Intramolecular [2 + 2] Photocycloaddition, 4[1] Synthesis of [4.*n*]Cyclophanes by [2 + 2] Photocycloaddition and Birch Reduction. A Rare Fragmentation of Tetramethylene Radical Anion

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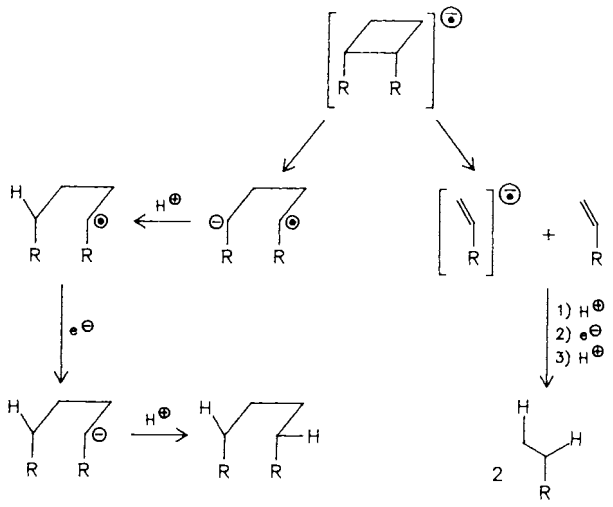
[4.*n*]Metacyclophanes **6** (*n* = 2–6), [4.*n*]paracyclophanes **7** (*n* = 3–6), [4.*n*](4,4')biphenylophanes **8** (*n* = 3, 4), and [2.3.2.4]-paracyclophane **9** were obtained from appropriate 1,2-ethano-[2.*n*]cyclophanes **1**–**5** by Birch reduction. Some strained cyclophanes, like **1a**, **1b**, and **2a**, gave linear open-chain compounds **10** by fragmentation of the cyclobutane radical anions. The synthetic method and the fate of the cyclobutane radical anion are discussed.

Intramolekulare [2 + 2]-Photocycloaddition, 4[1]. – Darstellung von [4.*n*]Cyclophanen durch [2 + 2]-Photocycloaddition und Birch-Reduktion. Eine ungewöhnliche Fragmentierung des Tetramethylen-Radikal-Anions

[4.*n*]Metacyclophane **6** (*n* = 2–6), [4.*n*]Paracyclophane **7** (*n* = 3–6), [4.*n*](4,4')Biphenylophane **8** (*n* = 3, 4) und [2.3.2.4]-Paracyclophane **9** wurden aus entsprechenden 1,2-Ethano-[2.*n*]cyclophanen **1**–**5** durch Birch-Reduktion hergestellt. Einige gespannte Cyclophane wie **1a**, **1b** und **2a** lieferten lineare, offenkettige Verbindungen **10** durch Fragmentierung des Cyclobutan-Radikal-Anions. Die Darstellungsmethode und das Schicksal des Cyclobutan-Radikal-Anions werden diskutiert.

Ring opening of cyclobutane radical anions leads to tetramethylene radical anions, which can subsequently react in situ with a proton donor, accept an electron, and finally be further protonated to give a saturated tetramethylene derivative[2]. Although fragmentation of tetramethylene *radical cations* to an olefin radical cation and an olefin is commonly observed in mass spectrometry, this kind of cleavage is very rarely encountered in solution reactions of *radical anions*. Recently, we observed this rare type of radical anion fragmentation using highly strained cyclobutane-ring-containing cyclophanes.

Scheme 1



In addition, we have developed a new synthetic method for obtaining [4.*n*]cyclophanes from 1,2-ethano[2.*n*]cyclophanes[1,3] by Birch reduction as shown in Scheme 2. On searching the literature, we found no generally applicable synthetic methods for [4.*n*]cyclophanes (vide infra); we, therefore, wish to report in detail a new synthetic method and to discuss the fate of the cyclobutane radical anion.

Birch Reduction of 1,2-Ethano[2.*n*]cyclophanes 1–5

The 1,2-ethano[2.*n*]cyclophanes **1**–**5** were prepared from olefins **11**–**14** by the known method[1,3]. Birch reduction of these cyclophanes was carried out under the usual conditions reported[4].

