

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** loses N₂ 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.

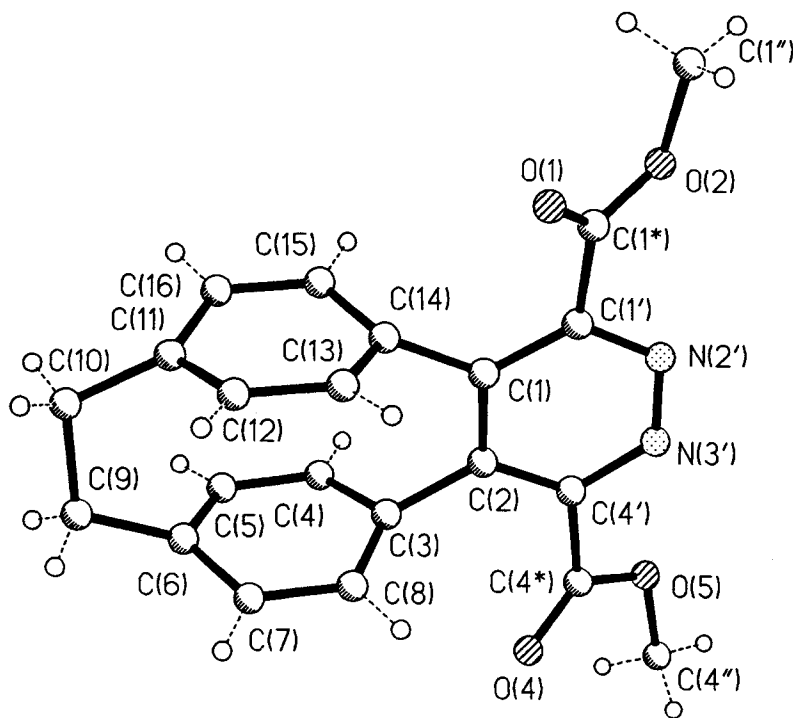


Figure. *Molecular Structure of 5d* ($C_{25.5}H_{22}N_2O_4$; incl. 0.5 toluene)¹⁾. Arbitrary numbering. Monoclinic crystals, space group $C2/c$, $Z = 8$; unit cell dimensions $a = 1778.2(2)$, $b = 1116.3(1)$, $c = 2267.5(4)$ pm, $\beta = 108.28(1)^\circ$, $V = 427.39(10)$ nm³, $\rho_{\text{calc.}} = 1.31$ g cm⁻³; 1979 observed reflections with $2\theta < 45^\circ$, 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

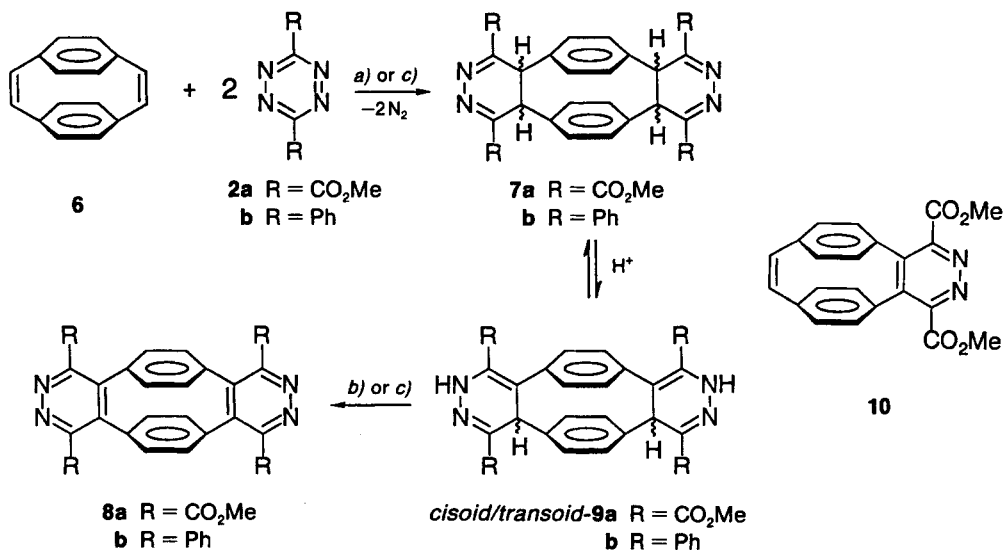
^{a)} Second-order rate constant k_2 .

