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Synthesis and Dynamic Behaviour of [7]- and [8]Metacyclophanes

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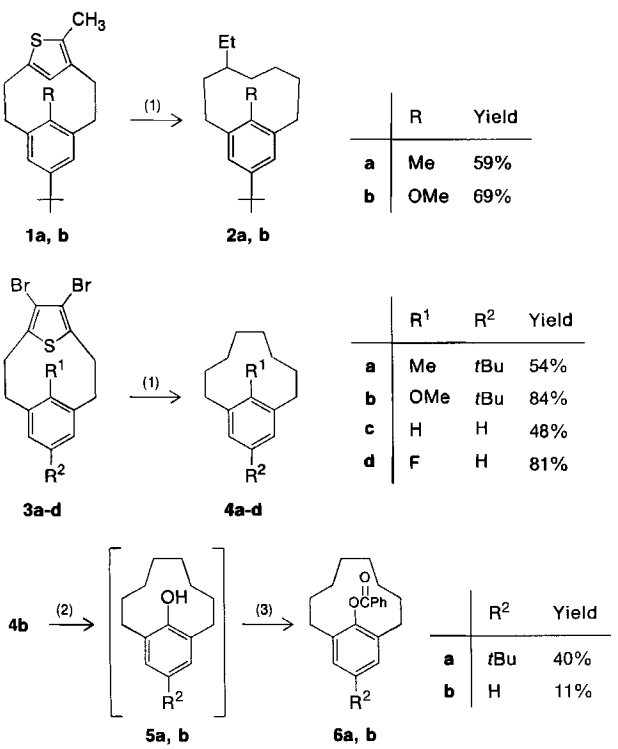
The synthesis and structure of [7]- and [8]metacyclophanes **2**, **4** are described. The reductive ring opening of the thiophene rings of [2]metacyclo[2](2,4)- and -(2,5)thiophenophanes **1** and **3** by Raney-Ni affords the corresponding [7]- and [8]metacyclophanes **2** and **4**, respectively. Two types of motion have been observed for the methylene chain of [8]metacyclophane **4c**, flipping and pseudorotation.

There are many reports about [*n*]cyclophanes because of their attractive novel structures and reactivities[1]. One of the most interesting features is the mode of motion of the methylene chain of these compounds. From this point of view, many types of [n]cyclophanes have been synthesized, and their dynamic features have been investigated. However, to the best of our knowledge, there are only a few reports on the preparation of [7][2] and [8]metacyclophanes[3].

Scheme 1



	R	Yield
a	Me	59%
b	OMe	69%

	R^1	R^2	Yield
a	Me	*t*Bu	54%
b	OMe	*t*Bu	84%
c	H	H	48%
d	F	H	81%

	R^2	Yield
a	*t*Bu	40%
b	H	11%

The dynamic behaviour of [7]metacyclophane has been described[2], but those of [8]metacyclophane has not been clarified. In order to obtain these cyclophanes, we used the reductive ring opening of [2]metacyclo[2](2,4)- and -(2,5)thiophenophanes (**1** and **3**)[4]. It has already been reported[5] that [8]paracyclophanes can be obtained by ring opening of [2]paracyclo[2](2,5)furanophanes. Indeed, **1** and **3** reacted with Raney-Ni (W-7)[6] under hydrogen to afford the corresponding [7]- and [8]metacyclophanes **2** and **4**, as shown in Scheme 1.

[7]Metacyclophanes **2a, b** are obtained as a mixture of diastereomers (1:1). The ^{1}H-NMR spectrum of the methylene chain of **2** is very complicated and its pattern does not changes below 150°C in [D$_6$]DMSO. Hence, neither pseudorotation nor flipping[2] of **2** occurs in this temperature range. Such a large energy barrier for the motions of **2** results from the bulky inner group and the ethyl group on the methylene chain.

The ^{1}H-NMR spectrum of the methylene bridge of **4c** shows four signals (4 protons each, 27°C). The lowest field signal appears as a triplet, and the others are multiplets. Two coalescence points were found, −73 and −48°C (VT ^{1}H-NMR, Figure 1).

