Isolation, Characterization, and Demethylation by BBr_3 of Two Conformers of 8,15,23-Trimethoxy[2.2.1]metacyclophane[1]

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Two conformers, (**5A**) and (**5B**), of trimethoxy[2.2.1]metacyclophane have been separated and characterized by ^{1}H NMR spectroscopy, *X*-ray crystallography, and demethylation.

Conformational studies of macrocyclic cyclophanes are interesting, but studies on [*n.m.l*]metacyclophanes (MCP) are limited. Recently, it was reported[2] that 8,16,24-trimethyl[2.2.2]MCP (**1**) adopted a folded conformation and, in the ^{1}H NMR spectrum, showed one of its three methyl groups at δ 0.60—0.84 owing to the shielding effect of two benzene rings. Variable temperature NMR studies of [2.2.0]MCP[3] and [2.2.1]MCP[4] suggested that conformational changes occur in these systems, but the processes were discussed only in general terms of conformational changes. The isolation of a particular conformer of these [2.2.*n*]MCP systems has not hitherto been reported.

Here we report the first example of the isolation of two conformers of trimethoxy[2.2.1]MCP (**5**) and their characterization by NMR and *X*-ray analysis. The preparation of (**5**) is shown in Scheme 1. After high-dilution coupling of (**2**) and (**3**), followed by oxidation with *m*-chloroperbenzoic acid (MCPBA) to give (**4**), pyrolysis of (**4**) at 450 °C (0.6 mmHg) afforded (**5**) in 60% yield. The ^{1}H NMR spectrum of (**5**) showed five kinds of methoxy protons, each as a singlet.

By careful column chromatography (silica gel, Wako C-300, benzene as eluant), two conformers, (**5A**) (R_f 0.57) and (**5B**) (R_f 0.49) were separated in 17 and 21% yield, respectively.†

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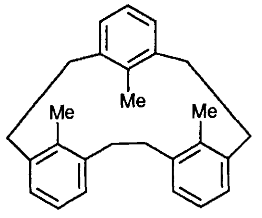
† Compounds (**5**), (**6**), and (**7**) gave satisfactory elemental analyses: (**5A**): colourless needles (m.p. 169—172 °C); ^{1}H NMR ($CDCl_3$) δ 1.21 (21H, s), 1.40 (9H, s), 2.28—3.00 (10H, m), 3.44 (6H, s), 6.90 (2H, d, *J* 3 Hz), 7.00 (2H, d, *J* 3 Hz), and 7.16 (2H, s).

(**5B**): colourless prisms (m.p. 256—258 °C); ^{1}H NMR ($CDCl_3$) δ 1.12 (9H, s), 1.24 (9H, s), 1.36 (9H, s), 2.20—3.00 (10H, m), 2.64 (3H, s), 3.17 (3H, s), 3.24 (3H, s), 6.67 (1H, d, *J* 3 Hz), 6.79 (2H, d, *J* 3 Hz), 6.90 (1H, d, *J* 3 Hz), and 7.09 (2H, s).

(**6**): colourless needles (m.p. 223—227 °C); IR (KBr) ν 3850 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.21 (18H, s), 1.42 (12H, s), 2.61—4.72 (10H, m), 5.42 (2H, s), 6.93 (2H, d, *J* 2.6 Hz), 6.99 (2H, d, *J* 2.6 Hz), and 7.41 (2H, s).

(**7**): colourless powder (m.p. 150—153 °C); IR (KBr) ν 3870 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.16 (3H, s), 1.25 (15H, s), 1.37 (9H, s), 2.48—4.20 (10H, m), 2.82 (1H, s), 3.80 (1/3H, s), 4.65 (1/3H, s), 5.45 (4/3H, s), 6.65—7.10 (4H, m), and 7.25 (2H, s).



