Pyrolysis of dimethoxy[*n*.2]metacyclophanes: an intramolecular condensation reaction to give oxa[*n*.2.1](1,3,2)cyclophanes

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Pyrolysis of *anti*-8,16-dimethoxy[2.2]metacyclophane at 500 °C gave 17-oxa[2.2.1](1,3,2)cyclophane in 35% yield arising from intramolecular condensation reaction of *syn*-8,16-dimethoxy[2.2]metacyclophane; similar results were also obtained in the pyrolysis of the higher *anti*- and *syn*-dimethoxy[3.2] metacyclophane to afford the corresponding 18-oxa[3.2.1](1,3,2)cyclophane. The mechanism of this novel intramolecular condensation reaction is discussed.

Keywords: cyclophanes, strained molecules, pyrolysis, intramolecular condensation reaction

The synthesis and stereochemical aspects of conformationally mobile [m.n]metacyclophanes (MCPs) have been of interest for the past two decades,[1,2] particular attention being paid to [2.2]MCPs, which possess an *anti*-stepped conformation.[3–7] Although the parent [2.2]MCP was first reported as early as in 1899 by Pellegrin,[8] the synthesis of *syn*-[2.2]MCP was not realised until 85 year later. Mitchel *et al.*[9] have successfully prepared *syn*-[2.2]MCP at low temperature by using (arene)chromium–carbonyl complexation to control the stereochemistry. However, *syn*-[2.2]MCP isomerises readily to the *anti*-isomer above 0 °C.[10] In contrast, a ring inversion of *anti*-[2.2]MCPs to the corresponding *syn*-[2.2]MCPs has not yet been reported. The meta-bridged benzene ring has not been shown to undergo conformational flipping above 200 °C. A large part of this high energy barrier is believed to arise from steric destabilisation of the transition state in which the 8 or 16 hydrogen to each *meta*-bridged ring impinges into the π-electron cloud of the opposing benzene ring. Therefore, the cleavage of the ethylene bridge must be necessary for the ring inversion. Whereas according to the spectroscopic findings, the [2.2]MCPs have the *anti* conformation with staggered benzene rings, the existence of a *syn* form for a [*n*.2]MCP has also been detected.[11–18]

On the other hand, we have reported[19] that nitration of *anti*-5,13-di-*tert*-butyl-8,16-dimethoxy[2.2]MCP *anti*-**1a** led to *ipso*-nitration at the *tert*-butyl group to give 5-*tert*-butyl-8,16-dimethoxy-13-nitro[2.2]MCP, as well as the corresponding 17-oxa[2.2.1](1,3,2)cyclophane arising from intramolecular condensation reaction via *anti–syn*-ring inversion of the nitration intermediate. Recently, Hopf *et al.* reported[20] the pyrolysis of 5,13-dibromo[2.2]paracyclophane in triglyme at 216 °C to afford 7,13-dibrom[2.2]paracyclophane through the ring clevage of ethylene bridge. Thus there is substantial interest in studying the pyrolysis of *anti*-8,16-disubstituted [2.2]MCPs to give the corresponding *syn*-[2.2]MCPs. We report here the first evidence for *anti–syn*-ring inversion under the pyrolysis of di-*tert*-butyl-dimethoxy[*n*.2]MCPs **1**. The mechanism of the present novel intramolecular condensation reaction is also discussed.

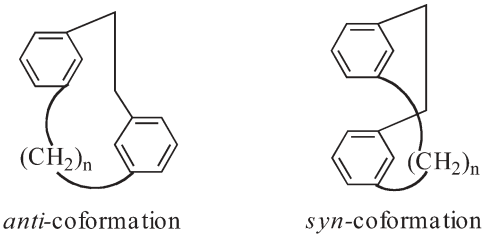

Fig. 1 Possible conformations of [n.2]MCPs.

