neq}$ of the individual rate coefficients and the corresponding differences $\Delta\Delta V^{\neq}$ and $\Delta\Delta H^{\neq}$ are summarized in Table 6. The activation enthalpies are found from experiments at 1500 bar. The numbers refer to 110°C. The activation volumes are derived from experiments at 110°C. In addition entropy values, referring to 1500 bar and 110°C, are given in Table 6. They are determined according to Eqs. (10) and (11).

$$\Delta S^{\neq} = R\,[\ln k - \ln(k_B T/h) - (\mathrm{d}\ln k/\mathrm{d}\,T^{-1})_p T^{-1} - 1] \quad (10)$$

$$\Delta\Delta S^{\neq} = R\,[\ln(c_{ortho}/c_{meta}) - (\mathrm{d}\ln(c_{ortho}/c_{meta})/\mathrm{d}\,T^{-1})_p\,T^{-1}] \quad (11)$$

Table 6. Activation parameters and activation parameter differences for the intramolecular cycloaddition of **1**

Solvent	$\Delta\Delta H^{\neq}$ [kJ/mol]	$\Delta H^{\neq}$(ortho) [kJ/mol]	$\Delta H^{\neq}$(meta) [kJ/mol]
Dichloromethane	- (2.7 ± 0.5)	(93.5 ± 0.8)	(96.3 ± 0.8)
1-Chlorobutane	- (4.6 ± 2.3)	(95.0 ± 0.8)	(99.6 ± 0.8)
THF	- (2.2 ± 1.8)	(94.9 ± 0.8)	(97.0 ± 0.8)
Toluene	- (2.5 ± 0.3)	(79.8 ± 1.8)	(82.4 ± 1.8)

T = 110 °C

Solvent	$\Delta\Delta S^{\neq}$ [J mol^{-1} K^{-1}]	$\Delta S^{\neq}$(ortho) [J mol^{-1} K^{-1}]	$\Delta S^{\neq}$(meta) [J mol^{-1} K^{-1}]
Dichloromethane	(5 ± 1)	- (110 ± 9)	- (116 ± 9)
1-Chlorobutane	(1 ± 2)	- (115 ± 10)	- (116 ± 10)
THF	(6 ± 2)	- (100 ± 8)	- (106± 9)
Toluene	(4 ± 2)	- (134 ± 11)	- (137± 11)

T = 110 °C, P = 1500 bar

Solvent	$\Delta\Delta V^{\neq}$ [cm^3/mol]	$\Delta V_o^{\neq}$(ortho) [cm^3/mol]	$\Delta V_o^{\neq}$(meta) [cm^3/mol]
Dichloromethane	- (1.5 ± 0.1)	- (33.7 ± 1.2)	- (32.1 ± 1.1)
1-Chlorobutane	- (2.1 ± 0.4)	- (30.1 ± 2.5)	- (28.0 ± 2.4)
THF	- (2.0 ± 0.2)	- (34.8 ± 1.6)	- (32.7 ± 1.4)
Acetonitrile	- (2.1 ± 0.3)	- (17.3 ± 4.1)	- (15.2 ± 4.1)
Toluene	- (1.3 ± 0.3)	- (13.4 ± 1.5)	- (12.1 ± 1.5)

T = 110 °C

Partial Molar Volumes

In almost all kinetic studies in the liquid phase, transition state theory forms the basis of the theoretical interpretation of the data. It is usually applied in a simplified form that does not take the dynamic interactions into account. This procedure also appears adequate to treat the data of this paper.

According to the transition state theory, the activation volume can be expressed as the difference in partial molar volume of the transition state (V_{TS}) and the reactants:

$$\Delta V^{\neq} = V_{TS} - \Sigma V_{reactants} \quad (12)$$

which simplifies into $\Delta V^{\neq} = V_{TS} - V_{reactant}$ for the intramolecular cyclization reaction of the present study.

The partial molar volume Φ of the reactant can be determined by measuring the density of a solution of known concentration according to Eq. (13).

$$\Phi_i = M/d_0 - 1000/c_i(d_i - d_0)/d_0 \quad (13)$$

where d_0 = density of the solvent, d_i = density of the solution, M = molar mass, and c_i = concentration of the solution.

