71. *Diels-Alder* Reactions of [2.2]Paracyclophan-1-ene and [2.2]Paracyclophane-1,9-diene with 3,6-Disubstituted 1,2,4,5-Tetrazines

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[2.2]Paracyclophan-1-ene (**1**) and [2.2]paracyclophane-1,9-diene (**6**) apparently act as dienophiles with inverse electron demand and smoothly react with dimethyl 1,2,4,5-tetrazine-3,6-dicarboxylate (**2a**) at room temperature forming dihydropyridazine adducts, which are dehydrogenated to the pyridazino-anellated [2.2]paracyclophanes **5a** and **8a**, respectively. The molecular structure of **5a** is determined by X-ray crystal-structure analysis. Under more rigorous conditions, phenyl-substituted derivatives **5b** and **8b** are obtained from **1** and **6**, respectively, with 3,6-diphenyl-1,2,4,5-tetrazine. Compounds **1** and **6** are less reactive dienophiles than other strained cyclic olefins as shown by kinetic measurements.

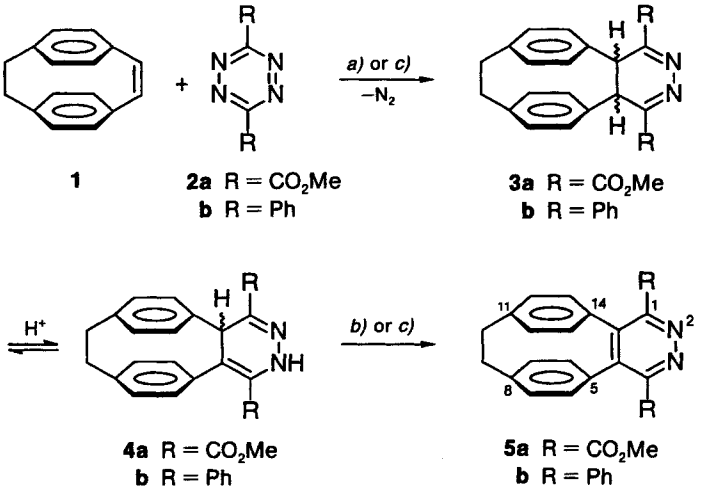
Since the first synthesis of [2.2]paracyclophan-1-ene (= tricyclo[8.2.2.$2^{4,7}$]hexadeca-2,4,6,10,12,13,15-heptaene; **1**) and [2.2]paracyclophane-1,9-diene (= tricyclo-[8.2.2.$2^{4,7}$]hexadeca-2,4,6,8,10,12,13,15-octaene; **6**) in 1958 by *Cram* [1], various attempts were made to react these unique olefins with dienes in *Diels-Alder* additions. But cycloadducts never were obtained, neither by the application of high pressure [1], nor in the presence of *Lewis*-acid catalysts [2], nor with very reactive dienes such as tetrachlorothiophene dioxide [3], known for its inverse electron demand.

All the more surprising is our observation that **1** [1b] reacts with dimethyl 1,2,4,5-tetrazine-3,6-dicarboxylate [4] (**2a**) at room temperature leading to dihydropyridazine **3a** in high yield (*Scheme 1*). As reported for other tetrazine *Diels-Alder* reactions [5], the primary adduct of **1** and **2** looses N_2 instantaneously, and a [1,3]-H shift occurs in **3a** thus formed (→ **4a**). The adduct **4a** is easily dehydrogenated by treatment with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (= 4,5-dichloro-3,6-dioxocyclohexa-1,4-diene-1,2-dicarbonitrile DDQ) to give **5a**. A crystal-structure analysis of **5a** confirms the proposed constitution (see *Fig.*). Bond lengths and angles in **5a** (see *Table 1*) are similar to the corresponding ones in the parent pyridazine system [6], [2.2]paracyclophane [7], and dibenzo[2.2]paracyclophane-1,9-diene [8].