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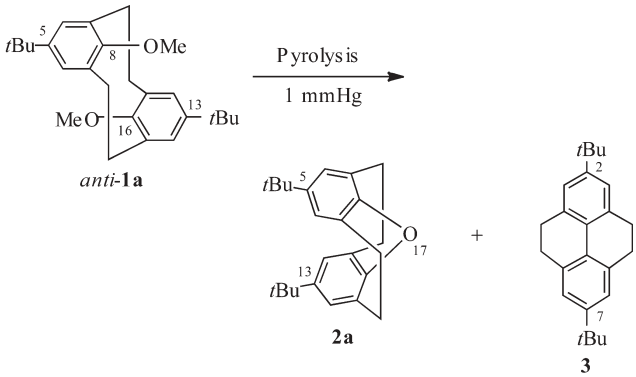
Results and discussion

Preparation of *anti*-5,13-di-*tert*-butyl-8,16-dimethoxy[2.2]MCP (*anti*-**1a**),[21] *syn*- and *anti*-6,14-di-*tert*-butyl-9,17-dimethoxy[3.2] MCP (**1b**)[22] has been described elsewhere. Attempted pyrolysis of *anti*-8,16-dimethoxy[2.2]MCP *anti*-**1a** was carried out in triglyme at 216 °C to recover the starting compound. No formation of the intramolecular condensation product, 17-oxa [2.2.1](1,3,2)cyclophane **2a**[19] has been observed under the reaction conditions used. Only the recovery of the starting compound was obtained. Interestingly, the present pyrolysis was carried out at 400 °C, the expected intramolecular condensation product **2a** was obtained in 2% yield along with the recovery of the starting compound *anti*-**1a** in 96% yield. Pyrolysis of *anti*-**1a** at 500 °C led to the intramolecular condensation reaction to give 17-oxa[2.2.1](1,3,2)cyclophane **2a** in 35% yield along with the transannular cyclisation product **3** in 37% yield. However, the increasing the temperature at 560 °C the yield of the transannular cyclisation product **3** increased to 65%. The present novel intra-annular condensation reaction is the first evidence for *anti–syn*-ring inversion under the pyrolysis of *anti*-8,16-dimethoxy[2.2]MCP *anti*-**1a**.

It was also found that the pyrolysis reaction of *anti*-8,16-dihydroxy[2.2]MCP *anti*-**4**[5,6] at 550 °C, which was prepared by demethylation of *anti*-**1a** with BBr_3 in CH_2Cl_2 in 80% yield, also led to the present intramolecular condensation reaction to afford **2a** in 13% yield along with the transannular cyclisation reaction product **3** in 23% yield.

Although the detailed mechanism of formation of 17-oxa [2.2.1](1,3,2)cyclophane **2a** is not clear from the available results, one might assume that the reaction pathway is similar to the radical mechanism proposed for the racemisation of 4-methoxycarbonyl[2.2]paracyclophanes at 200 °C.[23] as shown in Scheme 4. Although it is recognised that the *anti–syn* ring inversion is inhibited, that of the intermediate **A** generated arising from the high temperature at the ethylene bridge might be possible. Subsequently the *anti–syn*-ring inversion to form



Scheme 1

Table 1 Pyrolysis of *anti*-5,13-di-*tert*-butyl-8.16-dimethoxy [2.2]MCP *anti*-**1a**

Run	Temp./°C	Products yield/%[a,b]		Recovd. **1a**
		2a	**3**	
1	400	2	2	96 [90]
2	500	35 [25]	37	28
3	560	27 [15]	65	8

[a] Yields were determined by GLC analysis.
[b] Isolated yields are shown in square bracket.

the intermediate **B** might proceed to form the *syn*-8,16-dimethoxy[2.2]MCP *syn*-**1a**, from which the intramolecular condensation reaction of the two methoxy groups afford 17-ox a[2.2.1](1,3,2)cyclophane **2a**. The present novel intraannular condensation reaction is the first evidence for *anti–syn*-ring inversion under the pyrolysis of *anti*-5,13-di-*tert*-butyl-8,16-dimethoxy[2.2]MCP *anti*-**1a**.

The structure of **2a** was assigned on the basis of elemental analysis and spectral data. The ^{1}H NMR spectrum of **2a** in $CDCl_3$ shows the disappearance of two internal methoxy protons and *tert*-butyl protons as a singlet at δ 1.21 ppm, a bridged methylene protons as a multiplet at δ 2.64–3.66 ppm, and aromatic protons as a singlet at δ 6.85 ppm.