The Φ data often show a concentration dependence. Hence, it is common to use the partial molar volumes at infinite dilution. According to Eq. (13) the accuracy of the molar volumes is limited by the exact measurement of the small difference between the densities of the solvent and the solution. This problem can be overcome by measurements at several, also higher concentrations, providing sufficient solubility and extrapolation to zero concentrations. The partial molar volumes of **1** at 20°C, $V_{reactant}$, obtained by this procedure, are listed in Table 7 for the five solvents. All data refer to ambient pressure.

Results and Discussion

Kinetics

The temperature dependence of the experimental (overall) rate coefficient k for the cycloaddition of **1** in dichloromethane, 1-chlorobutane, tetrahydrofuran, and toluene measured at 1500 bar in the temperature range between 80 and 140°C is shown in Figure 1. For each solvent the data points can be fitted by a straight line. This may appear surprising, as according to Eq. (2), k is the sum of two individual rate coefficients, and no linear ln k vs. T^{-1} plot is to be expected. It should, however, be realised that due to the difference of individual activation energies being presumably quite small, a curvature will not be very pronounced and will hardly be detectable from the limited number of data points. Moreover, as will be evident from Figure 2, the reaction pathways to *ortho* and *meta* products under the experimental conditions are not of similar weight. The k data are essentially determined by the reaction to the *ortho* product which has the consequence of yielding an almost linear ln k vs. T^{-1} plot.

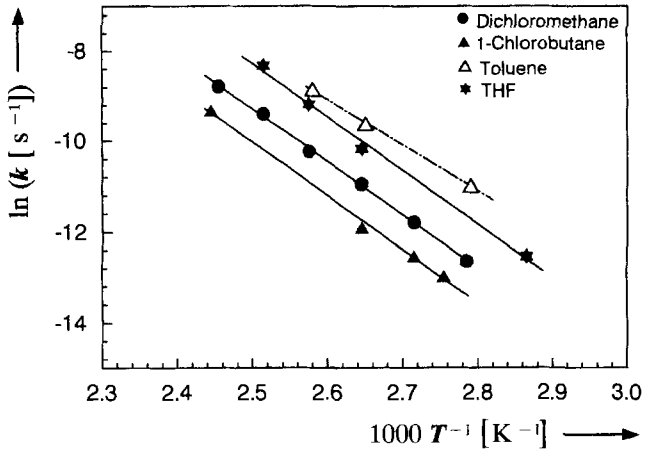


Figure 1. Temperature dependence of the overall rate coefficients k for the cycloaddition reaction of **1** at 1500 bar

All activation enthalpies are relatively small in comparison with typical values for intramolecular Diels-Alder reactions[7].

The temperature dependence of the ratio of product concentrations c_{ortho}/c_{meta} in dichloromethane, tetrahydrofuran, and toluene is depicted in Figure 2. The accuracy in the measurements with 1-chlorobutane as the solvent is lower, presumably due to side reactions. These data points are therefore not included in Figure 2. For all solvents the con-

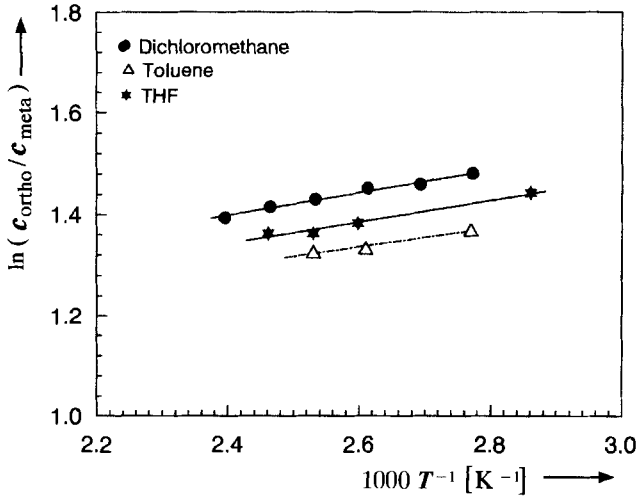


Figure 2. Temperature dependence of the product ratio of *ortho/meta* regioisomers for the cycloaddition reaction of **1** at 1500 bar