[2.2]Paracyclophane-1,9-diene (**6**) [1b] reacts with 2 equiv. of **2a** to give a mixture of the isomeric bis-adducts **7** and *cisoid/transoid*-**9a**, which yield a single product **8a** upon treatment with DDQ (*Scheme 2*). Due to its high symmetry, **8a** is only poorly soluble in organic solvents. The mono-anellated product **10** is obtained upon reacting an excess of **6** with **2a** and subsequent dehydrogenation with DDQ.

Only under more rigorous conditions, 3,6-diphenyl-1,2,4,5-tetrazine (**2b**) [9] cycloadds to **1** and **6**. In refluxing xylene, **5b** and **8b**, respectively, were obtained; the extremely poor solubility of **8b** prevented it from being characterised by NMR spectroscopy.

Scheme 1



a) $CHCl_3$, r. t., 12 h. *b*) $CHCl_3$, DDQ, r. t., 2 h. *c*) Xylene, reflux, 2 d.

Table 1. *Selected Bond Lengths* [pm] *and Angles* [°] *of* **5a**. Standard deviations in parentheses. For numbering, see *Figure*.

C(1)–C(2)	141.3(5)	C(11)–C(16)	139.1(6)	C(1)–C(14)	149.9(5)
C(5)–C(6)	138.9(6)	C(15)–C(16)	138.6(5)	C(3)–C(4)	139.8(6)
C(9)–C(10)	155.5(6)	O(2)–C(1*)	145.4(5)	C(6)–C(7)	138.6(7)
C(12)–C(13)	137.1(5)	C(4*)–O(5)	131.6(4)	C(10)–C(11)	150.8(6)
C(1*)–O(2)	131.1(5)	C(3)–C(8)	139.7(5)	C(13)–C(14)	140.2(5)
O(5)–C(4")	145.1(4)	C(6)–C(9)	150.8(5)	C(1*)–O(1)	118.8(5)
C(2)–C(3)	149.5(5)	C(11)–C(12)	139.1(7)	N(2')–N(3')	133.6(4)
C(4)–C(5)	138.9(5)	C(14)–C(15)	137.7(6)		
C(7)–C(8)	138.0(5)	C(4*)–O(4)	117.9(5)		
C(2)–C(1)–C(14)	118.0(3)	C(12)–C(11)–C(16)	116.8(4)	C(5)–C(6)–C(7)	117.5(4)
C(14)–C(1)–C(1')	125.5(3)	C(12)–C(13)–C(14)	120.4(4)	C(7)–C(6)–C(9)	120.6(4)
C(1)–C(2)–C(4')	116.5(3)	C(14)–C(15)–C(16)	119.5(4)	C(3)–C(8)–C(7)	119.9(4)
C(2)–C(3)–C(4)	119.8(3)	C(1)–C(1')–N(2')	123.8(3)	C(9)–C(10)–C(11)	113.4(3)
C(4)–C(3)–C(8)	118.0(3)	N(2')–N(3')–C(4')	119.7(3)	C(10)–C(11)–C(16)	121.2(4)
C(4)–C(5)–C(6)	120.7(4)	C(2)–C(1)–C(1')	116.5(3)	C(11)–C(12)–C(13)	120.7(4)
C(5)–C(6)–C(9)	120.5(4)	C(1)–C(2)–C(3)	116.9(3)	C(1)–C(14)–C(13)	118.7(4)
C(6)–C(7)–C(8)	121.1(4)	C(3)–C(2)–C(4')	126.7(3)	C(11)–C(16)–C(15)	121.4(4)
C(6)–C(9)–C(10)	113.7(3)	C(2)–C(3)–C(8)	119.6(4)	C(1*)–C(1')–N(2')	114.3(3)
C(10)–C(11)–C(12)	120.2(4)	C(3)–C(4)–C(5)	119.7(4)	C(2)–C(4')–N(3')	124.1(3)

