SHORT PAPER

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Medium-sized cyclophanes. Part 65.[1] *ipso*-bromination of di-*tert*-butyl-[*n*.2]metacyclophanes

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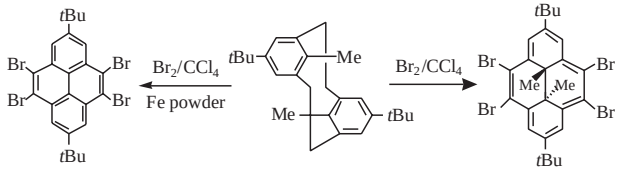
Bromination of 5,13-di-*tert*-butyl-8,16-dimethoxy[2.2]metacyclophane with excess bromine in the presence of iron powder afforded only the hexabromo compound arising from two-fold *ipso*-bromination at the *tert*-butyl groups.

Keywords: cyclophanes, *ipso*-bromination, through-space electronic interaction

Due to electronic interaction between the two benzene rings, the proximity of 8,16-positions, and considerable strain energy, [2.2]MCP (MCP= metacyclophane) is prone to undergo transannular reactions.[2–4] These have usually been rationalised as involving initial dehydrogenation to 4,5,9,10-tetrahydropyrene. Sato and Nishiyama[5] have reported that reaction of 8,16-unsubstituted [2.2]MCP with bromine in the presence of iron powder affords the corresponding tetrahydropyrene *via* the addition-elimination mechanism. Subsequently, we reported[6] that bromination of 5,13-di-*tert*-butyl-8,16-dimethyl[2.2]MCP in the presence or absence of iron powder as a catalyst afforded 2,7-di-*tert*-butyl-4,5,9,10-tetrabromo-*trans*-10b,10c-dimethyl-10b,10c-dihydropyrene and 2,7-di-*tert*-butyl-4,5,9,10-tetrabromopyrene, respectively (Scheme 1). The results suggested a useful route to *trans*-10b,10c-dialkyl-10b,10c-dihydropyrenes.

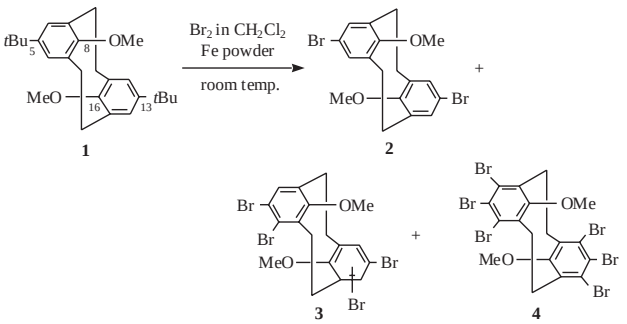


Scheme 1

Although *trans*-10b,10c-dihydropyrenes where the substituents at 10b and 10c positions are hydrogen or alkyl groups have been prepared by Boekelheide and his co-workers,[7] attempts at introducing other functional groups into the internal positions were unsuccessful. Thus, we undertook the present work in order to evaluate the possibility of the novel reaction mentioned above for the preparation of *trans*-10b,10c-dimethoxy-10b,10c-dihydropyrenes.

Results and discussion

Attempted bromination of 5,13-di-*tert*-butyl-8,16-dimethoxy[2.2]MCP (**1**)[8] with 4.1 equiv. of bromine or benzyl trimethylammonium tribromide in methylene dichloride at room temperature for 1 h led to the recovery of the starting compound in quantitative yield. None of the expected products, 2,7-di-*tert*-butyl-4,5,9,10-tetrabromo-*trans*-10b,10c-dimethoxy-10b,10c-dihydropyrene or 2,7-di-*tert*-butyl-4,5,9,10-tetrabromopyrene was detected. However, when bromination of **1** with 4.1 equiv. of bromine was carried out for 0.5 h in the presence of iron powder under the same



Scheme 2

Table 1 Bromination of 5,13-di-*tert*-butyl-8,16-dimethoxy [2.2]MCP **1** with bromine in the presence of Fe powder

