Inter- and Intramolecular *hetero* Diels-Alder Reactions, XXII[1)]

hetero Diels-Alder Reactions of Enamine Carbaldehydes at High Pressure Studied by On-Line IR Detection

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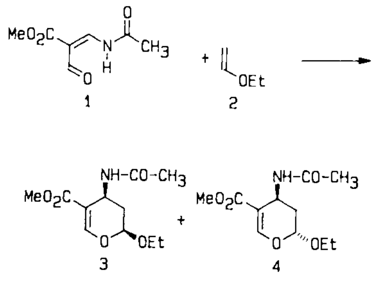
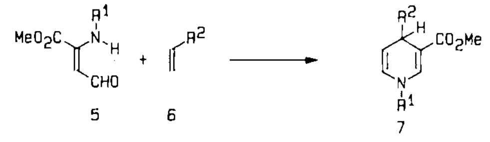
The *hetero* Diels-Alder reaction of **1** and **2** to the 4-aminodihydropyrans **3** and **4** in CH_2Cl_2 and isodurene solutions is studied between 45°C and 95°C by direct quantitative infrared spectroscopy under high pressure up to 3 kbar. The activation energies in isodurene and in CH_2Cl_2 are found to be 65 ± 5 kJ · mol^{-1}, and 58 ± 9 kJ · mol^{-1}, respectively. The activation volumes turn out to be practically identical: -25.1 ± 1.7 $cm^3 \cdot mol^{-1}$ in CH_2Cl_2 and -25.0 ± 1.8 $cm^3 \cdot mol^{-1}$ in isodurene. The promising aspects of applying high-pressure infrared spectroscopy to the detailed kinetic study of organic reactions are indicated.

Inter- und Intramolekulare *hetero*-Diels-Alder-Reaktionen, XXII[1)]. – Infrarotspektroskopische Untersuchung der *hetero*-Diels-Alder-Reaktion von Enamincarbaldehyden bei hohem Druck

Die *hetero*-Diels-Alder-Reaktion von **1** und **2** zu den 4-Aminodihydropyranen **3** und **4** wird in CH_2Cl_2 sowie in Isodurol bei Temperaturen zwischen 45°C und 95°C durch quantitative Infrarotspektroskopie unter hohem Druck (bis 3 kbar) untersucht. Die Aktivierungsenergien werden in Isodurol zu 65 ± 5 kJ · mol^{-1} und in CH_2Cl_2 zu 58 ± 9 kJ · mol^{-1} bestimmt. Für die Aktivierungsvolumina ergeben sich die fast gleichen Werte von -25.1 ± 1.7 $cm^3 \cdot mol^{-1}$ in CH_2Cl_2 und -25.0 ± 1.8 $cm^3 \cdot mol^{-1}$ in Isodurol. Es wird auf die vielversprechenden Anwendungsmöglichkeiten der Hochdruck-Infrarotspektroskopie zum detaillierten Studium der Kinetik organischer Reaktionen hingewiesen.

The dependence of chemical reaction rate coefficients on pressure has been studied for a wide variety of systems[2,3)]. Especially because of the large rate enhancement that can be achieved, high-pressure methods became a routine tool for the organic chemist. The preparative aspects have been of primary interest and only limited information is available on the direct time-dependent study of high-pressure reactions. It seemed rewarding to apply the techniques of quantitative infrared spectroscopy which have been developed for high-pressure polymerisation work[4)], to the detailed study of organic reactions in compressed fluid phase. The sensitive on-line detection, in addition to the measurement of educt and product concentrations, may enable intermediate species and also products which are unstable at ambient pressure to be safely detected.