To assess the reactivity of **1** in comparison to other dienophiles, its reaction with **2a** was monitored following the decrease of the *n*-π^*-absorption band of **2a** at different temperatures (see *Table 2*). In general, the reaction of **2a** is strongly influenced by steric factors; the second-order rate constant of **1** (30°, 1,4-dioxane) is 18 times smaller than that of styrene [10], but **1** reacts much faster (by a factor of 140) with **2a** than 1,1-diphenylethene [10]. The rate constants for strained cyclic olefins such as cyclopentene or norbornene are 10^3 to 10^4 times as high [10]. It can, thus, be concluded that the basically high reactivity of the strained

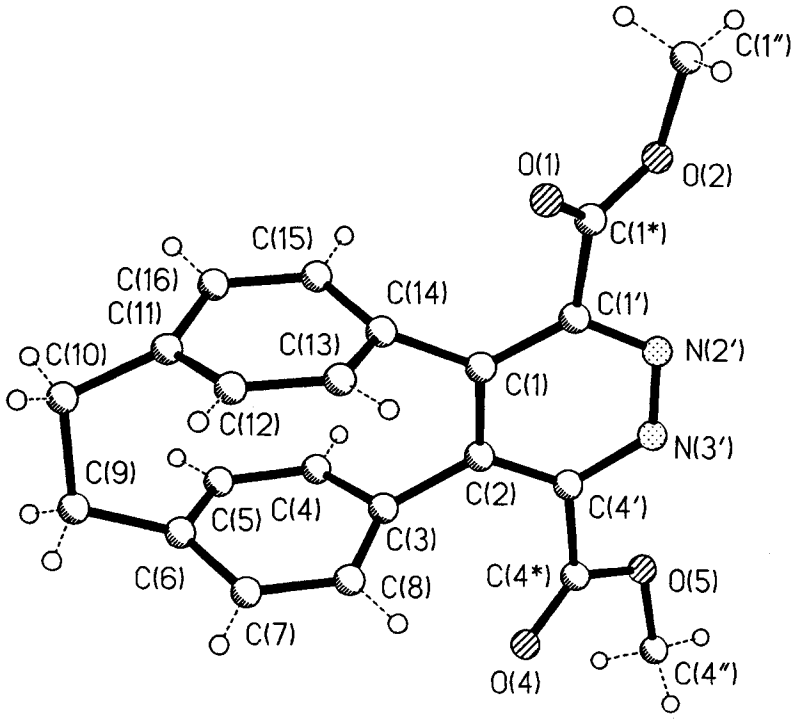


Figure. *Molecular Structure of* **5d** ($C_{25.5}H_{22}N_2O_4$; incl. 0.5 toluene)[1]). Arbitrary numbering. Monoclinic crystals, space group *C2/c*, $Z = 8$; unit cell dimensions $a = 1778.2(2)$, $b = 1116.3(1)$, $c = 2267.5(4)$ pm, $\beta = 108.28(1)°$, $V = 427.39(10)$ nm^3, $\rho_{calc.} = 1.31$ g cm^{-3}; 1979 observed reflections with $2\,\theta < 45°$, MoK_α, $R_w = 6.4\%$.

double bond in **1** is over-compensated by steric hindrance of the cycloaddend approach by the arene *ortho*-H-atoms.