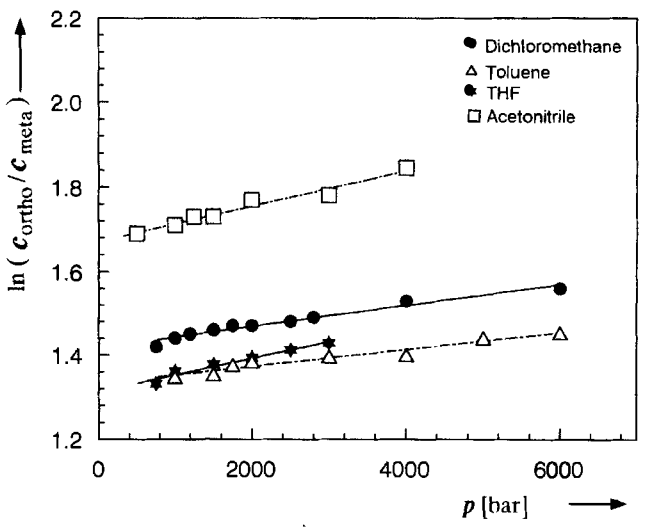


Figure 3. Pressure dependence of the product ratio of *ortho/meta* regioisomers for the cycloaddition reaction of **1** at T = 110°C

centration of the *ortho* product decreases with temperature.

The activation enthalpy differences ($\Delta\Delta H^{\neq}$) which, as a consequence of $c_{ortho}/c_{meta} = k_{ortho}/k_{meta}$, are directly obtained from the slope of the straight lines, are given in Table 6. No solvent effect on $\Delta\Delta H^{\neq}$ can be detected.

Inspection of the activation enthalpies (Table 6) for the individual reactions leading to *ortho* and *meta* products, $\Delta H^{\neq}$ (*ortho*) and $\Delta H^{\neq}$ (*meta*), tells that, for the same solvent, both numbers are close to each other with $\Delta\Delta H^{\neq}$ values of only a few kJ · mol^{-1}. Moreover, for the cycloaddition in dichloromethane, 1-chlorobutane, and in tetrahydrofuran the activation enthalpies are very similar. However, $\Delta H^{\neq}$ (*ortho*) and $\Delta H^{\neq}$ (*meta*) measured for the reaction in toluene are significantly lower. The activation entropies, also included in Table 6, show the same trends: The values of $\Delta S^{\neq}$ (*ortho*) and $\Delta S^{\neq}$ (*meta*) are close to each other in the four solvents with a clear difference in activation entropy for the cycloaddition of **1** in toluene as compared to reaction in other three solvents.

The pressure dependence of the product ratio in the cycloaddition of **1** at 110°C is given for four solvents in Figure 3. Towards higher pressure formation of the *ortho* product is favoured in all solvents. Thus, the reaction in acetonitrile shows a *meta*-to-*ortho* ratio of 1:5.54 at 1000 bar and of 1:6.33 at 4000 bar, while in toluene at 1000 bar a ratio of 1:3.85 and at 4000 bar of 1:4.06 is obtained. For each solvent the data points may be fitted with a straight line.

The activation volumes $\Delta V^{\neq}$ (*ortho*), $\Delta V^{\neq}$ (*meta*) and the activation volume difference $\Delta\Delta V^{\neq}$ in Table 6 are determined from straight line plots of ln k_{ortho}, ln k_{meta}, and ln (c_{ortho}/c_{meta}) vs. the El'yanov parameter φ [Eqs. (4) and (5)]. The rate coefficients k_{meta} are by about a factor of 6 below the corresponding k_{ortho} values.

The obvious finding from Figure 4 is that there are two classes of solvents. In dichloromethane, in tetrahydrofuran, and in 1-chlorobutane (not shown in Figure 4) the activation volume is about −30 cm^3/mol. Values of this size are also reported for other intramolecular Diels-Alder reactions[4]. On the other hand, in toluene and in acetonitrile the activation volume is around −15 cm^3 mol^{-1}. The activation volume differences, $\Delta\Delta V^{\neq}$, as has been mentioned earlier, are, however, rather similar for all solvents used.

The different size of activation volume for the two classes of solvents is surprising. An experimental error is unlikely. Assuming that a change in the mechanism of the cycloaddition causes the strong variation in $\Delta V^{\neq}$ is not very reasonable as such a change should also influence the selectivities, which is not observed (see Figure 3). In addition, the polarity of the two groups of solvents does not correlate with such an assumption. In particular, toluene and acetonitrile should not belong to the same class of solvents. Further evidence about this peculiar solvent effect is expected from volume profiles.