Reduction of the cyclobutane moiety occured readily at –60°C. The reaction sequence is shown in Scheme 2, and the results are summarized in Table 1. In most cases the reaction gave the desired product in almost quantitative yield, except for some cyclophanes, like **1a** (vide infra).

Structural analysis of the reduction products was done mainly by ^{1}H-NMR spectroscopy: high-field-shifted aromatic resonances and simple spin-coupling patterns clearly proved the cyclophane structures depicted. Spectroscopic data are summarized in Table 2. Cyclophanes **7**–**9** are free of isomers. Metacyclophanes **6** are concluded to have a stable *anti* conformation, because they all show a negative Δδ value, as defined by Lehner[5].

On photocycloaddition, olefin **14** gave an isomeric mixture of *cis*- and *trans*-cyclophanes **5** in 11% overall yield; **5** was treated under Birch reduction conditions to afford isomer-free macrocyclic cyclophane **9** in 80% yield. Macrocyclic cyclophanes of this type gain much attention as host molecules[5]. Here we present another synthesis of cyclophanes pos-

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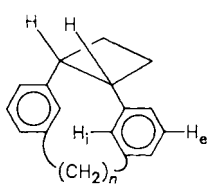

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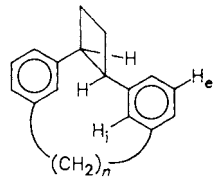

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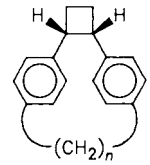

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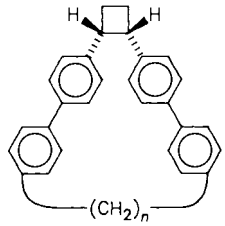

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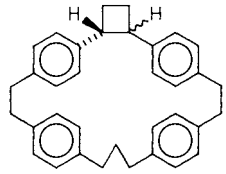

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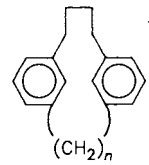

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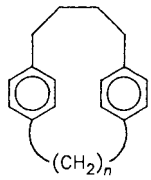

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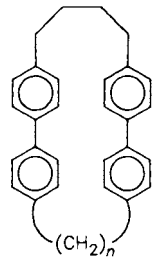

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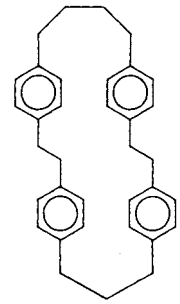

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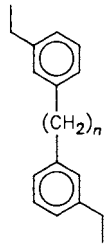

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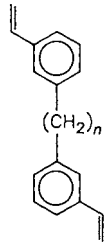

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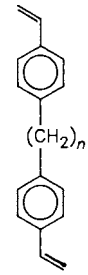

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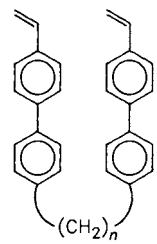

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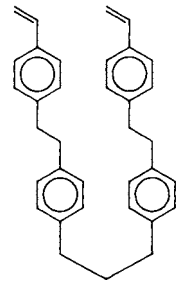

14

1, 6, 11	a	b	c	d	e
n	2	3	4	5	6

3, 7, 12	a	b	c	d
n	3	4	5	6

2, 4, 8, 13	a	b
n	3	4

10	a	b
n	2	3

sessing a large cavity; this allows their structures to be systematically changed.