Run	Bromine/**1** (mol/mol)	Time/h	Product Yield/%[a,b] **2**	**3**[c]	**4**
1	4.1	0.5	53 (30)	33	0
2	6.1	0.5	10	85 (60)	0
3	6.1	2	0	75	25
4	9.1	2	0	0	100 (90)

[a]Yields were determined by GLC. [b]Isolated yields are shown in parentheses. [c]A mixture of 4,5,12,13- (**3a**) and 4,5,13,14-tetrabromo-8,16-dimethoxy[2.2]metacyclophane (**3b**) was obtained in a ratio of 50:50.

reaction conditions the two-fold *ipso*-bromination product, 5,13-dibromo-8,16-dimethoxy[2.2]MCP (**2**) was obtained in 53% yield along with a mixture of tetrabrominated products **3a** and **3b** in a ratio of 50:50 (Table 1). Interestingly, the two *tert*-butyl groups are both *ipso*-brominated even in mild reaction conditions such as bromine in methylene dichloride at room temperature. This result is quite different from the result that only one *tert*-butyl group of di-*tert*-butyl[2.2]MCP **1** is *ipso*-nitrated even under the drastic reaction conditions.[9] Because of the much smaller deactivation of the second aromatic ring by the introduced bromo group than that of nitro group, the further second *ipso*-bromination occurred.

Furthermore, on bromination of **1** with 6.1 equiv. of bromine in the presence of iron powder in methylene dichloride at room temperature for 0.5 h, a mixture of tetrabrominated products **3a** and **3b** was obtained in the same ratio (50:50) in 85% yield along with 10% of 5,13-dibromo[2.2]MCP **2**. This result strongly suggests that in the first step the *ipso*-bromination at the *tert*-butyl groups must occur. In the second step, further bromination occurred to afford 4,5,13-tribromo-8,16-dimethoxy[2.2]MCP (**5**), from

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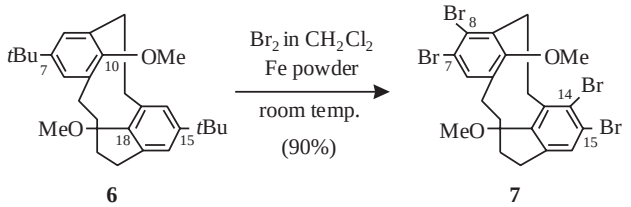
† This is a Short Paper, there is therefore no corresponding material in *J Chem. Research (M).*

which almost the same regioselectivity was then observed exclusively to complete bromination at the 12-position or the 14-position. The same effect was observed under the same reaction conditions by prolonging the reaction time from 0.5 h to 2 h to give a mixture of **3a** and **3b** in 75% yield, respectively, along with hexabrominated product **4**. The yield of hexabrominated product **4** increased as an increasing amount of bromine was used. It was also found that the exhaustive bromination of the di-*ipso*-brominated product, 5,13-dibromo-8,16-dimethoxy[2.2]MCP (**2**) with 9.1 equiv. of bromine in methylene dichloride in the presence of iron powder also afforded the hexabrominated product **4** in quantitative yield.

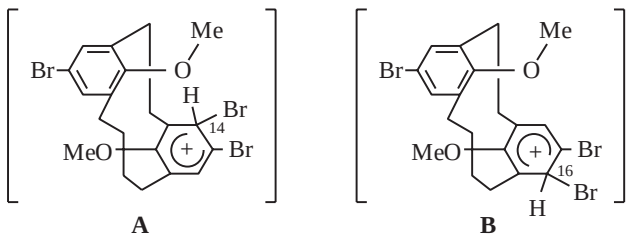
The structures of the products obtained in the present work were determined from their elemental analyses and spectral data. The mass spectral data for **3** and **4** strongly support the tetrabrominated and hexabrominated structures, respectively. The ^{1}H NMR spectrum of **3** in $CDCl_3$ shows two singlets at δ 3.02 and 3.03 for methoxy protons which are in a strongly shielded region opposite the meta-bridged benzene ring and two singlets at δ 7.33 and 7.37 for the aromatic C-6,14 protons (**3a**) or for the aromatic C-6,12 protons (**3b**) in a slightly deshielded region due to the bromo group, respectively. The integral ratio of methoxy protons and aromatic protons is found to be 3:1. These findings suggested that the tetrabrominated product **3** is a mixture of **3a** and **3b**. Unfortunately, several attempted separations of isomers **3a** and **3b** pure with column chromatography or recrystallisation failed. Thus, the absolute assignments of **3a** and **3b** are not yet known. On the other hand, no aromatic protons were observed from **4** and the internal methoxy proton was observed field at δ 2.97 as a singlet.