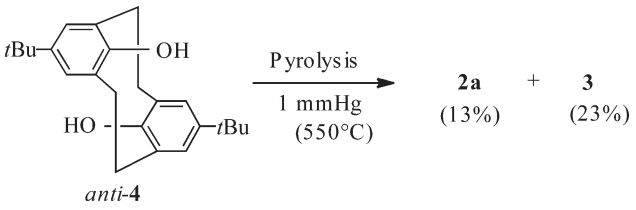
Similar results were also obtained in the pyrolysis of the higher *anti*- and *syn*-dimethoxy[3.2]MCPs *anti*-**1b** and *syn*-**1b** to afford the corresponding 18-oxa[3.2.1](1,3,2)cyclophane **2b**. In fact, pyrolysis of *anti*-**1b** was carried out under the same conditions as *anti*-**1a** at 500 °C only resulted the recovery of the starting compound *anti*-**1b**. However, increasing the temperature at 560 °C led to the intramolecular condensation reaction at the 9, 17 positions to afford **2b** in 46% yield along with 18-oxa[2.3.1](1,3,2)cyclophane-1-ene **5b** in 10% yield. The formation of the latter product **5b** strongly suggests that the present novel intraannular condensation reaction does occur through *anti–syn*-ring inversion followed by the dehydrogenation reaction at the 11, 12 bridged ethylene protons under the pyrolysis of *anti*-9,17-dimethoxy[3.2]MCP *anti*-**1b**.

In contrast, attempted pyrolysis of *syn*- and *anti*-7,15-di-*tert*-butyl-10,18-dihydroxy[4.2]MCP **1c**[22] at 560 °C resulted in the recovery of the starting compound. No formation of the intramolecular condensation product **2c** has been observed under the reaction conditions used. These findings suggest that the novel intramolecular condensation of internal methoxy groups in the *syn*-intra-annular positions is attributed to the release of strain in *syn*-9,17-dimethoxy[3.2]MCP *syn*-**1b** leading to the more strainless 18-oxa[3.2.1](1,3,2)cyclophane **2b** containing an ether linkage.

The structure assigned to **2b** is supported by its elemental analysis and spectral data. The ^{1}H NMR ($CDCl_3$) spectrum of **2b** shows the disappearance of methoxy protons (δ 3.02 ppm for *anti*-**1a** and δ 3.51 ppm for *syn*-**1b**[22], and exhibits a pattern quite different from those of *syn*- and *anti*-6,14-di-*tert*-butyl-9,17-dimethoxy[3.2]MCP **1b**. The structure **5b** was deduced from the ^{1}H NMR spectrum of a mixture of **2b** and **5b**. Thus, the ^{1}H NMR ($CDCl_3$) spectrum of a mixture of **2b** and **5b** shows the bridged olefinic protons for **5b** as a singlet at δ 6.91 ppm.

Several attempted separations of **2b** and 18-oxa[2.3.1](1,3,2) cyclophane-1-ene **5b** failed. However, a mixture of **2b** and **5b** (ratio of 70:30) was treated with hydrogen in the presence of 10% Pd–C in ethylacetate at room temperature to afford **2b** in quantitative yield.

The $AlCl_3$–$MeNO_2$-catalysed *trans-tert*-butylation of **2a** was carried out in benzene at 50 °C to afford 17-oxa[2.2.1](1,3,2) cyclophane **6a** in 75% yield along with *tert*-butyl-benzene **7**. The physical properties and spectral data were identical with those of the sample which has already been prepared by Boekelheide *et al.*[24] Similarly, 18-oxa[3.2.1](1,3,2) cyclophane **6b** was obtained in 80% yield.