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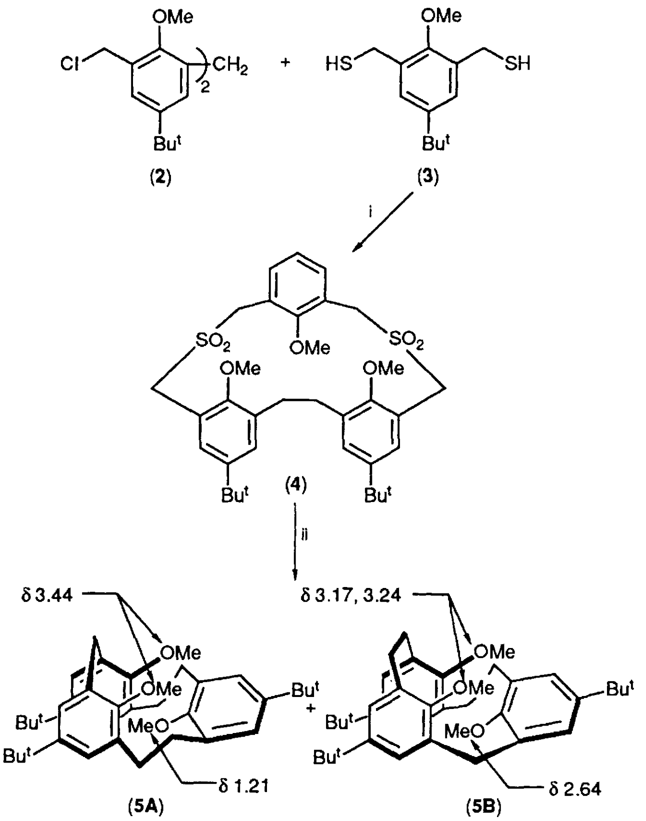

Scheme 1. *Reagents and conditions*: i, CsOH, EtOH, then MCPBA; ii, 450 °C, 0.6 mmHg.

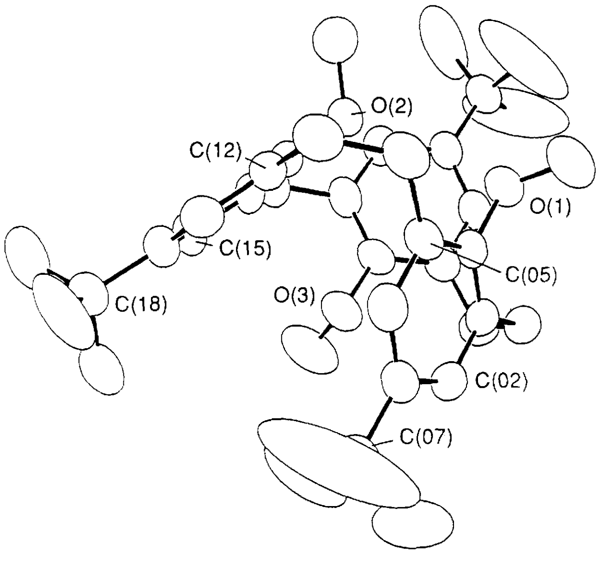

Figure 1. Perspective view of (**5B**). Selected interatomic distances (Å): C(02)—C(15), 5.714; C(05)-C(12), 3.005; C(07)-C(18), 5.665.

They are thermally stable and not interconvertible (at 180 °C in Me$_2$SO solution and at 400 °C in the solid state).

The ^{1}H NMR spectrum of conformer (**5A**) showed the methoxy protons at δ 1.21 and 3.44 (relative intensity 1 : 2), indicating a symmetrical structure. On the other hand, the other conformer (**5B**) showed these signals at δ 2.64, 3.17, and 3.24 (relative intensity 1 : 1 : 1), which corresponds to an asymmetric structure. From these data, it is deduced that (**5A**) adopts a symmetric conformation (C_s symmetry) and (**5B**) an asymmetric conformation (C_1 symmetry), and in each conformer one methoxy group was more affected by the benzene rings than the other two. Thus, (**5A**) and (**5B**) are concluded to have a folded conformation in which one methoxy group is folded into the π-cavity formed by two benzene rings (Scheme 1). One methoxy group of (**5A**) (δ 1.21) experiences a greater upfield shift than the corresponding group of (**5B**) (δ 2.64), suggesting that the methoxy group of (**5A**) is inserted more deeply in the π-cavity. The methylene ^{1}H NMR signals of (**5A**) and (**5B**) were observed as a broadened multiplet. The crystal structure of (**5B**) is shown in Figure 1.‡ It is clear that one methoxy group is present between two aromatic rings that are forced towards each other as predicted from the ^{1}H NMR data.

Conformers (**5A**) and (**5B**) behaved differently in demethylation with BBr$_3$ (Scheme 2), on treatment with a large excess of BBr$_3$ at room temperature for 24 h. Unexpectedly (**5A**) gave the dihydroxymonomethoxy derivative (**6**) (59%) and an inseparable complex mixture. The two hydroxy groups of (**6**) gave a ^{1}H NMR signal at δ 5.42, and the shielded methoxy group a signal at δ 1.42. Compound (**6**) thus adopts a symmetrically folded conformation like (**5A**). On the other hand, (**5B**) gave the expected trihydroxy derivative (**7**) (52%). Compound (**7**) was deduced to exist as a 2 : 1 mixture of two conformers (**7A**) and (**7B**) as its ^{1}H NMR spectrum showed four hydroxy signals (δ 2.82, 3.80, 4.65, and 5.45; relative intensity 3 : 1 : 1 : 4), each as a singlet. These conformers have not yet been separated.