When *anti*-[4.2]MCP **6**[10] was treated with 6.1 equiv. of bromine for 0.5 h under the same reaction conditions as [2.2]MCPs, the same result was obtained to afford the tetrabromination product **7** via two-fold *ipso*-bromination in quantitative yield. Interestingly, only one isomer was obtained.



6 **7**

Scheme 3



A **B**

Fig. 1 Possible intermediate for third bromination.

The structure of **7** was assigned on the basis of elemental analyses and spectral data. The ^{1}H NMR spectrum of **7** in $CDCl_3$ shows two singlets at δ 3.27 for methoxy protons and at δ 7.15 for aromatic protons, respectively. It was also found that one of the ethano-bridge protons was observed in a deshielded region (δ 3.02–3.18) in comparison with that of **6** (δ 2.68–2.79) due to the bromine atoms at positions 8 and 14. As a result **7** has been assigned as 7,8,14,15-tetrabromo-10,18-dimethoxy[4.2]MCP.

Interesting regioselectivity was observed exclusively to afford the third bromination product at the 14-position, *ortho* to the ethano-bridge, but not at the 16-position. The pseudo-geminal directing effect of the methoxy group might be attributed to the basicity and geometric availability of its oxygen. The oxygen is probably the strongest base in the medium. In the rate- and product-controlling step, the oxygen accepts a proton in the pseudo-geminal σ-complex (**A**) much more easily than in the intermediate (**B**) for geometric reasons to form an oxonium intermediate, and thus producing a pseudo-geminal substituted product **7** (Fig. 1). This result is consistent with Cram's reports[11] that acetyl and nitro groups in the position of the [2.2]paracyclophane nucleus directed acetyl substitution to occur nearly exclusively in the 12-position to give the pseudo-geminal disubstituted hydrocarbon.

In conclusion, the present *ipso*-bromination of **1** is quite different from the results of the bromination of the corresponding internally methyl substituted di-*tert*-butyl [2.2]MCP to afford 2,7-di-*tert*-butyl-4,5,9,10-tetrabromo-*trans*-10b,10c-dimethyl-10b,10c-dihydropyrene and 2,7-di-*tert*-butyl-4,5,9,10-tetrabromopyrene. Similar *ipso*-bromination was also observed in [4.2]MCP systems. Further studies of the *ipso*-bromination of [*n*.2]MCPs and chemical properties of the polybrominated [*n*.2]MCPs are in progress.

Experiment

All m.p.s and b.p.s are uncorrected. NMR spectra were determined at 270 MHz with a Nippon Denshi JEOL FT-270 NMR spectrometer with $SiMe_4$ as an internal reference: *J*-values are given in Hz. IR spectra were measured for samples as KBr pellets or a liquid film on NaCl plates in a Nippon Denshi JIR-AQ2OM spectrophotometer. Mass spectra were obtained on a Nippon Denshi JMS-01SG-2 spectrometer at 75 eV using a direct-inlet system through GC. VPC analyses were performed by a Shimadzu gas chromatograph, GC-14A; Silicone OV-1, 2 m; programmed temperature rise, 12°C/min; carrier gas nitrogen, 25 cm^3/min.

Materials: Preparations of 5,13-di-*tert*-butyl-8,16-dimethoxy [2.2]metacyclophane (**1**)[8] and 7,15-di-*tert*-butyl-10,18-dimethoxy [4.2]metacyclophane (**6**)[10] have been previously described.