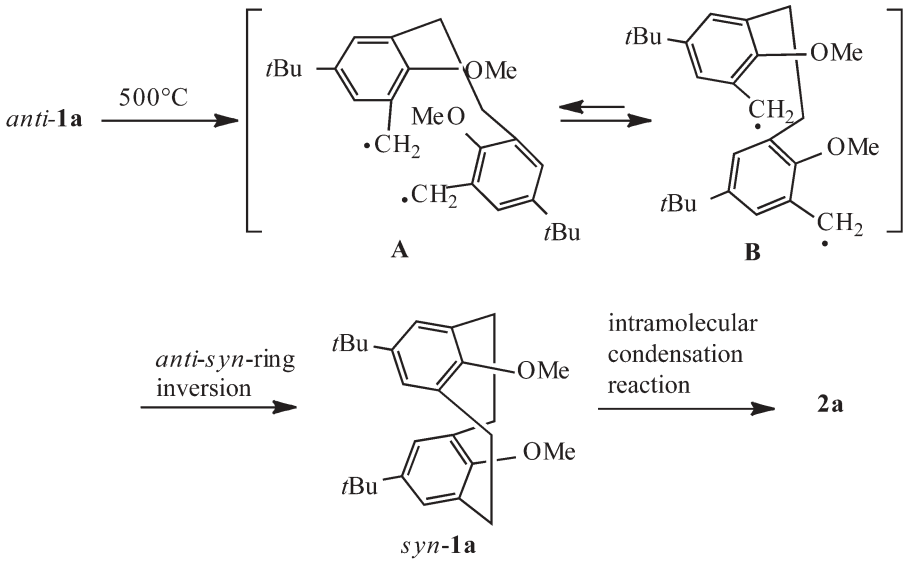


anti-**4**

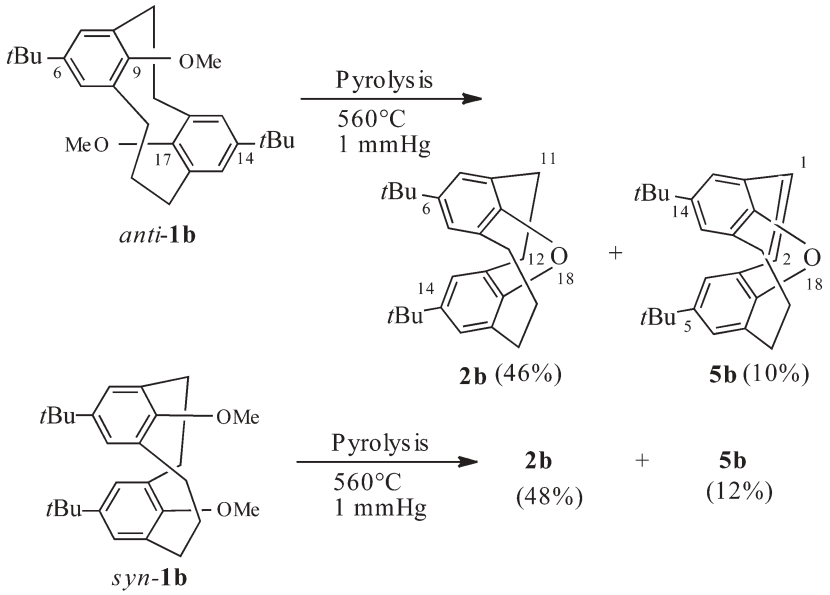
Scheme 2

Conclusions

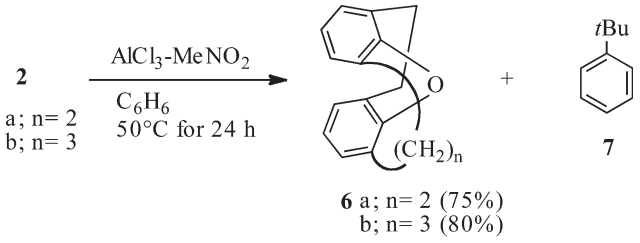
In conclusion, we have demonstrated that pyrolysis of *anti*-8,16-dimethoxy[2.2]MCP *anti*-**1** at 500 °C afforded 17-oxa [2.2.1](1,3,2)cyclophane **2a** in 35% yield arising from *anti–syn*-ring inversion and then intramolecular condensation reaction of *syn*-8,16-dimethoxy[2.2]MCP *syn*-**1a**. Similar results were also obtained in the pyrolysis of the higher *anti*- and *syn*-dimethoxy[3.2]MCPs *anti*-**1b** and *syn*-**1b** to afford the



Scheme 3



Scheme 4



Scheme 5

corresponding 18-oxa[3.2.1](1,3,2)cyclophane **2b** along with 18-oxa[2.3.1](1,3,2)cyclophane-1-ene **5b**. The presently developed novel intramolecular condensation reaction to afford oxa[*n*.2.1](1,3,2)cyclophanes will open up new mechanistic aspects for cyclophane chemistry. Further studies on chemical properties of oxa[*n*.2.1](1,3,2)cyclophanes **6a** and **6b** are in progress in our laboratory.

