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Behavior of [2.*n*]metacyclophane-fused cyclobutane rings in bromination

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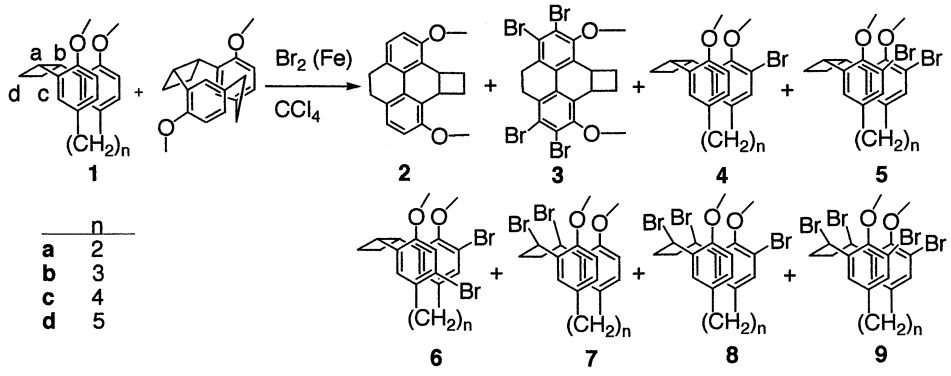
Abstract—Dimethoxy[2.2]metacyclophane mainly gave a tetrahydropyrene structure and the other [2.*n*]metacyclophane derivatives ($n=3$–5) gave aromatic bromides like pseudo-*ipso* and/or pseudo-*ortho* dibromides in the reaction with bromine. They also gave benzyl bromides by cyclobutane ring-opening.

Bromination is a most useful functionalization on *meta*- and *para*-cyclophanes.[1–3] *anti*-Metacyclophanes are known to give not only aromatic bromides but also transannular products.[3] Due to the difficulty of preparation, however, reports on bromination of their *syn*-conformer have been limited.[4] Accordingly, it is important to systematically examine the reactivity of metacyclophanes by using a stable *syn*-conformer. A dimethoxy[2.*n*]metacyclophane-fused cyclobutane ring ($n=3$–5) fits the purpose, because it takes exclusively *syn* conformation.[5–7] Also, interesting information can be obtained from the fact that dimethoxy[2.2]-metacyclophane can become any product through each conformer by the slow conformational change of two conformers as an equilibrium mixture in a ratio of *syn*/*anti*=4/3.[5–7] Furthermore, the cyclobutane ring fused on the strained metacyclophane system is also interesting if it retains some reactivity.[8] Therefore, we were prompted to investigate its reactivity in bromination. In this paper, we report the behavior of *syn*-[2.*n*]metacyclophanes-fused cyclobutane ring in bromination with or without an iron catalyst.

Dimethoxy[2.*n*]metacyclophanes **1** ($n=2$–5) were used in this bromination as shown in Scheme 1.[2,3] The reaction was performed with **1** (0.26 M) and bromine (0.15–5 equiv.) in CCl_4 for 2 h at 0°C. After extraction, the mixture was purified with column chromatography



Scheme 1.

Keywords: cyclophane; cyclobutane; bromination; ring-opening.

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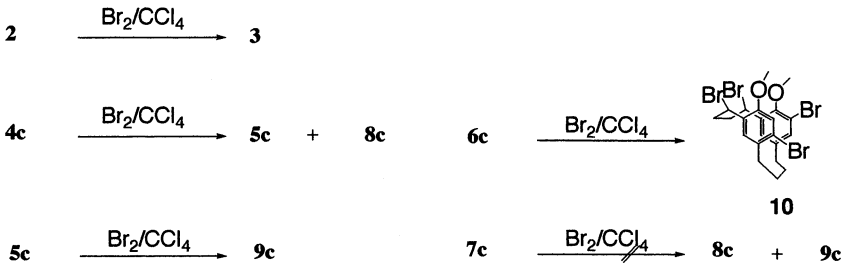
(SiO_2, benzene/ethyl acetate = 9/1). The results are summarized in Table 1. Generally speaking, **1a** mainly gave the transannular products, **2** and **3**, like a tetrahydropyrene structure (THP). By using 0.25 and 0.5 equiv. of bromine, **2** was exclusively produced in 44 and 58% yields, respectively (entries 1 and 2). By using excess bromine, tetrabromo-THP **3** was mainly produced in 85% yield and another tetrabromide **9a** to maintain the cyclophane structure was isolated in 7.2% yield (entry 3). These results suggest that the transannular reaction via *anti*-conformer to connect two benzene rings is faster than the bromination on the aromatic and cyclobutane rings. Furthermore, **3** is produced by the step-wise reaction. In fact, **2** produced **3** as the sole product in 60% yield by further bromination as shown in Scheme 2.