Bromination of 5,13-di-tert-butyl-8,16-dimethoxy[2.2] metacyclophane **(1)** *with bromine in methylene dichloride – typical procedure:* To a solution of **1** (100 mg, 0.263 mmol) and iron powder (20 mg, 0.36 mmol) in CH_2Cl_2 (35 cm^3) was added a solution bromine [400 mg (0.13 cm^3), 2.5 mmol] in CH_2Cl_2 (10 cm^3) at room temperature. After the reaction mixture was stirred for 2 h, it was poured into water (10 cm^3). The reaction mixture was extracted with CH_2Cl_2 (10 cm^3). The combined extracts were washed with water, dried with Na_2SO_4 and concentrated. The residue was washed and filtered with a small amount of hexane to give **4** in almost quantitative yield. Recrystallisation from benzene gave 4,5,6,12,13,14-hexabromo-8,16-dimethoxy[2.2]metacyclophane (**4**) as pale yellow prisms (176 mg, 90 %), m.p. 290–291°C; δ_H ($CDCl_3$) 2.6–2.74 (4 H, m), 2.97 (6 H, s) and 3.15–3.29 (4 H, m); *m*/*z* 736, 738, 740, 742. 744, 746 (M^+) (Found: C, 29.03; H, 1.86. $C_{18}H_{14}O_2Br_6$ requires C, 29.15; H, 1.9%).

Similarly, bromination of **1** with bromine was carried out in the same manner as described above under the various conditions of Table 1 where the yields are compiled.

5,13-Dibromo-8,16-dimethoxy[2.2]metacyclophane (**2**) was prepared as prisms, m.p. 211–214 °C (MeOH); IR (KBr) 2932, 1568, 1462, 1455, 1204, 1008, 855, 771 cm^{-1}; δ_H ($CDCl_3$) 2.46–2.63 (8 H, m), 2.92 (6 H, s) and 7.09 (4 H, s); *m*/*z* 424, 426, 428 (M^+) (Found: C, 50.62; H, 4.34. $C_{18}H_{18}O_2Br_2$ requires C, 50.73; H, 4.26%).

A mixture of 4,5,12,13- (**3a**) and 4,5,13,14-tetrabromo-8,16-methoxy[2.2]metacyclophane (**3b**) was prepared in a ratio of 50:50 as prisms, m.p. 183–186 °C (MeOH); δ_H ($CDCl_3$) (**3a**) 2.50–3.40 (8 H, m), 3.03 (6 H, s) and 7.37 (2 H, s); (**3b**) 2.50–3.40 (8 H, m), 3.02 (6 H, s) and 7.33 (2 H, s); *m*/*z* 580, 582, 584, 586, 588, 590 (M^+) (Found: C, 37.27; H, 2.64. $C_{18}H_{16}O_2Br_4$ requires C, 37.02; H, 2.76%).

Bromination of 7, 15-di-tert-butyl-10, 18-dimethoxy[4.2] metacyclophane **(6)** *with bromine in methylene dichloride:* To a solution of **6** (100 mg, 0.245 mmol) and iron powder (20 mg, 0.36 mmol) in CH_2Cl_2 (35 cm^3) was added a solution bromine [240 mg (0.075 cm^3), 1.50 mmol] of in CH_2Cl_2 (10 cm^3) at room temperature. After the reaction mixture was stirred for 2 h, it was poured into water (10 cm^3). The reaction mixture was extracted with CH_2Cl_2 (10 cm^3). The combined extracts were washed with water, dried with Na_2SO_4 and concentrated. The residue was washed and filtered with a small amount of hexane to give **7** in almost quantitative yield. Recrystallisation from benzene gave 7,8,14,15-tetrabromo-10,18-dimethoxy[4.2]metacyclophane (**7**) as prisms (135 mg, 90 %), m.p. 235–237°C; δ_H ($CDCl_3$) 1.15–1.30 (2 H, m), 1.32–1.45 (2 H, m), 1.97–2.10 (2 H, m), 2.64–2.75 (2 H, m), 3.02–3.18 (4 H, m), 3.27 (6 H, s) and 7.15 (2 H, s); *m*/*z* 608, 610, 612, 614, 616 (M^+) (Found: C, 39.47; H, 3.38. $C_{20}H_{20}O_2Br_4$ requires C, 39.25; H, 3.29%).