The estimated energy barriers ($\Delta G_c^{\neq}$) for each motion[2] are 8.7 and 10.2 kcal mol^{-1}, respectively. It is already known that [6]metacyclophane exhibits a conformational flipping and pseudorotation of the methylene chain, with coalescence temperatures of 76.5 and −31.5°C, respectively (Table 1)[2]. To clarify these processes for the [8]metacyclophane series, we have synthesized 14-(benzoyloxy)-[8]metacyclophane (**6a**) (Scheme 1), whose methylene chain is supposed not to flip its inner substituent due to the bulkiness of the *O*-benzoyl group.

Demethylation of **4b** with concd. hydrogen bromide in acetic acid gives a mixture of **5a** and de-*tert*-butylated **5b**. Without separating the mixture, it has been benzoylated to afford **6a** and **6b** in yields of 40 and 11%, respectively. The VT ^{1}H-NMR spectrum of **6a** indicates one coalescence point at −65°C and the estimated $\Delta G_c^{\neq}$ is 8.9 kcal mol^{-1} (Figure 2).

This frozen motion is assumed to be pseudorotation as shown in Scheme 2, and the value of $\Delta G_c^{\neq}$ shows a good agreement with that of the first coalescence point in **4c**. Obviously this is caused by the process of pseudorotation. It is concluded that the conformational flipping and pseudorotation exist for the movement of the methylene chain of [8]metacyclophane (**4c**) as shown in Scheme 3. These values are reasonable, compared with those for [6]- and [7]metacyclophanes[2] (Table 1).

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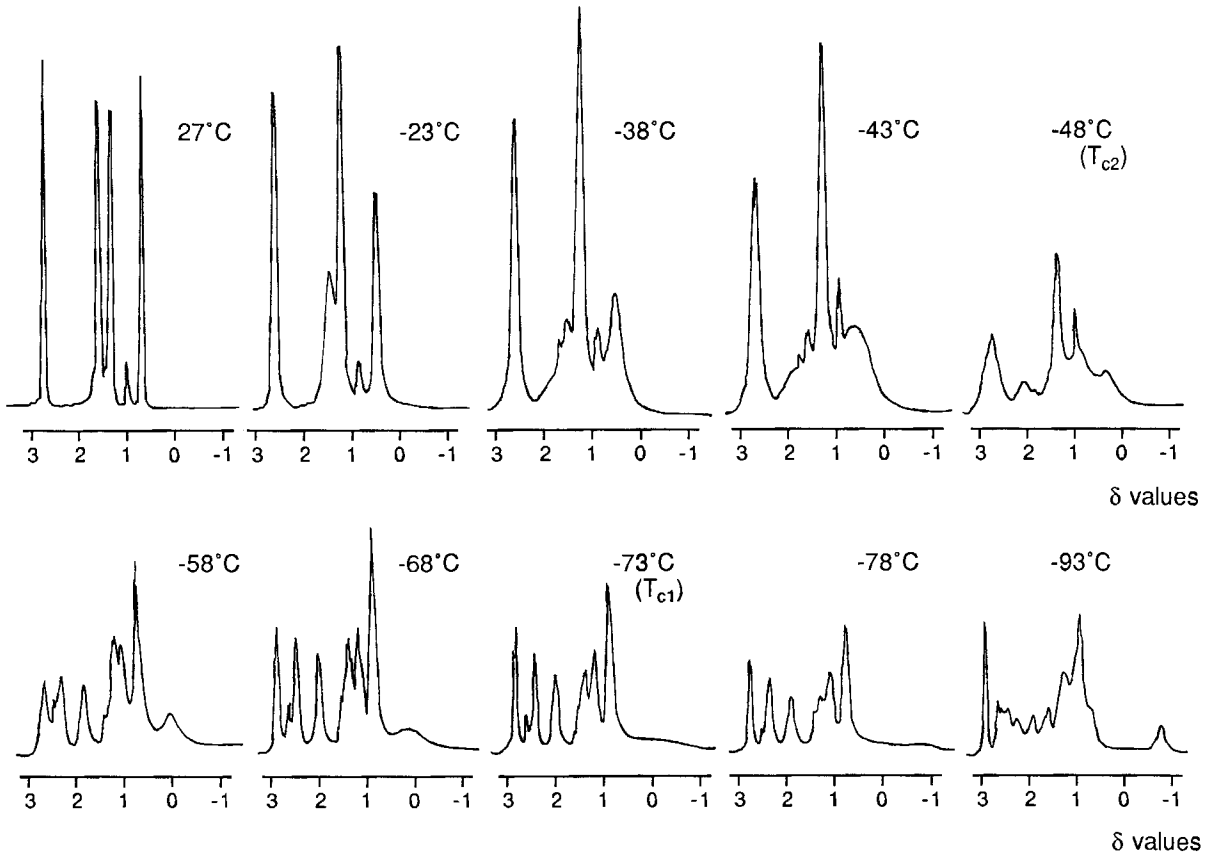
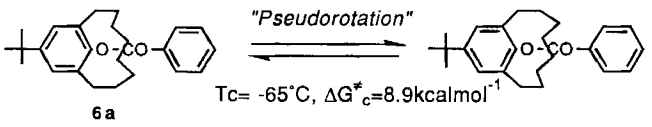