Volume Profiles

According to Eq. (13), the partial molar volumes of the substrate **1** and of the *ortho* product **2** in dichloromethane, 1-chlorobutane, tetrahydrofuran, acetonitrile, and toluene has been determined from density measurements using direct reading densitometer at 20°C. The data are given in Table 7.

Because of the limited availability of pure *meta* product, the partial molar volume of this material has only been determined in toluene solution, where is was found to be 212 ± 2 cm^3 mol^{-1} as compared to 214 ± 2 cm^3 mol^{-1} for the *ortho* product. Given this similarity the reaction volume of the overall reaction should be very close to the reaction volume of the cycloaddition leading to the *ortho* product **2**, in particular as in all these cycloadditions to more than 80 percent the *ortho* product is formed.

In order to calculate the partial molar volume of the transition structure $V_{substrate}$ and $\Delta V^{\neq}$ need to be available for identical temperature. As both $V_{substrate}$ and $V_{o\text{-product}}$ have been measured at 20°C, it was decided to estimate the size of activation volume (measured at 110°C) for 20°C.

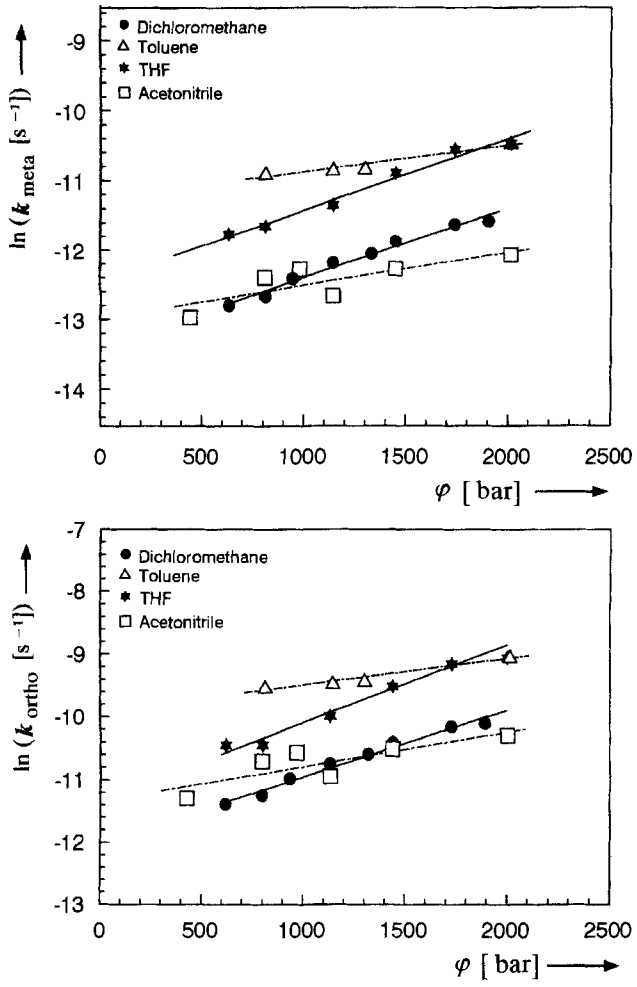


Figure 4. Above: Pressure dependence of the individual rate coefficient for the cycloaddition to the *meta* product **3** at 110°C. – Below: Pressure dependence of the individual rate coefficient for the cycloaddition to the *ortho* product **2** at 110°C

Investigations into the effect of temperature on the activation volumes are scarce. According to El'yanov and Gonikberg[8], the influence of temperature on the activation volume may be represented by the temperature dependence of the reaction volume. They have found Eq. (14) to hold in many cases.

$$\Delta V_T^{\neq} = \Delta V_0^{\neq} + (\delta \Delta V^{\neq}/\delta T)_p \cdot (T - T_0) \quad \text{and} \qquad (14)$$

$$\Delta V_T = \Delta V_0 \cdot [1 + K(T - T_0)] \qquad (15)$$

where

$\Delta V_T = \Delta V_0^{\neq}$ at 20°C and $\Delta V_0 = \Delta V_0^{\neq}$ at 110°C.

K is a characteristic constant which, following El'yanov and Gonikberg, should be $3.2 \cdot 10^{-3}$ K^{-1} at 110°C.