The two reaction steps of diene **6** with **2a** occur with similar rates. The overall disappearance of **2a** was monitored as for the reaction of **1**, and the individual rate constants

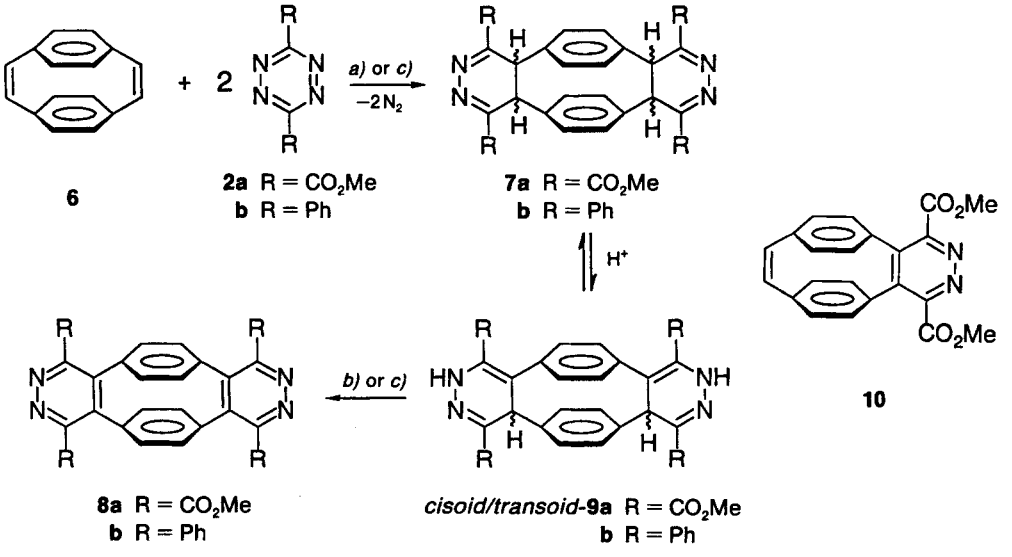
Table 2. *Second-Order Rate Constants for the Reaction of* **1** *with* **2a** *at Different Temperatures*

Temp. [°C]	k_2[a]) [l/mol · s]	A_0[b]) [mol/l]	r[c])
20.8	$1.634 \cdot 10^{-3} \pm 1.2 \cdot 10^{-6}$	$2.3742 \cdot 10^{-3} \pm 1.4 \cdot 10^{-7}$	0.99914
30.6	$3.619 \cdot 10^{-3} \pm 1.8 \cdot 10^{-6}$	$2.3698 \cdot 10^{-3} \pm 2.4 \cdot 10^{-7}$	0.99991
40.3	$7.196 \cdot 10^{-3} \pm 4.3 \cdot 10^{-6}$	$2.2864 \cdot 10^{-3} \pm 5.5 \cdot 10^{-7}$	0.99988
50.0	$1.549 \cdot 10^{-3} \pm 2.1 \cdot 10^{-5}$	$2.2580 \cdot 10^{-3} \pm 2.5 \cdot 10^{-6}$	0.99937

[a]) Second-order rate constant k_2.
[b]) Inverse y value, corresponding to the concentration at $t = 0$.
[c]) Correlation coefficient.

[1]) Further details of the crystal-structure investigation are deposited with the *Cambridge Crystallographic Data Center* or are available on request from the Fachinformationszentrum Energie Physik Mathematik GmbH, D–7514 Eggenstein-Leopoldshafen 2, on quoting the depository number CSD-56306, the names of the authors, and the journal citation.

Scheme 2



a) $CHCl_3$, r. t., 16 h. *b*) $CHCl_3$, DDQ, r.t., 2 h. *c*) Xylene, reflux, 2 d.

were adjusted by simulation of the overall kinetics [11]. According to the best fit, the first addition of **2a** to **6** occurs with a similar rate as that for **1**, whereas the second step is slower by a factor of four.

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Experimental Part

General. Column chromatography (CC): *Merck* silica gel *60*, mesh 70–230. TLC: *Merck* F_{254} silica gel. M.p.: electrothermal melting-point apparatus, uncorrected. UV/VIS: *Varian CARY 219*. IR (cm^{-1}): *Perkin Elmer 297* and *399*. ^{1}H-NMR: *Bruker-WM-250* spectrometer; chemical shifts in δ rel. to tetramethylsilane (= 0 ppm) as internal standard or $CHCl_3$ (= 7.26 ppm). ^{13}C-NMR: *Bruker-WM-250;* δ 77 ppm for $CDCl_3$; assignments are supported by DEPT (distortionless enhancement by polarization transfer) measurements; + designates primary or tertiary, – secondary, and quat. quaternary C-atoms. MS (*m/z* (%)): *Varian MAT CH7* (70 eV).