Figure 1. Dynamic behaviour of **4c** as shown by its ^{1}H-NMR spectra at various temperatures (in CD_2Cl_2, CH_2Cl_2 as reference, 270 MHz)

Scheme 2. Movement of **6a**



Scheme 3. Movement of [8]metacyclophane **4c**

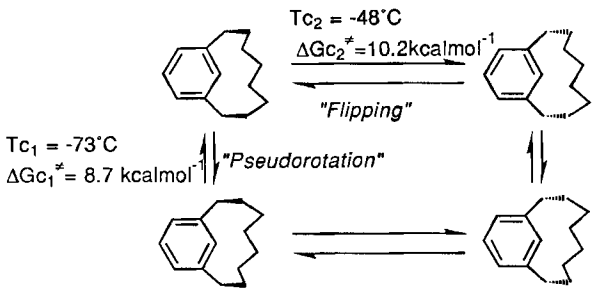


Table 1. T_c and $\Delta G_c^{\neq}$ of [n]metacyclophanes

[n]MCP[a]	Flipping		Pseudorotation	
	T_c [K]	$\Delta G_c^{\neq}$ [kcal/mol]	T_c [K]	$\Delta G_c^{\neq}$ [kcal/mol]
n = 6[2]	350	17.4	242	11.1
n = 7[2]	245	11.5		
n = 8 (**4c**)	225	10.2	200	8.7
S_2-8[b]	<203	< 9.1		

[a] MCP = Metacyclophane. — [b] S_2-8 = 2,7-Dithia[8]metacyclophane[7].

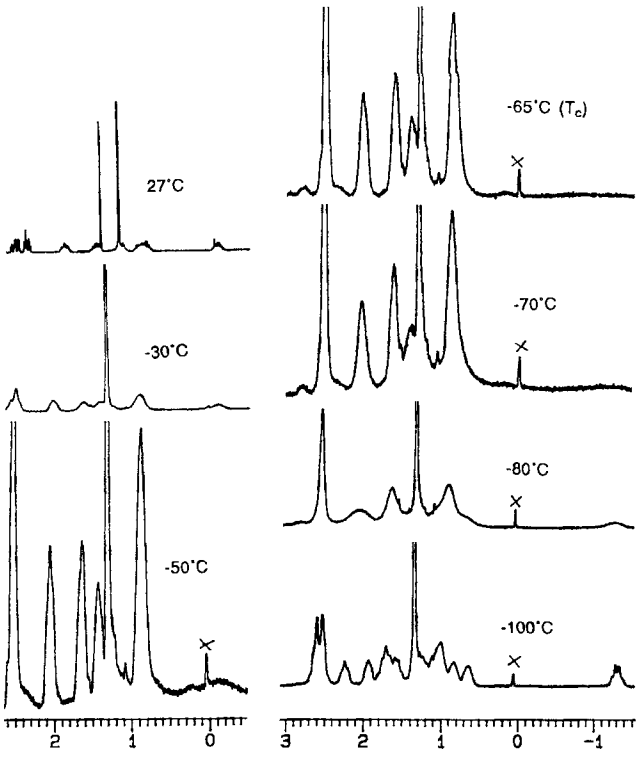


Figure 2. Dynamic behaviour of **6a**: ^{1}H-NMR spectra at various temperatures (in $CDCl_3$ + CS_2 (1:3), CH_2Cl_2 as reference, 270 MHz)

Experimental

Melting and boiling points are uncorrected. – IR (KBr): Jasco IR-700. – ^{1}H NMR: Jeol GSX-270 in $CDCl_3$, TMS as reference. – MS: Jeol JMS-01-SG-2. – Elemental analyses: Yanaco MT-5.