The data of $\Delta V_{20°C}^{\neq}$ for the cycloaddition of **1** at 20°C obtained by this procedure are given in Table 7.

From these data four findings are apparent. First, the reaction volumes show a similar remarkable solvent effect as do the activation volumes: In acetonitrile and toluene the reaction volume is rather similar, but only about half as large as in dichloromethane and tetrahydrofuran, where ΔV_R is around -30 cm^3 mol^{-1}. Secondly, the molar volume of the substrate **1** is significantly smaller in acetonitrile and toluene than in the other two solvents. Third, the molar volume of the transition structure and fourth the molar volume of the products are not strongly influenced by the solvent. The conclusion which may be drawn from these findings is that the significant differences observed for the reaction volume and for the activation volume of the cycloaddition of **1** as a function of solvent – toluene and acetonitrile on the one side and dichloromethane, tetrahydrofuran (and 1-chlorobutane) on the other side – are due to differences in solvation of the substrate **1**.

It should be emphasized that this argument is not invalidated by the uncertainty introduced by the estimate of $\Delta V^{\neq}$ for 20°C. The change in $\Delta V^{\neq}$ between 110 and 20°C (see Table 7) reveals to be fairly large. If the opposite were true and $\Delta V^{\neq}$ would be essentially independent of temperature, the following argument could be made by using the experimental $\Delta V_{110°C}^{\neq}$ values in conjunction with the ΔV_R data for 20°C: Both quantities are rather similar for dichloromethane and for tetrahydrofuran (around -30 cm^3 mol^{-1}) and also for toluene and acetonitrile (around -15 cm^3 mol^{-1}). The major effect of the solvents again seems to be the difference in solvation of **1**. In addition, a close similarity of ΔV_R and $\Delta V_{110°C}^{\neq}$ for each of the solvents would suggest fairly late transition states. It is certainly very rewarding to study the issue of a temperature dependence of activation volume in more detail. Work on this is already underway in our laboratories.

Conclusions

The experimental studies of the intramolecular cycloaddition of **1** in different solvents under high pressure show a large solvent effect on the activation volumes, but only a very minor solvent effect on the activation volume difference for the two pathways leading to the *ortho* and *meta* adducts **2** and **3**, respectively. Measurement of molar volumes of the substrate **1** and of the products **2** and **3** show that this quantity is strongly solvent dependent in the case of **1** whereas it is less influenced with **2** and **3**. The molar volume of the transition structure appears to be unaffected by solvent. The unusual large solvent effect on the experimental activation volume is thus understood as being due to a difference in solvation of the substrate in the different solvents. Thus, whenever solvent effects on organic reactions are studied by pressure-induced changes, it is recommendable to determine activation volumes and molar volumes of the substrates and products to locate the transition structure on the absolute volume scale.

Generous support of this work by the *Deutsche Forschungsgemeinschaft* (GK "Kinetik und Selektivität chemischer Prozesse in verdichteter fluider Phase") and the *Fonds der Chemischen Industrie* is gratefully acknowledged. We are also indebted to Prof. *F. G. Klärner* (Essen) for technical assistance and useful discussions in determining partial molar volumes. The authors are grateful to Dr. *H. P. Vögele* for checking the kinetic data and for preparing the final tables.

Table 7. Activation volumes, partial molar volumes of the reactant ($V_{Substrate}$), the *ortho* product ($V_{o\text{-}Product}$), and of the *ortho* transition state (V_{TS}) and reaction volume ($\Delta V_R = V_{Substrate} - V_{TS}$) for the intramolecular cycloaddition of **1**

Solvent	$V_{Substrate}$ [cm³/mol]	$\Delta V^{\ddagger}_{110\,°C}$ [cm³/mol]	$\Delta V^{\ddagger}_{20°C}$ [cm³/mol]	V_{TS} [cm³/mol]	$V_{o\text{-}Product}$ [cm³/mol]	ΔV_R [cm³/mol]
Dichloromethane	242 ± 2	-33.1 ± 1.2	-23.6 ± 2.1	218 ± 4	212 ± 2	-30 ± 4
THF	244 ± 2	-34.2 ± 1.5	-24.4 ± 2.1	220 ± 3	209 ± 2	-35 ± 2
Toluene	232 ± 2	-13.4 ± 1.5	-9.5 ± 1.8	222 ± 3	214 ± 2	-18 ± 2
Acetonitrile	232 ± 2	-17.0 ± 4.1	-12.1 ± 4.6	220 ± 4	217 ± 2	-15 ± 2