X-Ray Structure Analysis of **5a**: Intensity data were measured with a *Siemens-Stoe-AED2* diffractometer. The structure was solved with direct methods (SHELXTL PLUS, PC version), and was refined by full-matrix technique of F^2 using anisotropic temperature factors for non-H-atoms and isotropic temperature factors for H-atoms. Selected bond lengths and angles are listed in *Table 1*[1]).

*Dimethyl 9,10-Dihydro-5,8:11,14-diethenocyclododeca[*d*]pyridazine-1,4-dicarboxylate* (**5a**). A soln. of 100 mg (0.48 mmol) of [2.2]paracyclophan-1-ene [1b] (**1**) and 96 mg (0.48 mmol) of dimethyl 1,2,4,5-tetrazine-3,6-dicarboxylate (**2a**) in 30 ml of $CHCl_3$ was stirred at r.t. for 12 h, the solvent evaporated, and the residue subjected to CC (50 g of silica gel, CH_2Cl_2/AcOEt 9:1): 154 mg (85%) mixture of *dimethyl tetrahydro-5,8:11,14-diethenocyclododeca[*d*]pyridazine-1,4-dicarboxylates* (**3a/4a**). R_f 0.3. IR (KBr): 3362 (*s*, NH), 2928, 1728 (*s*,

C=O), 1435, 1198, 734. ^{1}H-NMR (250 MHz, $CDCl_3$): 3.05 (*m*, CH_2(9), CH_2(10)); 3.68, 3.70 (2*s*, 2 MeO); 3.95 (*s*, 1 H, H–C(4a) or H–C(14a)); 4.60 (*s*, 1 H, H–C(4a) or H–C(14a)); 6.30–6.80 (*m*, 8 arom H); 8.45 (br. *s*, 1 H, NH). ^{13}C-NMR (62.5 MHz, $CDCl_3$): 34.71, 35.06 (–, C(9), C(10)); 47.03, 52.30, 52.50 (+, C(1), C(4a), C(14a)); 122.87, 124.00 (quat.); 131.17–139.49 (+); 162.71, 164.00 (quat.).

A mixture of 150 mg (0.40 mmol) of **4a** and 90 mg (0.40 mmol) of DDQ in 30 ml of $CHCl_3$ was stirred under N_2 for 2 h at r.t. The solvent was evaporated and the solid residue chromatographed (50 g of silica gel, CH_2Cl_2/AcOEt 9:1): 135 mg (91%) of **5a**. R_f 0.2. M.p. 240°. IR (KBr): 1746 (*s*, C=O), 1439, 1267, 1202, 1169, 1062, 721. ^{1}H-NMR (250 MHz, $CDCl_3$): 3.14 (*s*, CH_2(9), CH_2(10)); 3.95 (*s*, 2 MeO); 6.57 (*AB*, δ_A 6.51, δ_B 6.63, $^3J_{AB}$ = 8.0, 8 H). ^{13}C-NMR (62.5 MHz, $CDCl_3$): 34.72 (–, C(9), C(10)); 53.24 (+, MeO); 131.19, 132.92 (+); 132.45, 140.90, 144.53, 150.35 (quat., C(1), C(4), C(4a), C(5), C(8), C(11), C(14), C(14a)); 164.70 (quat.). MS (70 eV): 375 (26, $[M+1]^+$), 374 (100, M^+). Anal. calc. for $C_{22}H_{18}N_2O_4$ (374.4): C 70.59, H 4.81, N 7.49; found: C 70.38, H 4.62, N 7.43; C 70.61, H 4.72, N 7.50.