Reductive Ring-Opening Reactions of **1a**: A mixture of 150 mg of **1a** (0.50 mmol) and 5 ml of Raney Ni (W-7) ethanolic suspension[6] (ca. 6.6 mmol) was heated at reflux under hydrogen for 5 h. The reaction mixture was cooled to room temp., and the precipitate was filtered off on Celite. The filtrate was concentrated in vacuo, hexane was added to the residue, and the precipitate was filtered off. The solvent was evaporated in vacuo. Purification of the residue by preparative silica gel thin-layer chromatography afforded 80 mg (59%) of **2a**.

10-tert-Butyl-3-ethyl-13-methyl[7]metacyclophane (**2a**): Colourless oil. – IR (NaCl): $\tilde{\nu}$ (cm^{-1}) = 2956, 2864, 1599, 1593, 1480, 1460, 1362, 871. – ^{1}H NMR ($CDCl_3$): δ = –1.86 to –1.76 (0.5H, m), –1.60 to –1.46 (0.5H, m), 0.54–0.85 (1H, m), 0.85–0.92 (3.5H, m), 0.92–1.35 (5H, m), 1.43 (4.5H, s), 1.44 (4.5H, s), 1.43–1.75 (1.5H, m), 1.77–2.10 (1.5H, m), 2.40–2.57 (0.5H, m), 2.57 (1.5H, s), 2.64 (1.5H, s), 2.72–2.85 (1.5H, m), 3.12–3.50 (2H, m), 3.45–3.55 (0.5H, m), 7.00 (0.5H, d, J = 2 Hz), 7.03 (0.5H, d, J = 2 Hz), 7.06 (1H, s). – MS: m/z = 272 [M$^+$].

$C_{20}H_{32}$ (272.5) Calcd. C 88.16 H 11.84
Found C 87.87 H 11.73

10-tert-Butyl-3-ethyl-13-methoxy[7]metacyclophane (**2b**): Synthesis from **1b** in 69% yield as described above; colourless oil. – IR (NaCl): $\tilde{\nu}$ (cm^{-1}) = 2958, 1484, 1462, 1362, 1291, 1206, 1169, 1107, 1022, 868. – ^{1}H NMR ($CDCl_3$): δ = –1.86 to –1.75 (1H, m), 0.57–0.77 (2H, m), 0.73 (1.5H, t, J = 7 Hz), 0.88 (1.5H, t, J = 7 Hz), 0.99–1.33 (4H, m), 1.27 (4.5H, s), 1.29 (4.5H, s), 1.75–1.95 (2H, m), 2.15–2.52 (4H, m), 2.77–3.10 (2H, m), 3.47 (1.5H, s), 3.65 (1.5H, s), 6.84 (0.5H, d, J = 2 Hz), 6.88 (0.5H, d, J = 2 Hz), 6.88 (0.5H, d, J = 3 Hz), 6.90 (0.5H, d, J = 3 Hz). – MS: m/z = 288.2453 (calcd. 288.2452 for $C_{20}H_{32}O$).

11-tert-Butyl-14-methyl[8]metacyclophane (**4a**): Synthesis from **3a** in 54% yield as described above; colourless oil. – IR (NaCl): $\tilde{\nu}$ (cm^{-1}) = 2954, 2862, 1604, 1481, 1458, 1361, 1286, 1229, 871, 724. – ^{1}H NMR ($CDCl_3$): δ = –0.28 to –0.08 (2H, m), 0.64–0.80 (2H, m), 0.90–1.62 (6H, m), 1.29 (9H, s), 1.88–2.04 (2H, m), 2.43 (3H, s), 2.52–2.64 (2H, m), 2.86–2.97 (2H, m), 6.92 (2H, s). – MS: m/z = 258.2340 (calcd. 258.2346 for $C_{19}H_{30}$).