Experimental

All melting points are uncorrected. ^{1}H NMR spectra were recorded at 300 MHz on a Nippon Denshi JEOL FT-300 NMR spectrometer in deuteriochloroform with Me_4Si as an internal reference. IR spectra were measured as KBr pellets on a Nippon Denshi JIR-AQ2OM spectrometer. Mass spectra were obtained on a Nippon Denshi JMS-HX110A Ultrahigh Performance Mass Spectrometer at 75 eV using a direct-inlet system. Elemental analyses were performed by Yanaco MT-5. GLC analyses were performed by Shimadzu gas chromatograph, GC-14A; Silicone OV-1, 2 m; programmed temperature rise, 12 °C min^{-1}; carrier gas nitrogen, 25 mL min^{-1}.

Preparations of *anti*-5,13-di-*tert*-butyl-8,16-dimethoxy[2.2]MCP (*anti*-**1a**),[21] *syn*- and *anti*-6,14-di-*tert*-butyl-9,17-dimethoxy[3.2]MCP (**1b**), *syn*- and *anti*-7,15-di-*tert*-butyl-10,18-dimethoxy[4.2]MCP (**1c**)[22] have been described elsewhere.

*Pyrolysis of anti-5,13-di-tert-butyl-8,16-dimethoxy-[2.2]metacyclophane (anti-***1a***); general procedure*

Pyrolysis of *anti*-5,13-di-*tert*-butyl-8,16-dimethoxy[2.2]metacycloph ane *anti*-**1a** was carried out in an apparatus consisting of a horizontal tube (15 mm in diameter) passing through two adjacent tube furnaces, each of which was 20 cm long. The first furnace provided a temperature that would induce sublimation of the metacyclophane; the second was used at a higher temperature (500 °C) that would assure pyrolysis. A vacuum pump was connected to the exit from the second furnace. The (150 mg, 0.395 mmol) was pyrolysed at 500 °C under reduced pressure at 1 mmHg using the same procedure as reported previously.[25,26] The sublimed product was collected and chromatographed on silica gel with hexane as an eluent to give a colourless solid. Recrystallisation from hexane afforded 33 mg (25%) of 5,13-di-*tert*-butyl-17-oxa[2.2.1](1,3,2)cyclophane, **2a** as colourless prisms (methanol), m.p. 207–209 °C; δ_H ($CDCl_3$) 1.21 (18H, s, *t*Bu), 2.64–3.66 (8H, m, CH_2) and 6.85 (4 H, s, Ar*H*); MS *m/z*: 334 (M^+) (Found: C, 86.05; H, 8.89%. $C_{24}H_{30}O$ (334.5) requires C, 86.18; H, 9.04%).

The formation of 2,7-di-*tert*-butyl-4,5,9,10-tetrahydropyrene, **3**[27] was confirmed by GLC analyses.

Pyrolysis of 6,14-di-tert-butyl-9,17-dimethoxy[3.2]metacyclophane (**1b**); *general procedure*

The *anti*-6,14-di-*tert*-butyl-9,17-dimethoxy[3.2]metacyclophane *anti*-**1b** (150 mg, 0.381 mmol) was pyrolysed at 550 °C under reduced pressure at 1 mmHg using the same procedure as reported previously. The sublimed product was collected and chromatographed on silica gel with hexane as an eluent to give a colourless oil. The residue was chromatographed on a silica gel with hexane:benzene (1:1) as an eluent to give a colourless oil (80 mg, 60%) as a mixture of 6,14-di-*tert*-butyl-18-oxa[3.2.1](1,3,2)cyclophane **2b** and 5,14-di-*tert*-butyl-18-oxa[2.3.1](1,3,2)cyclophane-1-ene **5b** in a ratio of 70:30. However, the attempted isolation of the pure product failed.