*Tetramethyl 5,8:13,16-Diethenocyclododeca[1,2-*d*:7,8-*d'*]dipyridazine-1,4,9,12-tetracarboxylate* (**8a**): A soln. of 352 mg (1.72 mmol) of [2.2]paracyclophane-1,6-diene [1b] (**6**) and 1.03 g (5.18 mmol) of **2a** in 40ml of $CHCl_3$ was stirred for 16 h at r.t. The mixture was evaporated and the solid residue subjected to CC (80 g of silica gel, CH_2Cl_2/AcOEt 8:2): 751 mg (80%) mixture of *tetramethyl tetrahydro-5,8:13,16-diethenocyclododeca[1,2-*d*:7,8-*d'*]dipyridazine-1,4,9,12-tetracarboxylates* (**7a**/**9a**). R_f 0.15. IR (KBr): 3360, 2955, 1713, 1437, 1337, 1198, 1169. ^{1}H-NMR (250 MHz, $CDCl_3$): 3.60–4.15 (*m*, 4 MeO); 4.50, 4.61, 4.65 (3*s*, 2 H); 6.30–7.10 (*m*, 8 H); 8.45, 8.50, 8.55 (3*s*, 2 H, NH). MS (70 eV): 544 (100, M^+). HR-MS: 544.1575 ($C_{28}H_{24}O_8N_4$, calc. 544.1594).

A mixture of 200 mg (0.37 mmol) of **9a** and 170 mg (0.75 mmol) of DDQ in 40 ml of $CHCl_3$ was stirred for 1 h at r.t. The white precipitate was collected by filtration and washed once with 50-ml portions each of dil. aq. NaOH soln., H_2O, EtOH, $CHCl_3$, and pentane and dried *in vacuo*: 120 mg (61%) of **8a**. M.p. 240° (dec.). IR (KBr): 1741(*s*, C=O), 1438, 1203, 1172. MS (70 eV): 541 (38, $[M+1]^+$), 540 (100, M^+), 482 (14, $[M+1-CO_2Me]^+$), 423 (39, $[M+1-2\ CO_2Me]^+$), 365 (22, $[M+1-3\ CO_2Me]^+$). HR-MS: 540.1272 ($C_{28}H_{20}O_8N_4$, calc. 540.1281).

*Dimethyl 5,8:11,14-Diethenocyclododeca[*d*]pyridazine-1,4-dicarboxylate* (**10**): A soln. of 300 mg (1.47 mmol) of **6** and 97 mg (0.49 mmol) of **2a** in 30 ml of $CHCl_3$ was stirred for 12 h at r.t. CC (50 g of silica gel, CH_2Cl_2/AcOEt 9:1) gave *Fr. I* (R_f 0.95; 220 mg of **6**), *Fr. II* (R_f 0.3; 110 mg (59%) of *dimethyl dihydro-5,8:11,14-diethenocyclododeca[*d*]pyridazine-1,4-dicarboxylate)*, and *Fr. III* (R_f 0.05; 55 mg (7%) of *cisoid/transoid*-**9a**). *Fr. II* was treated with 80 mg (0.35 mmol) of DDQ in 20 ml of $CHCl_3$ for 1 h at r.t. The solvent was evaporated and the residue subjected to CC (50 g of silica gel, CH_2Cl_2/AcOEt 9:1): 80 mg (74%) of **10**. R_f 0.25. M.p. 230° (dec.). IR (KBr): 1745 (*s*, C=O), 1268, 1169, 720. ^{1}H-NMR (250 MHz, $CDCl_3$): 3.95 (*s*, 2 MeO); 6.64 (*AB*, δ_A 6.60, δ_B 6.68, $^3J_{AB}$ = 8.0, 8 H); 7.30 (*s*, H–C(9), H–C(10)). ^{13}C-NMR (62.5 MHz, $CDCl_3$): 53.36 (+, MeO), 130.38, 131.45 (+); 132.33 (quat.); 137.21 (+, C(9), C(10)); 139.52, 143.79, 150.28 (quat.); 164.75 (quat.). MS (70 eV): 373 (24, $[M+1]^+$), 372 (100, M^+).