Table 1. Yields and physical and analytical data of the cyclophanes

Compd.	n	Yield (in %)	Mp [°C]	C/H Analysis Calcd. (Found)	MS (m/z, M$^+$) Calcd. (Found)
6a	2	17	oil		236.1566 (236.1562)
6b	3	82	oil		250.1723 (250.1716)
6c	4	90	105.5 – 106.5	90.85 (90.80)/9.15 (9.26)	264.1879 (264.1876)
6d	5	98	oil		278.2036 (278.2033)
6e	6	98	oil		292.2192 (292.2185)
7a	3	99	117.0 – 119.0		250.1753 (250.1723)
7b	4	88	146.0 – 147.5	90.85 (90.59)/9.15 (9.20)	264.1879 (264.1877)
7c	5	94	130.0 – 131.0	90.59 (90.38)/9.41 (9.48)	278.2036 (278.2034)
7d	6	88	94.0 – 95.0	90.35 (90.13)/9.65 (9.59)	292.2192 (292.2180)
8a	3	63	233.0 – 237.0	92.49 (92.71)/7.51 (7.50)	402.2349 (402.2329)
8b	4	76	241.0 – 245.0		416.2506 (416.2496)
9		80	163.0 – 164.0	91.65 (91.53)/8.35 (8.54)	458.2975 (458.2965)

Scheme 2

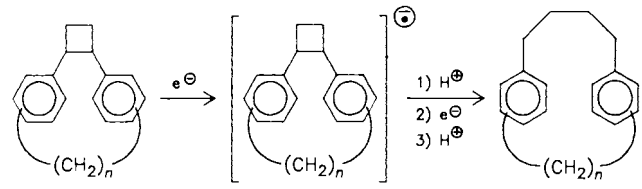

Table 2. ^{1}H-NMR data of the cyclophanes

Compd.	n	Chemical shift δ (multiplicity, J [Hz])	Δδ[a]
6a	2	0.88 – 1.81 (4H, m), 2.10 – 3.44 (4H, m), 6.75 (2H, t, 1.2), 6.95 (2H, dt, 6.6, 1.2), 7.09 (2H, dt, 6.6, 1.2), 7.24 (2H, t, 6.6).	−0.49
6b	3	1.53 (4H, m), 2.13 (2H, m), 2.53 (8H, t, 6.6), 6.12 (2H, t, 1.2), 6.90 (2H, dt, 7.4, 1.2), 7.04 (2H, dt, 7.4, 1.2), 7.17 (2H, t, 7.4).	−1.05
6c	4	1.44 (8H, quint, 2.9), 1.53 (8H, t, 2.9), 6.57 (2H, t, 1.2), 6.91 (2H, dt, 6.6, 1.2), 6.92 (2H, dt, 6.6, 1.2), 7.12 (4H, dd, 8.2, 6.6).	−0.55
6d	5	1.09 (2H, m), 1.51 (4H, m), 1.53 (4H, m), 2.58 (8H, m), 6.80 (2H, t, 1.5), 6.92 (4H, dt, 7.4, 1.5), 7.14 (2H, t, 7.4, 1.5).	−0.34
6e	6	1.14 (4H, m), 1.55 (8H, m), 2.58 (8H, m), 6.77 (2H, t, 1.5), 6.96 (2H, dt, 7.4, 1.5), 6.97 (2H, dt, 7.4, 1.5), 7.17 (2H, dd, 8.0, 7.4).	−0.40
7a	3	1.59 (4H, m), 2.17 (2H, m), 2.27 (4H, m), 2.73 (4H, m), 6.53 (4H, *A*Bq, 8.0), 6.69 (4H, A*B*q, 8.0).	
7b	4	1.50 (8H, m), 2.24 (8H, m), 6.61 (8H, s),	
7c	5	0.62 (2H, m), 1.45 (4H, m), 1.54 (4H, m), 2.26 (4H, m), 2.47 (4H, t, 6.2), 6.74 (4H, *A*Bq, 8.6), 6.80 (4H, A*B*q, 8.6).	
7d	6	0.91 (4H, m), 1.56 (8H, quint, 2.8), 2.42 (4H, m), 2.48 (4H, m), 6.82 (8H, s).	
8a	3	1.66 (4H, m), 2.25 (2H, m), 2.38 (4H, m), 2.80 (4H, m), 6.78 (4H, *A*Bq, 8.4), 6.89 (8H, A*B*q, 8.4), 6.90 (4H, *A*Bq, 8.4), 6.99 (4H, A*B*q, 8.4).	
8b	4	1.66 (8H, quint, 0.8), 2.40 (8H, t, 0.8), 6.72 (8H, *A*Bq, 8.1), 6.92 (8H, A*B*q, 8.1).	
9		1.53 (4H, m), 1.83 (2H, quint, 7.2), 2.42 (4H, t, 7.2), 2.53 (4H, m), 2.87 (8H, s), 6.71 (4H, *A*Bq, 8.0), 6.75 (4H, A*B*q, 7.0), 6.86 (4H, *A*Bq, 7.0), 6.90 (4H, A*B*q, 8.0).	