Experimental

The high-pressure cells used and details on the experimental set-up and procedures as well as the methods for determining the rate coefficients have already been described[5,9]. For the kinetic experiments the initial concentration of the substrate was 0.03 mol kg^{-1}. The experimental pressure was determined to be higher than ±10 bar, the uncertainty in temperature was below ±0.5°C. The density measurements were performed by using a direct reading densitometer which employs the principle of a submerged tuning fork whose frequency depends on the density of the medium. The densitometer was calibrated to 20°C by using a thermostat (RCS 6-D MWG Lauda) with an uncertainty in temperature below 0.01 K causing an error in the density measurements of about $\pm 5 \cdot 10^{-6}$ g cm^{-3}. As pointed out before, the accuracy of the molar volumes depends on the exact measurement of the small density difference between the solvent and the solution. In order to reduce scattering, the measurement density differences were plotted against the concentration and fitted by least-squares fit methods to a parabolic function. The calculated density differences were used to determined molar volumes according to Eq. (13). The estimated errors of the molar volumes are included in Table 7.

HPLC of **2/3**: Column: 2 sequentially connected LiChrospher 100 RP-18, 250 mm, 5 µm with eluent acetonitrile/water (40:60) and flow rate 0.8 ml/min; detection wavelength 264 nm; t_R (**2**) = 22 min, t_R (**3**) = 14 min. Knauer HPLC hardware/software package using version 2.11. 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, VXR-200, and VXR-500 S, 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. Melting points (corrected values): Kofler melting point apparatus. – Elemental analyses: Analytical laboratory of the university. – All solvents were distilled prior to use.

1,3-Dimethyl-5-[2-(2-propenyloxy)benzylidene]pyrimidine-2,4,6-trione (**1**): To a stirred suspension of 1,3-dimethylbarbituric acid (2.34 g, 15.0 mmol) and ethylenediammonium diacetate (EDDA)[10] (30.0 mg) in dichloromethane (80 ml) was added a solution of 2-(2-propenyloxy)benzaldehyde[11] (3.24 g, 20.0 mmol) in dichloromethane (20 ml). The mixture was stirred for 4 h at room temp., the solvent then removed in vacuo and the product purified by crystallization from methanol. Yield 4.24 g (94%) of **1**; R_f = 0.56 [ethyl acetate/petroleum ether (1:1)], m.p. 146°C. – IR (KBr): $\tilde{\nu}$ = 1670 cm^{-1} (C=O), 1586 (C=C), 1460, 1420 (CH_2, CH_3). – UV (CH_3CN): λ_{max} (lg ε) = 220 nm (4.068), 245 (4.041), 316 (3.890), 369 (4.058). – ^{1}H NMR (200 MHz, $CDCl_3$): δ = 3.34 (s, 3H, CH_3), 3.42 (s, 3H, CH_3), 4.63 (dt, *J* = 5.0, 1.5 Hz, 2H, CH_2), 5.33 (dq, *J* = 10, 1.5 Hz, 1H, 3″-H), 5.40 (dq, *J* = 17, 1.5 Hz, 1H, 3″-H), 6.04 (ddt, *J* = 17, 10, 5.0 Hz, 1H, 2″-H), 6.88–7.06 (m, 2H, 3′,5′-H), 7.41–7.51 (m, 1H, 4′-H), 8.01–8.07 (m, 1H, 6′-H), 8.92 (s, 1H, α-H). – ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 28.33 (CH_3), 28.91 (CH_3), 69.27 (C-1″), 111.7 (C-3′), 117.4 (C-5), 117.9 (C-3″), 119.9 (C-5′), 122.4 (C-1′), 132.5 (C-2″), 132.7 (C-4′), 134.3 (C-6′), 151.4 (C=O), 155.0 (α-C), 158.6 (C-2′), 160.4 (C=O), 162.5 (C=O). – MS (70 eV), *m/z* (%): 300 (20) [M^+], 243 (100) [$M^+ - OCH_2CH{=}CH_2$], 41 (22) [$CH_2CH{=}CH_2^+$]. – $C_{16}H_{16}N_2O_4$ (300.3): calcd. C 63.99, H 5.37; found C 64.13, H 5.50.