In this paper we describe the *hetero* Diels-Alder reaction of the enamine carbaldehyde **1** with ethyl vinyl ether **2** under high pressure. The transformation to the 4-aminodihydropyrans **3** and **4** in CH_2Cl_2 and isodurene solution is studied by Fourier transform infrared spectroscopy at several temperatures and at pressures up to 3 kbar. The cycloaddition of enamine carbaldehydes such as **1** was chosen as it constitutes a highly efficient method for the formation of aminosugars of the garosamine type[5)], being components of the valuable antibiotic gentamicine[6)]. Moreover, depending on the solvent, the formed 4-aminodihydropyrans **3** and **4** can be distinguished by the IR spectrum in the N – H stretching region. This is of importance with respect to the direct investigation of a pressure dependence of the diastereoselectivity in the *hetero* Diels-Alder reaction of **1**[7)]. Another interesting aspect of enamine carbaldehyde – alkene systems is that they can also undergo photochemical cycloadditions, e.g. **5** reacts with **6** to give 1,4-dihydropyridines **7**[8)]. With R^1 = sugar and R^2 = H this is, so far, one of the best procedures to obtain NADH-analogues. The photochemical cycloaddition reaction of enamine carbaldehydes with alkenes under high pressure using an excimer laser as a light source is presently under investigation[9)].

The reactions are carried out in a high-pressure (3 kbar) cell with optical windows from synthetic sapphire (Figure 10, below). The reaction mixture is contained within a closed thin-walled poly(tetrafluoroethylene) (Teflon®) bag which is

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transmitted by the IR light. Cycloadditions were studied between 45.3°C and 80.2°C in dichloromethane and between 60.2°C and 94.9°C in 1,2,3,5-tetramethylbenzene (isodurene). With respect to the enamine carbaldehyde **1**, ethyl vinyl ether **2** was used in a 10-fold excess in isodurene solution and in a 25-fold excess in CH_2Cl_2 solution.

Experimental IR absorbance spectra measured during the cycloaddition of **1** and **2** in dichloromethane solution at 60°C and 1500 bar are shown in Figure 1. The solvent absorption may easily be eliminated by subtracting the first spectrum (which is recorded immediately after the system has reached the reaction temperature) from all measured spectra. Applying this procedure to the data in Figure 1, yields the N–H stretching spectra in Figure 2. Positive absorbance is due to N–H absorption of the Diels-Alder products **3** and **4** (around 3438 cm^{-1}) whereas the negative absorbance demonstrates the disappearance of **1** by its N–H stretching fundamental around 3262 cm^{-1}. Only about one third of the experimental spectra is shown in Figures 1 and 2. The reaction time for almost complete conversion is 4.5 hours.

IR absorbance spectra (after elimination of the solvent absorption as in Figure 2) for the cycloaddition of **1** and **2** in isodurene solution at 75°C and 1000 bar measured during a reaction time of 14 hours are shown in Figure 3. The N–H band contour of **1** is similar in CH_2Cl_2 and in isodurene solutions. Only the wave number of the band maximum is shifted by about 14 cm^{-1} toward lower values. The N–H stretching spectra of **3** and **4** (Figures 2 and 3) are, however, clearly different for the two components in isodurene. From independent studies on the two diastereomers, the 3437 cm^{-1} band is assigned to **3** and the 3405 cm^{-1} band to **4**. The shoulder around 3335 cm^{-1} is due to the N–H absorption of associated species, probably dimers of **3** and **4**. Unfortunately, component **4**, even at the higher experimental temperatures, is not sufficiently soluble in isodurene to allow the measurement of calibration spectra which might be helpful to provide direct information about diastereomer selectivity induced by pressure.