[a] $\Delta\delta = \delta H_i - \delta H_e$; see ref.[5].

Cleavage of the Cyclophane Skeleton under Birch Reduction Conditions

1,2-Ethano[2.*n*]cyclophanes **1a**, **1b**, and **2a** gave open-chain-reduced products **10a** and **10b** in yields of 10 to 87%. **2a**, especially, was selectively reduced to **10b**. As shown in Table 3, the reduction conditions had some influence on the product ratio **6**/**10**; the highest ratio was found in methanol (the most acidic solvent used) with sodium as metal source. This is due to facile protonation of the radical anion. The degree of ring cleavage to open-chain compound **10**, however, depends mainly on the substrate.

Scheme 3

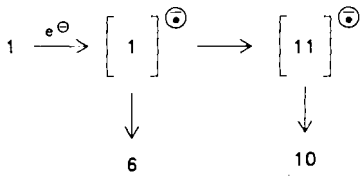

Table 3. Ring opening of the 1,2-ethano[2.3]metacyclophanes

Substrate (mM)	M	ROH (mM)	Yield of **6** (in %)	Yield of **10** (in %)	Ratio **6**/**10**
1a (5.70)	Na	EtOH (11.38)	17.4	59.2	0.29
1b (2.86)	Na	MeOH (8.24)	83.3	8.8	9.47
1b (3.56)	Na	EtOH (14.22)	86.8	9.7	8.95
1b (3.55)	Na	s-BuOH (13.30)	24.7[a]	7.5	3.29
1b (6.40)	Li	EtOH (28.44)	86.1	14.0	6.15
1b (7.00)	K	EtOH (28.44)	63.5	15.7	4.04
2a (1.71)	Na	EtOH (5.69)	0	86.8	0

[a] Containing unknown cyclophanes.

Discussion

Cram and co-workers have reported pioneering work on the synthesis of [4.4]paracyclophane, using acyloin condensation as a key cyclization method[7] and also a ring expansion of commercially available [2.2]paracyclophane[8]. Hammond and Longone have observed the formation of [2.4]paracyclophane by 1,8-Hofmann degradation[9]. Misumi and co-workers prepared several [4.*n*]cyclophanes from dithiacyclophanes by ring contraction[10]. Compared with these previously reported methods, the present one has advantages in the easy preparation of starting materials[11,12], the clean photochemical cyclization reaction[1,3], the mild ring opening of cyclobutane units to tetramethylene linkages[4], and especially in the versatile preparation of [4.*n*]cyclophanes whose structures can be easily designed using only one starting material. [4.*n*]Paracyclophanes ($n \geqslant 3$), for example, were prepared from bromobenzene by Grignard coupling, Friedel-Crafts acetylation, reduction, dehydration, [2 + 2] photocycloaddition, and Birch reduction[1,3,11,12].

When the substrates are highly strained, fragmentation appears to occur during the reduction. The strain energies were estimated by MM2 calculation[13] and are listed in Table 4.

Table 4. Strain energies E_{st} of the cyclophanes[a]

Compd.	Fragmentation	E_{st} [kcal/mol]	ΔE_{st}[b] [kcal/mol]
1a	yes	61.6	32.9
3a	no	52.6	23.9
2a	yes	50.8	22.1
1b	yes	45.6	16.9
3b	no	43.5	14.8
2b	no	42.8	14.1
1c	no	38.9	10.2
1d	no	35.4	6.7
1e	no	34.5	5.8

[a] Strain energies were calculated by MM2. — [b] Strain energy differences based on *cis*-diphenylcyclobutane as standard (E_{st} = 28.7 kcal/mol).