Cyclization of **1**[12]: A solution of **1** (300 mg, 1.00 mmol) in xylene (70 ml) was heated for 92 h under reflux. After cooling to room temp. the solvent was evaporated in vacuo and the residue purified by chromatography on silica gel in ethyl acetate, R_f = 0.47 (**2**), 0.40 (**3**).

Fraction 1. (6aS,12bR)-(±)-6a,7-Dihydro-2,4-dimethyl-6H,12bH-[1]benzopyrano[3′,4′:5,4]pyrano[2,3-d]pyrimidine-1,3(2H,4H)-dione (**2**): Yield 166 mg (55%), m.p. 193°C. – IR (KBr): $\tilde{\nu}$ = 3036 cm^{-1}, 2950 (C–H), 1700 (C=O), 1636 (C=C), 1490, 1456 (CH_2, CH_3). – UV (CH_3CN): λ_{max} (lg ε) = 264 nm (4.001). – ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.36 (m_c, 1H, 6a-H), 3.33 (s, 3H, CH_3), 3.44 (s, 3H, CH_3), 4.32 (dd, *J* = 11.5, 2.0 Hz, 1H, 6-H_{ax}), 4.33 (dd, *J* = 12.0, 11.0 Hz, 1H, 7-H_{ax}), 4.39 (br d, *J* = 5.0 Hz, 1H, 12b-H), 4.39 (dd, *J* = 11.5, 2.0 Hz, 1H, 6-H_{eq}), 4.58 (ddd, *J* = 11.0, 4.5, 2.0 Hz, 1H, 7-H_{eq}), 6.78 (dd, *J* = 8.0, 1.5 Hz, 1H, 9-H), 6.88–6.92 (m, 1H, 11-H), 7.10–7.15 (m, 1H, 10-H), 7.46 (m_c, 1H, 12-H). – ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 28.37 (CH_3), 28.61 (C-12b), 28.82 (CH_3), 29.57 (C-6a), 65.52 (C-7), 67.86 (C-6), 90.34 (C-12c), 116.7 (C-9), 121.7 (C-11), 123.6 (C-12a), 128.0 (C-10), 130.5 (C-12), 150.8 (C-3), 151.8 (C-8a), 156.2 (C-4a), 164.1 (C-1). – MS (70 eV); *m/z* (%): 300 (100) [M^+], 144 (30) [$M^+ - C_6H_8O_3N_2$]. – $C_{16}H_{16}N_2O_4$ (300.3): calcd. C 63.99, H 5.37; found C 64.15, H 5.50.

Fraction 2. (6R,13S)-(±)-6,7-Dihydro-2,4-dimethyl-6,13-methano-13H-[1,4]benzodioxonino[5,6-d]pyrimidine-1,3(2H,4H)-dione (**3**): Yield 36.6 mg (12%), m.p. 186°C. – IR (KBr): $\tilde{\nu}$ = 3058 cm^{-1}, 2932 (C–H), 1698 (C=O), 1636 (C=C), 1488, 1458 (CH_2, CH_3). – UV (CH_3CN): λ_{max} (lg ε) = 264 nm (4.001). – ^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.17 (dt, *J* = 14, 1.5 Hz, 1H, 14-H_{ax}), 2.42 (dtd, *J* = 14, 5.5, 2.0 Hz, 1H, 14-H_{eq}), 3.24 (s, 3H, CH_3), 3.43 (s, 3H, CH_3), 3.79 (d, *J* = 13 Hz, 1H, 7-H_{ax}), 4.01 (br d, *J* = 5.5 Hz, 1H, 13-H), 4.64 (ddd, *J* = 13, 3.5, 2.0 Hz, 1H, 7-H_{eq}), 4.83–4.92 (m, 1H, 6-H), 6.95 (dd, *J* = 7.0, 2.0 Hz, 1H, 9-H), 7.08 (dt, *J* = 7.0, 2.0 Hz, 1H, 11-H), 7.16 (dt, *J* = 7.0, 2.0 Hz, 1H, 10-H), 7.48 (dd, *J* = 7.0, 2.0 Hz, 1H, 12-H). – ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 27.81 (CH_3), 28.73 (CH_3), 29.09 (C-14), 33.02 (C-13), 73.34 (C-7), 76.54 (C-6), 88.80 (C-13a), 121.7 (C-9), 124.6 (C-11), 128.3 (C-10), 131.0 (C-12), 135.0 (C-12a), 151.0 (C-3), 156.1 (C-4a), 158.1

(C-8a), 162.1 (C-1). – MS (70 eV), *m/z* (%): 300 (100) [M^+], 144 (49) [$M^+ - C_6H_8N_2O_3$]. – $C_{16}H_{16}N_2O_4$ (300.3): calcd. C 63.99, H 5.37; found C 63.97, H 5.47.