Reduction of a mixture of **2b** *and with H_2 in the presence of Pd–C*: To a solution of a mixture of **2b** and **5b** (54 mg, 0.16 mmol) in ethyl acetate (30 mL) was added Pd-C (10%, 15 mg) and stirred for 12 h under the hydrogen atomosphere at room temperature. The reaction mixture was concentrated. The residue was chromatographed over silica gel (Wako C-300, 100 g) with hexane:benzene (1:1) as eluents to give 6,14-di-*tert*-butyl-18-oxa[3.2.1](1,3,2)cyclophane, **2b** (54 mg, 100%) as a colourless oil; ν_{max} (NaCl)/cm^{-1} 2922, 2899, 2851, 1468, 1460, 1433, 1424, 1265, 1207, 1184, 885 and 877; δ_H ($CDCl_3$) 1.24 (18H, s, *t*Bu), 1.30–1.40 (1H, m, CH_2), 2.29–2.40 (1H, m, CH_2), 2.66–2.79 (4H, m, CH_2), 3.24–3.33 (2H, m, CH_2), 3.53–3.61 (2H, m, CH_2), 6.91 (2H, d, *J* = 2.4, Ar*H*) and 6.97 (2H, d, *J* = 2.4, Ar*H*); MS *m/z*: 348 (M^+) (Found: C, 86.39; H, 9.52%. $C_{25}H_{32}O$ (348.53) requires C, 86.15; H, 9.25%).

*5,14-Di-*tert*-butyl-18-oxa[3.2.1](1,3,2)cyclophan-1-ene* (**5b**): δ_H ($CDCl_3$) 1.27 (18H, s, *t*Bu), 1.30–1.40 (1H, m, CH_2), 2.55–2.47 (1H, m, CH_2), 2.73–2.83 (2H, m, CH_2), 3.35–3.48 (2H, m, CH_2), 6.91 (2H, s, *CH*), 7.09 (2H, d, *J* = 2.4, Ar*H*) and 7.14 (2H, d, *J* = 2.4, Ar*H*).

Trans-tert-butylation of **2a**: To a solution of **2a** (30 mg, 0.09 mmol) in benzene (3 mL) was added a solution of aluminum chloride (200 mg, 1.50 mmol) and nitromethane (1 mL) at 0 °C. The mixture was stirred at 50 °C for 24 h, poured into ice-water, and extracted with CH_2Cl_2. The extracts were washed with water, then 10% sodium bicarbonate, dried over anhydrous sodium sulfate, and concentrated

in vacuo. Chromatography on silica gel (Wako, C-300; 100 g) eluting with hexane afforded a colourless solid. Recrystallisation from hexane afforded 15 mg (75%) of 18-oxa[2.2.1](1,3,2)cyclophane, **6a** as colourless prisms (hexane), m.p. 91–94 °C (lit.[24] m.p. 94–95 °C); δ_H ($CDCl_3$) 2.52–2.69 (4H, m, CH_2), 3.52–3.65 (4H, m, CH_2) and 6.79–6.99 (6H, s, Ar*H*); MS *m/z*: 222 (M^+) (Found: C, 86.39; H, 6.54%. $C_{16}H_{14}O$ (222.3) requires C, 86.45; H, 6.35%).

Trans-tert-butylation of **2b**: To a solution of **2b** (64 mg, 0.212 mmol) in benzene (6 mL) was added a solution of aluminum chloride (975 mg, 7.32 mmol) and nitromethane (1 mL) at 0 °C. The mixture was stirred at 50 °C for 24 h, poured into ice-water, and extracted with CH_2Cl_2. The extracts were washed with water, then with 10% sodium bicarbonate, dried over anhydrous sodium sulfate, and concentrated *in vacuo*. Chromatography on silica gel (Wako, C-300; 100 g) eluting with hexane afforded a colourless solid. Recrystallisation from hexane afforded 40 mg (80%) of 18-oxa[3.2.1](1,3,2)cyclophane, **6b** as colourless prisms (methanol), m.p. 96–98 °C; δ_H ($CDCl_3$) 1.30–1.40 (1 H, m, CH_2), 2.33–2.42 (1H, m, CH_2), 2.68–2.81 (4H, m, CH_2), 3.24–3.33 (2H, m, CH_2), 3.55–3.63 (2H, m, CH_2) and 6.90–6.99 (6H, m, Ar*H*); MS *m/z*: 236 (M^+) (Found: C, 86.61; H, 6.85%. $C_{17}H_{16}O$ (236.3) requires C, 86.41; H, 6.82%).

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