The difference in the N–H band maximum positions of **3** and **4** increases with the number of methyl substituents of the aromatic solvent as is shown in Figure 4. The variation of $\tilde{\nu}$(max) in component **4** with the number of methyl substituents closely parallels the situation found for the O–H stretching fundamental of phenol in aromatic solvents[10]. There, the pronounced red-shift has been assigned to hy-

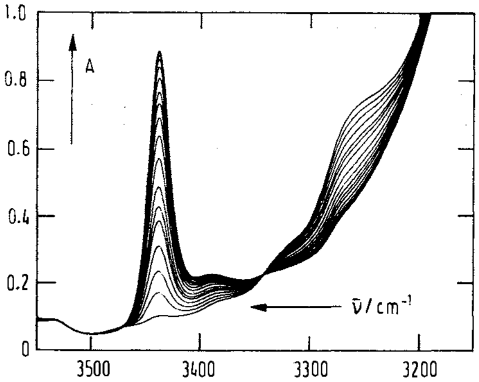

Figure 1. Infrared absorbance in the N–H stretching region measured during the cycloaddition reaction of **1** and **2** in CH_2Cl_2 at 60°C and 1500 bar. The products **3** and **4** absorb around 3438 cm^{-1}, the enamine carbaldehyde **1** around 3262 cm^{-1}

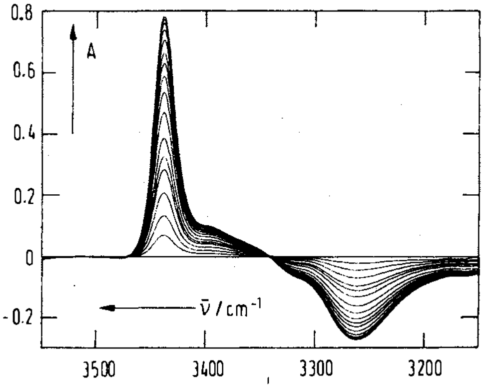

Figure 2. Infrared absorbance in the N–H stretching region measured during the cycloaddition reaction of **1** and **2** in CH_2Cl_2 at 60°C and 1500 bar. Same spectra as in Figure 1 with the first spectrum (lowest product absorption in Figure 1) being subtracted from all absorbance curves

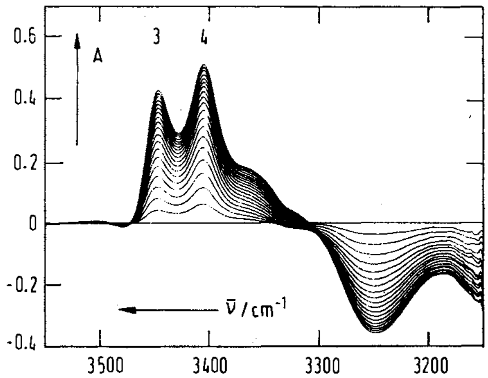

Figure 3. Infrared absorbance in the N–H stretching region measured during the cycloaddition reaction of **1** and **2** in isodurene at 75°C and 1000 bar. As for Figure 2, the first spectrum after reaching the experimental temperature is subtracted

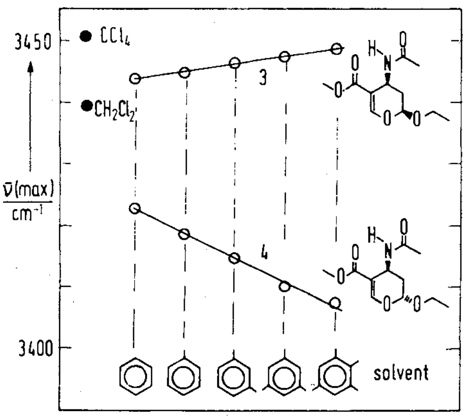

Figure 4. Position of the N–H band maxima of **3** and **4** in different solvents. In CCl_2 and in CH_2Cl_2 only one band is observed for both diastereomers. All data refer to ambient temperature and pressure

drogen bonding interactions between the O—H group and the aromatic system of the solvent molecules. In CCl_4 and in polar solvents, e.g. CH_2Cl_2 (Figures 1 and 2) and in heptane, only one N—H stretching mode occurs for **3** and **4**. Because of the promising aspects of a direct IR detection of diastereomer selectivity, the search for an appropriate solvent providing both, sufficient solubility and characteristic band positions for each of the two diastereomers, will be continued.