On the other hand, the cyclobutane ring of **1b–d** surprisingly reacted to mainly give bromides **7**, **8**, and **9**, which are the ring-opening products. MOPAC (PM3) calculations showed that the bond length of the cyclobutane ring at Ca-Cb (benzyl position) is longer than that at other positions and also gradually reduces when the oligomethylene chain length increased. These results suggest that the reactivity of the cyclobutane ring at the benzyl position greatly increased for radical bromination but not for cationic bromination. The reactivity of the cyclobutane ring is in the order of **1b**>**1c**>**1d** (entries 4, 9, and 13), judging from the yield of **7b–d**. By using 0.15–0.5 equiv. of bromine, monobromide **4** and dibromide **7** were mainly produced in 6–64% and 7–52% yields, respectively. By adding powdered Fe, bromination at the aromatic ring moderately increased (entries 6 and 11). Dibromides **5** and **6**, which reacted at the aromatic rings, were produced in the case of **1c** and **1d**. Note that the pseudo-*ipso* product **5** is always obtained preferentially to the pseudo-*ortho* product **6** (entries 9–11 and 13–15). By using excess bromine, tetrabromide **9** was isolated as the sole product in 75–97% yields (entries 7, 12, and 15). Further bromination of products **4–7** was examined as shown in Scheme 2. Monobromide **4c** gave dibromide **5c** and tribromide **8c** in 13 and 20% yields, respectively. Dibromide **5c** only gave tetrabromide **9c** in 33% yield. Also, dibromide **6c** only gave tetrabromide **10** in 20% yield, although it could not be isolated. On the other hand, dibromide **7c**, which gave a complex mixture suggesting the bromination at the oligomethylene chain, did not give **8–10** at all. Accordingly, dibromides **5** and **6** were intermediates for tetrabromides **9** and **10**, but dibromide **7** did not become an intermediate for tribromide **8** and tetrabromide **9**. Thus, the aromatic bromides proceeded to give further brominated products, while the benzyl bromides did not give isolable products at all.

The structures of products were determined by ^{1}H NMR and mass spectroscopy.[4,9] The molecular symmetry of **4–9** was also used in this determination because of the C_1 symmetry for **4**, **6**, and **8** or the C_s symmetry for **5**, **7**, and **9**. The essential spectroscopic aspects are

Table 1. Reaction conditions and product distribution of bromination in CCl_4

Entry	Compd	Conditions			Yield (%)								
		Br_2 (equiv.)	Fe (equiv.)	Time (h)	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	Total
1	**1a**	0.25	–	2	44	0	0	0	0	0	0	0	44
2	**1a**	0.5	–	2	58	0	0	0	0	0	0	0	58
3	**1a**	5.0	–	2	0	85	0	0	0	0	0	7.2	92
4	**1b**	0.25	–	2			21	0	0	36	0	0	57
5	**1b**	0.5	–	2			13	0	0	34	2.8	0	50
6	**1b**	0.5	0.05	2			0	0	0	52	14	0	66
7	**1b**	5.0	–	2			0	0	0	0	0	97	97
8	**1c**	0.15	–	2			24	0	0	27	0	0	51
9	**1c**	0.25	–	2			56	4.1	0	39	0	0	99
10	**1c**	0.5	–	2			6.3	6.8	0.7	40	0	0	54
11	**1c**	0.5	0.05	2			27	19	2.7	19	0	0	68
12	**1c**	5.0	–	2			0	0	0	0	0	97	97
13	**1d**	0.25	–	2			64	19	5	11	0	0	99
14	**1d**	0.5	–	2			51	36	6	7	0	0	100
15	**1d**	5.0	–	2			0	14	0	0	0	75	89