11-tert-Butyl-14-methoxy[8]metacyclophane (**4b**): From **3b** in 84% yield as described above, colourless oil, b.p. 180°C/0.2 Torr (oven temp.). – IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 2924, 2880, 1484, 1460, 1362, 1293, 1204, 1171, 1108, 1020, 872. – ^{1}H NMR ($CDCl_3$): δ = –0.14 to 0.09 (2H, m), 0.77–1.15 (6H, m), 1.28 (9H, s), 1.40–1.60 (2H, m), 1.93–2.08 (2H, m), 2.36–2.46 (2H, m), 2.86–2.98 (2H, m), 3.61 (3H, s), 7.23 (2H, s). – MS: m/z = 274.2298 (calcd. 274.2295 for $C_{19}H_{30}O$).

[8]Metacyclophane (**4c**): From **3c** in 48% yield as described above: colourless oil; b.p. 140°C (oven temp.)/15 Torr. – MS: m/z = 188.1564 (calcd. 188.1566 for $C_{14}H_{20}$). – Other spectral data were supported in the literature[3a,c].

14-Fluoro[8]metacyclophane (**4d**): From **3d** in 81% yield in the same manner as described above; colourless oil. – IR (NaCl): $\tilde{\nu}$ (cm^{-1}) = 2930, 2866, 1460, 1394, 1260, 1181, 1092, 1019, 800, 730. – ^{1}H NMR ($CDCl_3$): δ = 0.14–0.19 (2H, m), 0.90–1.68 (8H, m), 2.05–2.12 (2H, m), 2.46–2.55 (2H, m), 3.02 (2H, dt, J = 4/12 Hz), 6.94–7.40 (3H, m). – ^{19}F NMR ($CDCl_3$): δ = 46.09 (s). – MS: m/z = 206.1468 (calcd. 206.1470 for $C_{14}H_{19}F$).

Synthesis of [8]Metacyclophane 14-Benzoates (**6**): A mixture of 270 mg of **4b** (1.0 mmol) and 1.0 ml of 47% hydrogen bromide in 10 ml of acetic acid was heated at reflux for 21 h. The mixture was poured into ice-cold water and extracted with dichloromethane. The organic layer was washed twice with brine and dried with magnesium sulfate. The solvent was evaporated in vacuo, and 240 mg of benzoyl chloride (1.7 mmol) and 4 ml of pyridine were added to the residue, which was stirred 20 h at room temp. The reaction mixture was poured into 3% hydrogen chloride and extracted with ether. The organic layer was washed twice with brine and dried with magnesium sulfate. The solvent was evaporated in vacuo, and the residue was separated by silica-gel column chromatography (hexane/chloroform = 4:1). Recrystallization of the first eluate from methanol afforded 160 mg of **6a** (0.44 mmol, 44%), and recrystallization of the second eluate from 80% aqueous methanol afforded 36 mg of **6b** (0.12 mmol, 12%).

14-(Benzoyloxy)-11-tert-butyl[8]metacyclophane (**6a**): Colourless prisms (methanol), m.p. 148.5–155.0°C. – IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 2960, 1732, 1601, 1479, 1451, 1393, 1362, 1268, 1169, 1107, 1025, 873, 705. – ^{1}H NMR ($CDCl_3$): δ = 0.08–0.23 (2H, m), 0.96–1.22 (4H, m), 1.26–1.37 (2H, m), 1.37 (9H, s), 1.61–1.75 (2H, m), 2.03–2.20 (2H, m), 2.53–2.67 (2H, m), 2.69–2.82 (2H, m), 7.10 (2H, s), 7.57–7.74 (3H, m), 8.28–8.31 (2H, m). – MS: m/z = 364 [M$^+$].

$C_{25}H_{32}O_2$ (364.5) Calcd. C 82.37 H 8.85
Found C 82.28 H 8.80

14-(Benzoyloxy)[8]metacyclophane (**6b**): Colourless prisms (methanol/water), m.p. 124.0–125.0°C. – IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 2950, 1735, 1452, 1265, 1163, 1083, 1064, 1025, 792, 711. – ^{1}H NMR ($CDCl_3$): δ = 0.14–0.22 (2H, m), 0.92–1.24 (4H, m), 1.26–1.45 (2H, m), 1.56–1.80 (2H, m), 2.12–2.20 (2H, m), 2.58–2.69 (2H, m), 2.75–2.82 (2H, m), 7.12–7.32 (3H, m), 7.59–7.76 (3H, m), 8.30–8.33 (2H, m). – MS: m/z = 308 [M$^+$].

$C_{21}H_{24}O_2$ (308.4) Calcd. C 81.78 H 7.84
Found C 81.90 H 7.97

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