The ease of the fragmentation is qualitatively correlated with the calculated strain energies. We conclude, therefore, that strain is one of the major factors facilitating the fragmentation. Quantitatively, though, the correlation between fragmentation and calculated strain energies is not strictly parallel. What factors, other than strain, affect this type of anion-radical fragmentation is, therefore, still an open question.

Experimental

Elemental analyses were performed at the Microanalysis Center of Kyoto University. — Melting points are not corrected. — NMR spectra were recorded on a Varian XL-200 FT-NMR spectrometer. — Mass spectra were recorded on a Hitachi M-80A mass spectrometer. — High performance liquid chromatographic analyses (HPLC) were carried out using Altex Model 100A and Knauer 64 pumps with a Hitachi wavelength-tunable effluent monitor and a Shimadzu SPD-6A UV spectrophotometric detector. — MM2 calculation was performed on an NEC PC-9801-VM2 personal computer using the program provided[13]. — Solvents like benzene, THF, and ether were distilled from sodium diphenylketyl after prolonged reflux. Other commercially available highest grade reagents were used without further purification. Monomers **11**—**14** and 1,2-ethano[2.*n*]cyclophanes **1**—**5** were prepared conveniently by our methods reported previously[1,3,11,12].

1) *Preparation of Macrocyclic Cyclophane* **5**: Olefin **14** (2.280 g, 5 mmol) was irradiated in dry and N_2-degassed benzene (650 ml) under N_2 using a 400-W high-pressure mercury lamp with a Pyrex filter. After 35 h, the reaction mixture was concentrated by evaporation and treated with an excess of diborane in THF to convert any unconsumed monomer into more polar material with higher molecular weight. Macrocyclic compound **5** was easily isolated by column chromatography (SiO_2, cyclohexane/benzene); the yield was 0.225 g (11%). The ^{1}H-NMR spectrum showed two cyclobutane methine protons with a ratio of 1:5. The product was used for the reduction without further purification.

2) *Birch Reduction of* **3b**, *Formation of [4.4]paracyclophane* (**7b**) *(General Procedure)*: Cyclophane **3b** (68 mg, 0.26 mmol) was dissolved in 5 ml of dry THF containing 20 µl (0.34 mmol) of EtOH. This solution was added over 3 min with vigorous stirring to 20 ml of liquid ammonia (−60°C), in which Na (20 mg, 0.87 mmol) had been dissolved. Within 10 min the blue color had disappeared. After stirring at −60°C for 4 h, 10 ml of water was added to stop the reaction. The reaction mixture was then allowed to warm to room

temp. and, after spontaneous evaporation of the ammonia, was extracted three times with 30 ml of benzene. The combined organic layers were washed with water and dried with anhydrous Na_2SO_4. After evaporation of the solvents, **7b** was isolated by column chromatography (SiO_2, *n*-hexane); the yield was 60 mg (88%) after recrystallization from methanol.

CAS Registry Numbers

1a: 116467-65-3 / **1b**: 116467-66-4 / **1c**: 116467-67-5 / **1d**: 116561-18-3 / **1e**: 116467-69-7 / **2a**: 116559-82-1 / **2b**: 116559-83-2 / **3a**: 116559-78-5 / **3b**: 116559-79-6 / **3c**: 116559-80-9 / **3d**: 116559-81-0 / **4a**: 109530-20-3 / **4b**: 109530-21-4 / *cis*-**5**: 116504-46-2 / *trans*-**5**: 116561-20-7 / **6a**: 86496-61-9 / **6b**: 86496-64-2 / **6c**: 116561-19-4 / **6d**: 116504-40-6 / **6e**: 116504-41-7 / **7a**: 7215-89-6 / **7b**: 502-08-9 / **7c**: 4423-66-9 / **7d**: 116504-42-8 / **8a**: 116504-43-9 / **8b**: 116504-44-0 / **9a**: 116504-45-1 / **10a**: 82639-84-7 / **10b**: 116504-47-3 / **14**: 107485-12-1

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[13] The authors are indebted to Prof. Eiji Ōsawa, Hokkaido University, for providing the MM2 program.

[121/88]