^{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) CHCl₃, r. t., 16 h. b) CHCl₃, 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 F₂₅₄ silica gel. M.p.: electrothermal melting-point apparatus, uncorrected. UV/VIS: Varian CARY 219. IR (cm⁻¹): Perkin Elmer 297 and 399. ¹H-NMR: Bruker-WM-250 spectrometer; chemical shifts in δ rel. to tetramethylsilane (= 0 ppm) as internal standard or CHCl₃ (= 7.26 ppm). ¹³C-NMR: Bruker-WM-250; δ 77 ppm for CDCl₃; 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 1¹.

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 CHCl₃ was stirred at r.t. for 12 h, the solvent evaporated, and the residue subjected to CC (50 g of silica gel, CH₂Cl₂/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. ¹H-NMR (250 MHz, CDCl₃): 3.05 (*m*, CH₂(9), CH₂(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). ¹³C-NMR (62.5 MHz, CDCl₃): 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 CHCl₃ was stirred under N₂ for 2 h at r.t. The solvent was evaporated and the solid residue chromatographed (50 g of silica gel, CH₂Cl₂/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. ¹H-NMR (250 MHz, CDCl₃): 3.14 (*s*, CH₂(9), CH₂(10)); 3.95 (*s*, 2 MeO); 6.57 (*AB*, δ_A 6.51, δ_B 6.63, ³*J*_{AB} = 8.0, 8 H). ¹³C-NMR (62.5 MHz, CDCl₃): 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 C₂₂H₁₈N₂O₄ (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 40 ml of CHCl₃ was stirred for 16 h at r.t. The mixture was evaporated and the solid residue subjected to CC (80 g of silica gel, CH₂Cl₂/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. ¹H-NMR (250 MHz, CDCl₃): 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 (C₂₈H₂₄O₈N₄, 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 CHCl₃ 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., H₂O, EtOH, CHCl₃, 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–CO₂Me]⁺), 423 (39, [M+1–2 CO₂Me]⁺), 365 (22, [M+1–3 CO₂Me]⁺). HR-MS: 540.1272 (C₂₈H₂₀O₈N₄, 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 CHCl₃ was stirred for 12 h at r.t. CC (50 g of silica gel, CH₂Cl₂/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 CHCl₃ for 1 h at r.t. The solvent was evaporated and the residue subjected to CC (50 g of silica gel, CH₂Cl₂/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. ¹H-NMR (250 MHz, CDCl₃): 3.95 (*s*, 2 MeO); 6.64 (*AB*, δ_A 6.60, δ_B 6.68, ³*J*_{AB} = 8.0, 8 H); 7.30 (*s*, H-C(9), H-C(10)). ¹³C-NMR (62.5 MHz, CDCl₃): 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, CHCl₃): 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. ¹H-NMR (250 MHz, CDCl₃): 3.07 (*s*, CH₂(9), CH₂(10)); 6.55 (*AB*, δ_A 6.52, δ_B 6.58, ³*J*_{AB} = 8.0, 8 arom. H). ¹³C-NMR (62.5 MHz, CDCl₃): 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 CHCl₃ 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 ($\epsilon_{524} = 512$) in a thermostated UV spectrometer. Equal amounts of prethermostated 2.5 · 10^{–3} mol/L 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].

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

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

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 $k_1^1 = 3.07 \cdot 10^{-3} (\pm 0.17 \cdot 10^{-3}) \text{ l} \cdot \text{mol}^{-1} \cdot \text{s}^{-1}$ and $k_2^2 = 7.33 \cdot 10^{-4} (\pm 0.28 \cdot 10^{-4}) \text{ l} \cdot \text{mol}^{-1} \cdot \text{s}^{-1}$.

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