With the concentration of ethyl vinyl ether **2** largely exceeding the concentration of **1** the Diels-Alder reaction can be treated by first-order kinetics. As was pointed out by Kezdy and Swinbourne[11], the time dependence of any physical variable x which is linearily related ($x = a \cdot c + b$) to the concentration c of an educt or product (following first-order kinetics), may be expressed as:

$$x(t_2) = x(t_1)\exp(-k' \cdot \Delta t) + [\exp(-k' \cdot \Delta t) - 1] \cdot b \cdot a^{-1} \qquad \text{Eq. (1)}$$

$x(t_1)$ and $x(t_2)$ are the values of the physical variable x at times t_1 and t_2, respectively. Δt is the time interval between t_2 and t_1. The first-order rate coefficient k' is related to the second-order Diels-Alder rate coefficient k by $k' = k \cdot c_0$ where c_0 is the concentration of the educt species being present in large excess. Rearrangement of Eq. (1) yields:

$$x(t_2) - x(t_1) = x(t_1) \cdot [\exp(-k' \cdot \Delta t) - 1] + [\exp(-k' \cdot \Delta t) - 1] \cdot b \cdot a^{-1} \qquad \text{Eq. (2)}$$

Several quantities from the spectra as in Figures 2 and 3, e.g. absorbances at fixed wave number or integrated absorbances over half bands or total bands may be identified with x. Plotting $x(t_2) - x(t_1)$ versus $x(t_1)$, according to Eq. (2), should yield a straight line of slope $\exp(-k' \cdot \Delta t) - 1$ with x at t versus infinity being obtained from the abscissa value at $x(t_2) - x(t_1) = 0$. A straight line is, indeed, observed as is illustrated in Figure 5 for the cycloaddition reaction in CH_2Cl_2 solution at 60°C and 1500 bar with the integral over the product absorbance from 3480 cm^{-1} to 3400 cm^{-1} being taken as x. The time intervals between successive spectra are 5.1 minutes. From the slope, k' is obtained to be $(9.6 \pm 1.3) \cdot 10^{-5}\ s^{-1}$. A corresponding plot for the Diels-Alder reaction in isodurene solution at 75°C and 1000 bar is shown in Figure 6. The two symbols refer to x being derived from two sources: from the integrated absorbance between 3480 cm^{-1} and 3427 cm^{-1} (○) and from the integrated absorbance between 3480 cm^{-1} and 3365 cm^{-1} (△). A mean value of rate coefficient is found to be $k' = (3.75 \pm 0.25) \cdot 10^{-5}\ s^{-1}$. In order to circumvent problems due to concentration changes induced by pressure and temperature without any reaction taking place, the

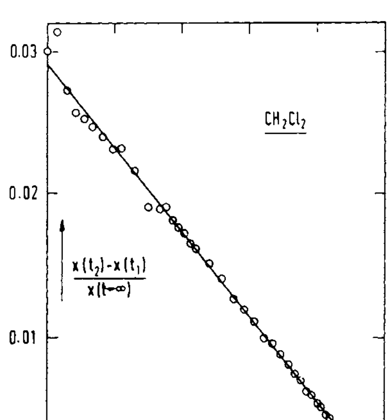

Figure 5. Plot of $x(t_2) - x(t_1)$ versus $x(t_1)$ for the cycloaddition reaction of **1** and **2** in CH_2Cl_2 at 60°C and 1500 bar. x is the integrated absorbance between 3480 cm^{-1} and 3400 cm^{-1} (see Figure 2). The data are reduced over x at t approaching infinity. $t_2 - t_1$ was chosen to be 5.1 minutes