*9,10-Dihydro-1,4-diphenyl-5,8:11,14-diethenocyclododeca[*d*]pyridazine* (**5b**): For 2 h, 200 mg (0.97 mmol) of **1** and 227 mg (0.97 mmol) of 3,6-diphenyl-1,2,4,5-tetrazine (**2b**) were heated in 5 ml of xylene at 140°. The precipitate was filtered and chromatographed (50 g of silica gel, $CHCl_3$): 323 mg (80%) of **5b**. R_f 0.1. M.p. 210° (dec.). IR (KBr): 2937, 1439, 1364, 1180, 1124, 783, 758, 725, 700, 623. ^{1}H-NMR (250 MHz, $CDCl_3$): 3.07 (*s*, CH_2(9), CH_2(10)); 6.55 (*AB*, δ_A 6.52, δ_B 6.58, $^3J_{AB}$ = 8.0, 8 arom. H). ^{13}C-NMR (62.5 MHz, $CDCl_3$): 34.77 (–, C(9), C(10)); 128.10, 128.83, 130.22, 132.42, 133.14 (+); 131.56, 135.25, 137.21, 140.30, 155.70 (quat.). MS (70 eV): 411 (35, $[M+1]^+$), 410 (100, M^+).

*1,4,9,12-Tetraphenyl-5,8:13,16-diethenocyclododeca[1,2-*d*:7,8-*d'*]dipyridazine* (**8b**). For 2 d, 100 mg (0.49 mmol) of **6** and 459 mg (1.96 mmol) of **2b** were refluxed in 10 ml of xylene. The precipitate was filtered off and washed with 50-ml portions each of $CHCl_3$ and pentane: 92 mg (33%) of **8b**. M. p. 230° (dec.). MS (70 eV): 612 (100, M^+).

Kinetic Measurements: The progress of the reaction **1** + **2a** was followed by the decrease of the *n*-π*-absorption band of **2a** at 524 nm (ε_{524} = 512) in a thermostated UV spectrometer. Equal amounts of prethermostated $2.5 \cdot 10^{-3}$ M solns.[2]) of the reactants in 1,4-dioxane (*UVASOL*®) were mixed, and the reaction was followed for 12 h, corresponding to 70% conversion. During this time, 660 extinction values were recorded. Activation energies E_a and preexponential factors A were calculated by linear regression [12].

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[2]) The linear correlation between extinction and concentration was verified for this concentration range.

Arrhenius activation energy E_a = 60.5 (± 4.7) kJ · mol^{-1}, preexponential factor $A = 7.7 \cdot 10^7$ (± $8 \cdot 10^6$) s^{-1}, correlation coefficient of the *Arrhenius* plot r = 0.9995, activation enthalpy $\Delta H^{\neq}$ = 58.1 (± 4.7) kJ · mol^{-1}, and activation entropy $\Delta S^{\neq}$ = –97.9 (± 0.9) J · mol^{-1} · K^{-1}.

The progress of the reaction of a stoichiometric mixture of **6** and **2a** in 1,4-dioxane was followed at 28° over a period of 60 h (56% conversion) as described above. Fitting of the experimental data to the kinetic model for two consecutive reactions was performed by simulation [11], to give $k_2^1 = 3.07 \cdot 10^{-3}$ (± $0.17 \cdot 10^{-3}$) l · mol^{-1} · s^{-1} and $k_2^2 = 7.33 \cdot 10^{-4}$ (± $0.28 \cdot 10^{-4}$) l · mol^{-1} · s^{-1}.

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