Finally, it should be noted that, although the methoxy group

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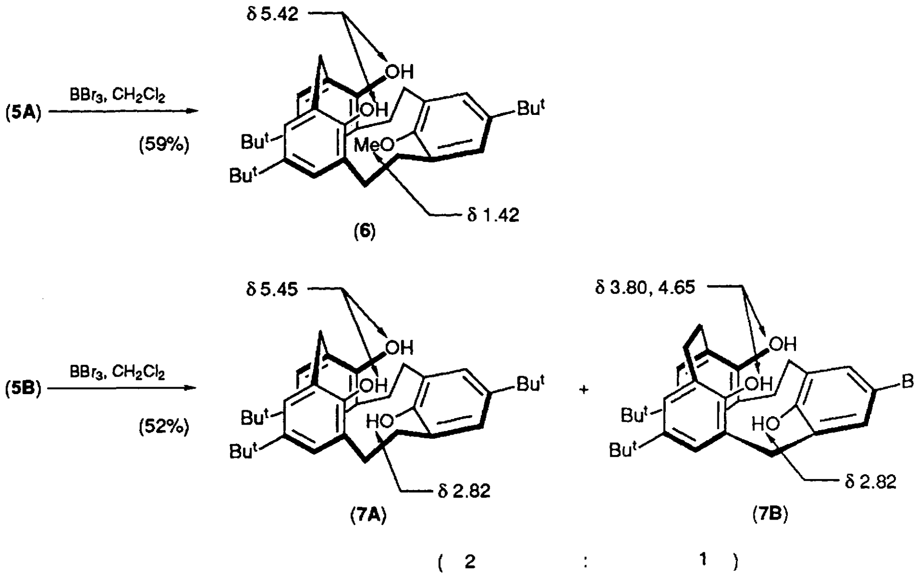
‡ *Crystal data* for (**5B**): $C_{38}H_{52}O_3$, M = 556.84, monoclinic, space group $C2/c$, a = 33.461(9), b = 9.167(3), c = 32.099(8) Å, β = 133.94(4)°, U = 7089.8 Å^3, Z = 8, D_c = 1.043 g cm^{-3}, λ(Mo-K_α) = 0.71073 Å, μ(Mo-K_α) = 0.60 cm^{-1}. Data were collected on an Enraf-Nonius CAD-4 diffractometer. 9547 independent reflections were measured in the range $2 < 2\theta < 44°$ (θ–2θ scan type, graphite-monochromatized Mo-K_α radiation). The crystal (0.3 × 0.5 × 0.8 mm) did not show any significant decay during the data collection. 2995 observed reflections with $I_o > 3\sigma(I_o)$ were used for the structure analysis. Position parameters were determined by direct methods using MULTAN-82, and were refined by full-matrix least-squares calculations. The thermal parameters were anisotropic for all non-H atoms and isotropic (fixed at 4.0 Å^2) for H atoms. Final R = 0.074, R_w = 0.111 $\{w = 4F_o^2/[\sigma(F_o)^2]^2\}$. Atomic co-ordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. See Notice to Authors, Issue No. 1.



Scheme 2

of (**5B**) in the π-cavity was attacked by BBr_3, the corresponding methoxy group of (**5A**) is inert to attack by BBr_3. This result is consistent with the difference of chemical shifts between these methoxy groups.

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References

1 For Part 26 of the series Metacyclophanes and Related Compounds, see: M. Tashiro, A. Tsuge, T. Makishima, T. Sawada, S. Horie, T. Arimura, S. Mataka, and T. Yamato, *J. Org. Chem.*, 1990, **55**, 2404.
2 M. Tashiro, T. Watanabe, A. Tsuge, T. Sawada, and S. Mataka, *J. Org. Chem.*, 1989, **54**, 2632.
3 F. Voegtle, *Liebigs Ann. Chem.*, 1969, **728**, 17.
4 T. Sato, M. Wakabayashi, K. Hata, and M. Kainosho, *Tetrahedron*, 1971, **27**, 2737.

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