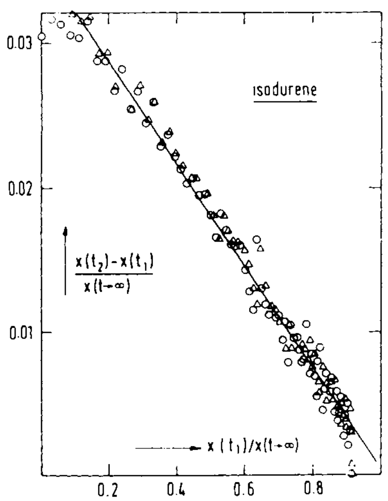

Figure 6. Plot of $x(t_2) - x(t_1)$ versus $x(t_1)$ for the cycloaddition reaction of **1** and **2** in isodurene at 75°C and 1000 bar. Both quantities are reduced by x at t approaching infinity. x is chosen to be the integrated absorbance from 3480 cm^{-1} to 3427 cm^{-1} (○) and from 3480 cm^{-1} to 3365 cm^{-1} (△), respectively

Table 1. Rate coefficients k [(kg solution) · mol^{-1} · s^{-1}] for the Diels-Alder reaction of **1** and **2** in CH_2Cl_2 and in isodurene

Solvent: CH_2Cl_2 *T = 60.0°C* p[bar]	 k[10^{-5} kg · $mol^{-1} \cdot s^{-1}$]	Solvent: Isodurene *T = 75.0°C* p[bar]	 k[10^{-5} kg · $mol^{-1} \cdot s^{-1}$]
400	2.94	50	1.51
500	3.45	250	2.00
1000	5.98	500	2.67
1500	9.58	1000	3.80
2000	15.3	1500	6.48
2200	15.4	2000	8.31
2400	18.6	2500	13.4
2900	29.9	2500	13.5
2950	33.2	2600	16.0
3000	33.8	2750	18.3
		2900	17.1
		3000	23.3

p = 1000 bar T[°C]	k[10^{-5} kg · $mol^{-1} \cdot s^{-1}$]	*p = 1000 bar* T[°C]	k[10^{-5} kg · $mol^{-1} \cdot s^{-1}$]
45.3	2.47	60.2	1.42
55.1	5.35	65.2	2.09
60.0	5.98	75.0	3.73
75.3	16.5	84.9	7.87
80.2	22.3	90.2	10.3
		94.9	12.6

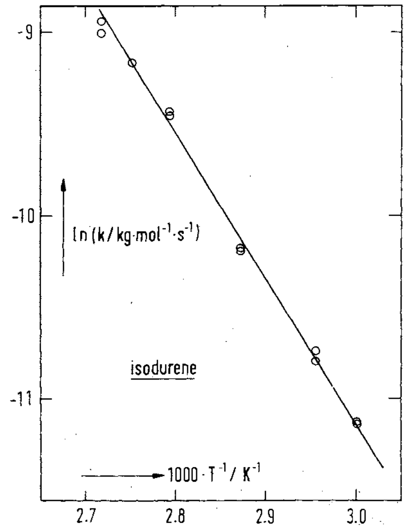

Figure 7. Temperature dependence of the cycloaddition rate coefficient k in isodurene solution at 1000 bar

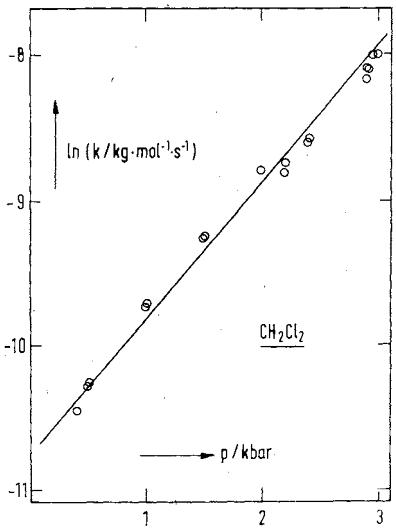

Figure 8. Pressure dependence of the cycloaddition rate coefficient k in CH_2Cl_2 solution at 60°C