[1] Part 48: L. F. Tietze, A. Montenbruck, C. Schneider, *Synlett* **1994**, 509–510.

[2] R. Winter, J. Jonas, *High Pressure Chemistry, Biochemistry and Materials Science*, Kluwer Academic Publishers, Dordrecht, **1993**; N. S. Isaacs, *Tetrahedron* **1991**, *47*, 8463–8497; K. Matsumoto, R. M. Acheson, *Organic Synthesis at High Pressures*, Wiley-Interscience, New York, **1991**; F. G. Klärner, *Chem. Unserer Zeit*, **1989**, *23*, 53–63; R. van Eldik, T. Asano, W. J. le Noble, *Chem. Rev.* **1989**, *89*, 549–688; J. Jurczak, B. Baranowski, *High Pressure Chemical Synthesis*, Elsevier, Amsterdam, **1989**; W. J. le Noble, *Organic High Pressure Chemistry*, Elsevier, Amsterdam, **1988**; L. F. Tietze, T. Hübsch, E. Voß, M. Buback, W. Tost, *J. Am. Chem. Soc.* **1988**, *110*, 4065–4066; K. Matsumoto, A. Sera, T. Uchida, *Synthesis* **1985**, 1–26; K. Matsumoto, A. Sera, *ibid.* **1985**, 999–1027.

[3] [3a] R. A. Grieger, C. A. Eckert, *Ind. Eng. Chem. Fund.* **1971**, *10*, 369–372. – [3b] J. R. McCabe, C. A. Eckert, *Ind. Eng. Chem. Fund.* **1974**, *13*, 168–179.

[4] [4a] B. A. Keay, P. W. Dibble, *Tetrahedron Lett.* **1989**, *30*, 1045–1046. – [4b] C. Ferroud, G. Revial, J. d'Angelo, *Tetrahedron Lett.* **1985**, *26*, 3981–3984. – [4c] S. J. Burrell, A. E. Derome, M. S. Edenborough, L. M. Harwood, S. A. Leeming, N. S. Isaacs, *Tetrahedron Lett.* **1985**, *26*, 2229–2232. – [4d] N. S. Isaacs, P. V. v. d. Beeke, *Tetrahedron Lett.* **1982**, *23*, 2147–2149.

[5] [5a] W. Tost, Thesis, Universität Göttingen, **1988**. – [5b] L. F. Tietze, T. Hübsch, J. Oelze, C. Ott, W. Tost, G. Wörner, M. Buback, *Chem. Ber.* **1992**, *125*, 2249–2269. – [5c] M. Buback, W. Tost, L. F. Tietze, E. Voß, *Chem. Ber.* **1988**, *121*, 781–795. – [5d] K. Gerke, Thesis, Universität Göttingen, **1993**.

[6] B. El'yanov, E. M. Gonikberg, G. Jenner, *J. Chem. Soc., Perkin Trans. 2*, **1992**, 137–142.

[7] [7a] T. Asano, W. J. le Noble, *Chem. Rev.* **1978**, *78*, 407–489. – [7b] K. Matsumoto, A. Sera, *Synthesis* **1985**, 999–1027.

[8] B. El'yanov, E. M. Gonikberg, *J. Chem. Soc., Farad. Trans.* **1979**, *75*, 172–191.

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

[10] L. F. Tietze, T. Eicher, *Reaktionen und Synthesen im organisch-chemischen Praktikum*; 2nd Edition, Georg Thieme Verlag, Stuttgart, **1991**.

[11] L. F. Tietze, T. Brumby, M. Pretor, G. Remberg, *J. Org. Chem.* **1988**, *53*, 810–820.

[12] L. F. Tietze, H. Stegelmeier, K. Harms, T. Brumby, *Angew. Chem.* **1982**, *94*, 868–869; *Angew. Chem. Int. Ed. Engl.* **1982**, *21*, 863.

[163/94]