Scheme 2.

as follows: (1) Mass spectra showed the tetrabromide structures for **3** and **9**. (2) Tetrabromo-THP **3** showed no Ar protons. (3) THP **2** showed the two *ortho* coupling peaks (δ 6.70 and 6.99 $J=8.1$ Hz). (4) Monobromide **4** shows two doublets (δ 6.81–6.93 and 7.04–7.17 $J=1.8$–2.1 Hz) of Ar protons with *meta* coupling on the substituted Ar ring. (5) Dibromide **5** lost the *ortho* couplings of Ar protons of **4** and only showed the two *meta* coupling peaks (δ 6.89–6.99 and 7.19–7.20 $J=2.0$–2.1 Hz). (6) Dibromide **6** showed two peaks (δ 6.84–6.96 and 7.05–7.21 $J=1.9$–2.0 Hz) of one Ar ring with *meta* coupling and two singlets (δ 6.62–6.71 and 7.06–7.12) of the other Ar ring. (7) Dibromide **7** shows the same pattern of aromatic ring protons of **1** and new benzylic methine peaks at the carbons with Br at δ 5.50–5.65. (8) Tribromide **8** shows the benzylic methine peaks at δ 5.45 and the same aromatic proton pattern of **4**. (9) Tetrabromide **9** shows the benzylic methine peaks at the carbons with Br at δ 5.31–5.51 and the same aromatic proton pattern of **5**.

Application of the cyclophane bromides obtained was examined to be a starting material of biphenylophane synthesis by the Suzuki coupling reaction. The reaction was performed with dibromide **5d**, phenyl boric acid (2 equiv.), $Pd(PPh_3)_4$ (0.25 equiv.), Na_2CO_3 (2 equiv.) in dry DMF at 110–120°C for 24 h under a nitrogen atmosphere. After usual work-up, the corresponding biphenylophane was obtained in 34% yield. Thus, cyclophane bromides are powerful precursors of oligophenylene-type structures.

In conclusion, dimethoxy[2.2]metacyclophane mainly gave a tetrahydropyrene structure in the reaction with bromine. The other *syn*-[2.*n*]metacyclophane derivatives gave aromatic bromides like pseudo-*ipso* and/or pseudo-*ortho* dibromides in bromination. They also gave benzyl bromides by cyclobutane ring-opening. Further investigation is now in progress and will be reported elsewhere.