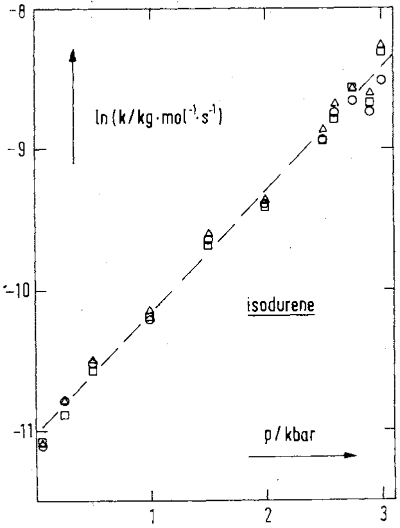

Figure 9. Pressure dependence of the cycloaddition rate coefficient k in isodurene solution at 75°C

second-order rate coefficient k is calculated for a rate law in concentration units of mol · (kg solution)$^{-1}$:

$$r = k \cdot m_1 \cdot m_2 \qquad \text{Eq. (3)}$$

where m_1 and m_2 refer to **1** and **2**, respectively. The experimental rate coefficients k are summarized in Table 1.

At identical temperature and pressure, k values measured in CH_2Cl_2 clearly exceed those determined in isodurene solution. An increase of Diels-Alder reaction rates with solvent polarity has already been reported[12]. The temperature dependence of k for the cycloaddition in isodurene is shown in Figure 7. Different k values at the same temperature are obtained from one experiment by choosing different parts of the IR spectrum as the variable x. From the slope of the straight line fitted to the data measured at 1000 bar between 60°C and 95°C, the activation energy is found to be (65 ± 5) kJ · mol^{-1}. The corresponding kinetic analysis of the Diels-Alder reaction at 1000 bar in CH_2Cl_2 solution yields an activation energy of (58 ± 9) kJ · mol^{-1}. With the concentrations in terms of moles per kg solution, the activation entropies for the experimental pressure p = 1000 bar are obtained to be: (−145 ± 15) J · mol^{-1} · K^{-1} in isodurene and (−151 ± 27) J · mol^{-1} · K^{-1} in CH_2Cl_2 solution. Using mol · dm^{-3} as concentration unit and referring to ambient pressure, gives: (−152 ± 15) J · mol^{-1} · K^{-1} and (−162 ± 27) J · mol^{-1} · K^{-1}, respectively.

Special interest relates to the pressure dependence of the rate coefficient. ln k is plotted versus pressure for Diels-Alder reactions within CH_2Cl_2 and within isodurene solution in Figures 8 and 9, respectively. Several data points at identical pressure are due to a different choice of x within the same experiment. From the straight line slope, the activation volumes $\Delta V^{\neq}$ are found to be:

$$\Delta V^{\neq} = -(25.1 \pm 1.7)\ \text{cm}^3 \cdot \text{mol}^{-1}\ (\text{in } CH_2Cl_2)$$

$$\Delta V^{\neq} = -(25.0 \pm 1.8)\ \text{cm}^3 \cdot \text{mol}^{-1}\ (\text{in isodurene})$$

Solvent polarity thus has no pronounced influence on the pressure dependence of the rate coefficient of the Diels-Alder reaction of **1** and **2**. This observation agrees with previous data from experiments using unsymmetrical dienophiles which indicated a concerted reaction.

In order to assign the structure of the products **3** and **4**, the mixture of diastereomers was separated by chromatography. Moreover, the ratio of **3**:**4** was determined via HPLC on the crude reaction mixture to be about 0.7:1 for the cycloaddition at 75°C and 1 kbar. This demonstrates that the reaction proceeds under kinetic control as the ratio of **3**:**4**, after equilibration with BF_3-Et_2O (at 20°C), is found to be 7.1:1. In subsequent studies on the high pressure cycloaddition of **1** and **2**, the influence of pressure on the diastereoselectivity will be studied in more detail.

In conclusion, we would like to emphasize that quantitative IR spectroscopy suggests promising and very broad applications in the direct and detailed study of organic reaction kinetics up to high pressure.