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References

1 Medium-sized Cyclophanes. part 64: K. Tanaka, H. Tsuchiya, Y. Kakinaga, T. Hironaka and T. Yamato, *J. Chem. Res. (S)*, 2003, 66.

2 (a) R.W. Griffin, Jr., *Chem. Rev.*, 1963, **63**, 45; (b) B.H. Smith, *Bridged Aromatic Compounds*, Academic Press, New York, N.Y., 1964; (c) *Cyclophanes* (P.M. Keehn and S.M. Rosenfield (eds)), Academic Press, New York, 1983, vol. 1, chap. 6, p. 428; (d) F. Vögtle, *Cyclophane-Chemistry*, Wiley, Chichester, 1993.

3 N.L. Allinger, B.J. Gordon, H.-E. Hu, and R.A. Ford, *J. Org. Chem.*, 1967, **32**, 2272.

4 (a) T. Sato, E. Yamada, Y. Okamura, T. Amada, and K. Hata, *Bull. Chem. Soc. Jap.*, 1965, **38**, 1049; (b) M. Fujimoto, T. Sato, and K. Hata, *Bull. Chem. Soc. Jap.*, 1967, **40**, 600; (c) T. Sato, M. Wakabayashi, Y. Okamura, T. Amada, and K. Hata, *Bull. Chem. Soc. Jap.*, 1967, **40**, 2363; (d) T. Sato, and K. Nishiyama, *J. Chem. Soc., Chem. Comm.*, **1973**, 220; (e) T. Sato, K. Nishiyama, S. Shimada, and K. Hata, *Bull. Chem. Soc. Jap.*, 1971, **44**, 2858; (f) S. Hayashi, and T. Sato, *Bull. Chem. Soc. Jap.*, 1972, **45**, 2360.

5 T. Sato and K. Nishiyama, *J. Org. Chem.*, 1972, **37**, 3254.

6 M. Tashiro, K. Koya and T. Yamato, *J. Am. Chem. Soc.*, 1982, **104**, 3707.

7 (a) V. Boekelheide and T. Miyasaka, *J. Am. Chem. Soc.*, 1967, **89**, 1709; (b) V. Boekelheide and E. Sturm, *J. Am. Chem. Soc.*, 1969, **91**, 902; (c) V. Boekelheide, P.H. Anderson, *J. Am. Chem. Soc.*, 1973, **38**, 3928.

8 M. Tashiro and T. Yamato, *J. Org. Chem.*, 1981, **46**, 1543.

9 (a) M. Tashiro, S. Mataka, Y. Takezaki, M. Takeshita, T. Arimura, A. Tsuge and T. Yamato, *J. Org. Chem.*, 1989, **54**, 451; (b) T. Yamato, H. Kamimura and T. Furukawa, *J. Org. Chem.*, 1997, **62**, 7560.

10 (a) T. Yamato, J. Matsumoto, K. Tokuhisa, M. Kajihara, K. Suehiro and M. Tashiro, *Chem. Ber.*, 1992, **125**, 2443; (*b*) T. Yamato, J. Matsumoto, M. Sato, K. Noda and M. Tashiro, *J. Chem. Soc., Perkin Trans 1*, **1995**, 1299; (c) T. Yamato, J. Matsumoto, M. Sato, K. Noda, T. Moriguchi and M. Tashiro, *Liebigs Ann.*, **1995**, 995.

11 (a) D.T. Hefelfinger and D.J. Cram, *J. Am. Chem. Soc.*, 1971, **93**, 4754; (b) D.J. Cram, R.B. Hornby, E.A. Truesdale, H.J. Reich, M.H. Delton and J.M. Cram, *Tetrahedron*, 1974, **30**, 1757.