Acknowledgements

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References

1. *Cyclophanes*, *I and II*; Keehn, P. M.; Rosenfeld, S. M., Eds; Academic Press: New York, 1983.
2. (a) Cram, D. J.; Cram, J. M. *Acc. Chem. Res.* **1971**, *4*, 204; (b) Reich, H. J.; Cram, D. J. *J. Am. Chem. Soc.* **1969**, *91*, 3505.
3. (a) Yamato, T.; Matsumoto, J.; Tokuhisa, K.; Shigekuni, M.; Suehiro, K.; Tashiro, M. *J. Org. Chem.* **1992**, *57*, 395; (b) Yamato, T.; Ide, S.; Tokuhisa, K.; Tashiro, M. *J. Org. Chem.* **1992**, *57*, 271; (c) Wada, Y.; Sugata, K.; Tago, T.; Nishimura, J. *J. Org. Chem.* **1992**, *57*, 5955.
4. Okada, Y.; Kaneko, M.; Nishimura, J. *Tetrahedron Lett.* **2001**, *42*, 25.
5. (a) Okada, Y.; Mabuchi, S.; Kurahayashi, M.; Nishimura, J. *Chem. Lett.* **1991**, 1345; (b) Okada, Y.; Ishii, F.; Kasai, Y.; Nishimura, J. *Tetrahedron* **1994**, *42*, 12159.
6. (a) Okada, Y.; Sugiyama, K.; Kurahayashi, M.; Nishimura, J. *Tetrahedron Lett.* **1991**, *32*, 2367; (b) Okada, Y.; Ishii, F.; Akiyama, I.; Nishimura, J. *Chem. Lett.* **1992**, 1579.
7. Okada, Y.; Sugiyama, K.; Wada, Y.; Nishimura, J. *Tetrahedron Lett.* **1990**, *31*, 107.
8. Laali, K. K.; Borodkin, G. I.; Okazaki, T.; Hayashida, Y.; Nakamura, Y.; Nishimura, J. *J. Chem. Soc., Perkin Trans. 2* **2000**, 2347.
9. Compd.: MS (M^+): ^{1}H NMR in $CDCl_3$ δ (intensity, multiplicity, J in Hz). **2**: Calcd for $C_{20}H_{20}O_2$: 292; 2.08 (2H, m), 2.55 (2H, m), 2.84 (4H, m), 3.80 (6H, s), 3.91 (2H, m), 6.70 (2H, d, 8.1), 6.99 (2H, d, 8.1). **3**: Calcd for $C_{20}H_{16}O_2Br_4$: 604; 2.10 (2H, m), 2.60 (2H, m), 3.10 (4H, m), 3.76 (6H, s), 3.92 (2H, m) in CD_2Cl_2. **4b**: Calcd for $C_{21}H_{23}O_2Br$: 386: 1.50 (1H, m), 2.21 (1H, m), 2.33 (1H, m), 2.52 (2H, m), 2.63 (3H, m), 2.92 (2H, m), 3.54 (3H, s), 3.58 (3H, s), 4.50 (1H, m), 4.69 (1H, m), 6.32 (1H, d, 8.2), 6.65 (1H, dd, 2.0 and 8.2), 6.81 (1H, d, 1.8), 7.04 (1H, d, 1.8), 7.07 (1H, d, 2.0). **4c**: Calcd for $C_{22}H_{25}O_2Br$: 400: 1.37 (1H, m), 1.48 (1H, m), 1.92 (2H, m), 2.29 (3H, m), 2.56 (5H, m), 3.59 (3H, s), 3.62 (3H, s), 4.50 (1H, m), 4.63 (1H, m), 6.38 (1H, d, 8.2), 6.61 (1H, dd, 2.1 and 8.2), 6.81 (1H, d, 2.1), 7.09 (1H, d, 2.1), 7.14 (1H, d, 2.1). **4d**: Calcd for $C_{23}H_{27}O_2Br$: 414: 0.26 (1H, m), 0.94 (1H, m), 1.55 (2H, m), 1.79 (2H, m), 2.23 (1H, m), 2.44 (3H, m), 2.64 (2H, m), 2.74 (2H, m), 3.63 (3H, s), 3.64 (3H, s), 4.51 (1H, m), 4.63 (1H, m), 6.51 (1H, d, 8.2), 6.74 (1H, dd, 1.8 and 8.2), 6.93 (1H, d, 2.0), 7.17 (1H, d, 2.0), 7.18 (1H, d, 1.8). **5c**: Calcd for $C_{22}H_{24}O_2Br_2$: 478: 1.44 (2H, m), 1.96 (2H, m), 2.29 (2H, m), 2.42 (2H, m), 2.59 (4H, m), 3.65 (6H, s), 4.56 (2H, m), 6.89 (2H, d, 2.1), 7.19 (2H, d, 2.1). **5d**: Calcd for $C_{23}H_{26}O_2Br_2$: 492: 0.29 (1H, m), 0.98 (1H, m), 1.58 (2H, m), 1.82 (2H, m), 2.44 (4H, m), 2.57 (2H, m), 2.75 (2H, m), 3.68 (6H, s), 4.56 (2H, m), 6.99 (2H, d, 2.0), 7.20 (2H, d, 2.0). **6c**: Calcd for $C_{22}H_{24}O_2Br_2$: 478: 1.47 (2H, m), 1.92 (2H, m), 2.24 (1H, m), 2.31 (1H, m), 2.38 (1H, m), 2.55 (4H, m), 2.90 (1H, m), 3.58 (3H, s), 3.62 (3H, s), 4.50 (2H, m), 6.62 (1H, s), 6.84 (1H, d, 1.9), 7.05 (1H, d, 1.9), 7.06 (1H, s). **6d**: Calcd for $C_{23}H_{26}O_2Br_2$: 492: 0.26 (1H, m), 1.02 (1H, m), 1.62 (2H, m), 1.86 (2H, m), 2.18 (1H, m), 2.40 (2H, m), 2.64 (3H, m), 2.78 (1H, m), 2.88 (1H, m), 3.62 (3H, s), 3.64 (3H, s), 4.44 (1H, m), 4.54 (1H, m), 6.71 (1H, s), 6.96 (1H, d, 2.0), 7.12 (1H, s), 7.21 (1H, d, 2.0). **7b**: Calcd for $C_{21}H_{24}O_2Br_2$: 466: 1.65 (2H, m), 2.30–2.50 (4H, m), 2.65–3.05 (4H, m), 3.81 (6H, s), 5.65 (2H, m), 6.74 (2H, d, 8.0), 7.02 (2H, dd, 2.0 and 8.0), 7.34 (2H, d, 2.0). **7c**: Calcd for $C_{22}H_{26}O_2Br_2$: 480: 1.60 (4H, m), 2.22 (2H, m), 2.36 (2H, m), 2.66 (4H, m), 3.84 (6H, s), 5.61 (2H, m), 6.78 (2H, d, 8.2), 7.02 (2H, dd, 2.1 and 8.2), 7.32 (2H, d, 2.1). **7d**: Calcd for $C_{23}H_{28}O_2Br_2$: 492: 0.88 (1H, m), 1.40–2.00 (5H, m), 2.40–2.80 (8H, m), 3.83 (6H, s), 5.50 (2H, m), 6.78 (2H, d, 8.1), 7.01 (2H, dd, 2.0 & 8.1), 7.58 (2H, d, 2.0). **8b**: Calcd for $C_{21}H_{23}O_2Br_3$: 544: 1.65–2.10 (4H, m), 2.20 (2H, m), 2.40–2.80 (4H, m), 3.82 (3H, s), 3.85 (3H, s), 5.45 (2H, m), 6.25 (1H, d, 2.0), 6.72 (1H, d, 8.0), 7.01 (1H, d, 2.0 and 8.0), 7.31 (1H, d, 2.0), 7.42 (1H, d, 2.0). **9a**: Calcd for $C_{20}H_{20}O_2Br_4$: 608; 2.23 (2H, m), 2.44 (2H, m),