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Experimental

The optical cell (Figure 10) for operation up to 3 kbar and to maximum temperatures around 300°C is made from stainless steel (RGT 601, W.-Nr. 2.4668, Arbed Saarstahl). Infrared radiation penetrates the cell through the cylindrical bore. The windows *W* from synthetic sapphire are sealed with conical steel plugs *P* pressed against the cell body with flanges *Fl* by means of eight screws *S* on each side. The reaction mixture is contained in a small bag prepared from 0.1 mm poly(tetrafluoroethylene) (Teflon®) foil and sealed by welding. The lower part of this internal cell (which is not shown in Figure 10) is transmitted by the IR light. Through the upper part, by means of a spring positioned into the cross-bore at right angle to the light path, the bag is slightly pressurized and thus tightly fitted against the sapphire windows. With the subtraction of twice the bag foil thickness, the distance between the internal surfaces of the sapphire windows is the optical path length being typically of the order of 1.4 mm. Through the capillary borings which are not shown in Figure 10, the cell is charged with heptane (which is used to transmit pressure onto the reacting system in the bag) and a sheathed thermocouple is introduced into the heptane fluid. The cell is heated (*H*) electrically from outside with sheathed resistance wire positioned onto a brass matrix. Pressures are determined to better than ± 4 bar even at 3 kbar. Temperatures are measured to better than ± 0.5°C. More details about optical high-pressure cells and about experimental procedures are presented elsewhere[4]. The high-pressure cell is adjusted into the optical compartment of a Fourier transform spectrometer (Bruker IFS 88).

HPLC: Investigations are carried out on a Varian LC 5000 Chromatograph using a Nucleosil 7C18 column. Detection by a Varian LC 558 photometer at 240 nm.

Ethyl vinyl ether **2** (Fluka, purum) is of 99% purity and methyl 3-acetylamino-2-formylpropenoate (**1**) is prepared according to ref.[5]. The concentrations are 0.04 mol of **1** and 1 mol of ethyl vinyl ether (**2**) per kg solution in CH_2Cl_2 (Merck, p.a.) and 0.1 mol of **1** and 1 mol of **2** in isodurene (Fluka, containing 10% of durene). 0.9 g of 2-*tert*-butyl-4-methylphenol (Ega) per kg solution are added to the CH_2Cl_2 solution in order to prevent free-radical polymerisation. During the reactions which are followed up to complete conversion in CH_2Cl_2 and in isodurene up to concentrations where the *trans* cycloadduct **4** precipitates, about fifty IR spectra are measured, and the absorbances for the wave number region from 6500 cm^{-1} up to 2000 cm^{-1} are stored. HPLC: Eluent: acetonitrile, flow: 1.0 ml, **3**: t_R = 6.85 min, **4**: t_R = 4.23 min.

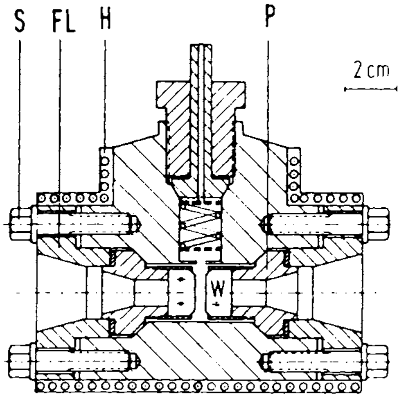

Figure 10. Optical high-pressure cell (*S*: screw, *Fl*: flange, *H*: heating, *P*: plug, *W*: sapphire window)

Methyl (2RS,4RS)-4-(Acetylamino)-2-ethoxy-3,4-dihydro-2H-pyran-5-carboxylate (**4**): R_f = 0.24 (chloroform/*tert*-butyl methyl ether, 1:1). – M.p. 102°C (dichloromethane/diethyl ether). – IR (KBr): ν = 3270 cm^{-1} (NH), 3080, 1715 (CO), 1635 (C=C). – UV (acetonitrile): λ_{max} (lg ε) = 232 nm (4.10). – ^1H NMR ($CDCl_3$): δ = 1.24 (t, *J* = 7.0 Hz, 3H, OCH_2CH_3), 1.94 (s, 3H, $COCH_3$), 1.96 (ddd, *J* = 2.8 Hz, 5.8 Hz, 14.7 Hz, 1H, 3-H_{ax}), 2.19 (ddd, *J* = 1.3 Hz, 2.1 Hz, 14.7 Hz, 1H, 3-H_{eq}), 3.60 (dq, *J* = 7.0 Hz, 9.6 Hz, 1H, OCH_2CH_3), 3.76 (s, 3H, OCH_3), 3.87 (dq, *J* = 7.0 Hz, 9.6 Hz, 1H, OCH_2CH_3), 5.06 (ddd, *J* = 1.2 Hz, 5.8 Hz, 9.5 Hz, 1H, 4-H), 5.33 (dd, *J* = 2.2 Hz, 2.8 Hz, 1H, 2-H), 6.14 (d, br, *J* = 9.5 Hz, 1H, NH), 7.60 (s, 1H, 6-H). – MS (70 eV): *m/z* (%) = 243 (3) [M^+], 200 (21) [M – CH_3CO], 154 (28) [M – CH_3CO, – C_2H_5OH], 72 (98) [$C_2H_5OCH=CH_2$], 43 (100) [CH_3CO].

$C_{11}H_{17}NO_5$ (243.2) Calcd. C 54.32 H 7.05 N 5.77
Found C 54.23 H 7.14 N 5.77

Methyl (2RS,4SR)-4-(Acetylamino)-2-ethoxy-3,4-dihydro-2H-pyran-5-carboxylate (**3**): R_f = 0.15 (chloroform/*tert*-butyl methyl ether, 1:1). – M.p. 164–167°C (dichloromethane/*tert*-butyl methyl ether). – IR (KBr): ν = 3320 cm^{-1} (NH), 2990 (CH), 1705 (CO), 1630 (C=C), 1290, 1160, 1080. – UV (acetonitrile): λ_{max} (lg ε) = 234 nm (4.07). – ^1H NMR ($CDCl_3$): δ = 1.27 (t, *J* = 7.0 Hz, 3H, OCH_2CH_3), 1.88 (ddd, *J* = 4.8 Hz, 9.6 Hz, 14.2 Hz, 1H, 3-H_{ax}), 2.00 (s, 3H, OCH_3), 2.31 (ddd, *J* = 2.2 Hz, 3.2 Hz, 14.2 Hz, 1H, 3-H_{eq}), 3.67 (dq, *J* = 7.0 Hz, 9.4 Hz, 1H, OCH_2CH_3), 3.75 (s, 3H, OCH_3), 4.01 (dq, *J* = 7.0 Hz, 9.4 Hz, 1H, OCH_2CH_3), 4.82 (ddd, *J* = 3.2 Hz, 4.8 Hz, 5.8 Hz, 1H, 4-H), 5.02 (dd, *J* = 2.2 Hz, 9.6 Hz, 1H, 2-H), 6.65 (d, br, *J* = 5.8 Hz, 1H, NH), 7.65 (s, 1H, 6-H). – MS (70 eV): *m/z* (%) = 243 (4) [M^+], 200 (21) [M – CH_3CO], 154 (28) [M – CH_3CO, – C_2H_5OH], 72 (61) [$C_2H_5OCH=CH_2$], 43 (100) [CH_3CO].

$C_{11}H_{17}NO_5$ (243.2) Calcd. C 54.32 H 7.05 N 5.77
Found C 54.17 H 6.92 N 5.79

CAS Registry Numbers

1: 112112-54-6 / **2**: 109-92-2 / **3**: 112112-55-7 / **4**: 112112-56-8

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