2.64 (2H, m), 2.74 (2H, m), 3.91 (6H, s), 5.51 (2H, dd, 3.0 and 13), 6.14 (2H, d, 2.0), 7.45 (2H, d, 2.0). **9b**: Calcd for $C_{21}H_{22}O_2Br_4$: 622: 1.69 (2H, m), 2.10 (2H, m), 2.17 (2H, m), 2.44 (2H, m), 2.78 (2H, m), 3.91 (6H, s), 5.31 (2H, dd, 2.9 and 13), 6.26 (2H, d, 2.0), 7.40 (2H, d, 2.0). **9c**: Calcd for $C_{22}H_{24}O_2Br_4$: 636: 1.33 (2H, m), 1.59 (2H, m), 1.76 (2H, m), 2.31 (4H, m), 2.85 (2H, m), 3.90 (6H, s), 5.39 (2H, dd, 3.0 and 13), 6.84 (2H, d, 2.0), 7.29 (2H, d, 2.0). **9d**: Calcd for $C_{23}H_{26}O_2Br_4$: 650: 0.96 (1H, m), 1.32 (3H, m), 1.68 (2H, m), 1.80–2.00 (2H, m), 2.30 (4H, m), 2.86 (2H, m), 3.90 (6H, s), 5.38 (2H, dd, 3.0 & 13), 6.85 (2H, d, 2.0), 7.26 (2H, d, 2.0).