Medium-sized cyclophanes. Part 72. Synthesis and structures of 9-methoxy(1,4)naphthaleno[3.3]metacyclophane-2,11-diones

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Syn- and *anti*-9-Methoxy(1,4)naphthaleno[3.3]MCP-2,11-diones (**4**) are obtained by the coupling reaction of 2,6-bis[2-cyano-2-(toluenesulfony)ethyl]anisoles (**2**) and 1,4-bis(bromomethyl)naphthalene (**3**) in dimethylformamide (DMF) with an excess of sodium hydride.

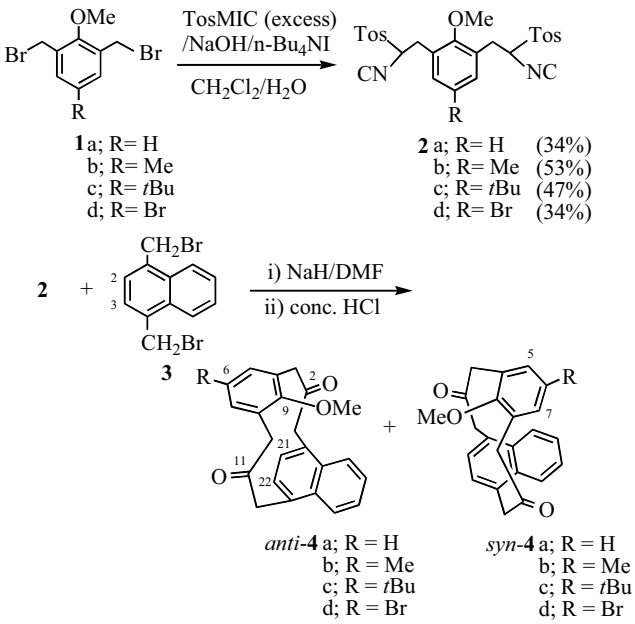
Keywords: metacyclophanes, cyclisation, conformation, through-space interaction

[3.3]MPCP (MPCP = metaparacyclophane) was first prepared by Shinmyozu and co-workers[2] using (*p*-tolylsulfonyl)methyl isocyanide (TosMIC) as the cyclisation reagent, followed by Wolff–Kishner reduction. The meta-bridged benzene ring of [3.3]MPCP has been shown to undergo conformational flipping[2,3] with a significantly lower energy barrier than that in [2.2]MPCP (*ca* 80 kJ mol^{-1}).[4] Recently, we have reported the synthesis of 9-substituted [3.3]MPCP-2,11-diones and conversion to the corresponding [3.3]MPCPs by Wolff–Kishner reduction.[5] The different orientation for the acetylation was observed depending on the substituent at C (9) position.

On the other hand, we reported the preparation of 2,11-dithia(1,4)naphthaleno[3.3] MCPs (MCP = metacyclophane) and an internal substituent such as Me or OMe group is sufficient to allow the isolation of a discrete *syn* or *anti* isomer.[6] Thus, there is substantial interest that employing a naphthalene ring instead of a benzene ring of the para-bridged ring will provide good information about the π–π-interaction between the two stacking aromatic rings. Furthermore, the conformations of 9-substituted [3.3]MCPs having a naphthalene skeleton are so far not known in spite of the formation of two conformers, *i.e.* *syn*- and *anti*-conformers, being possible like 2,11-dithia(1,4)-naphthaleno[3.3]MCPs. In this paper, we report on the synthesis and the structures of *syn*- and *anti*-9-methoxy(1,4) naphthaleno[3.3]MCP-2,11-diones (**4**).

Results and discussion

Vögtle reported[7] the preparation of [3$_n$]MCP-triones using (*p*-tolylsulfonyl)methyl isocyanide (TosMIC)[8] as the cyclisation reagent, which was applied in a new cyclisation procedure without phase-transfer conditions.[9] This strategy can be employed for the preparation of (1,4)naphthaleno[3.3]MCP-2,11-diones containing two aryl rings. In fact, we have selected the stepwise cyclisation of TosMIC adduct **2** with 1,4-bis(bromomethyl)naphthalene (**3**) to prepare the desired cyclic diketones **4** as shown in Scheme 1. The starting compound, 1,4-bis(bromomethyl)naphthalene (**3**) was prepared from 1,4-dimethylnaphthalene according to the reported procedure.[10] The preparations of the 2,6-bis(bromomethyl)anisoles (**1a**–**d**)



Scheme 1

have already been described in earlier paper.[11] TosMIC adducts **2a**, **2b** and **2d** were obtained in 34–53% yield by the reaction of **1a**, **1b** and **1d** with TosMIC as a mixture of two isomers, *i.e. meso* and *dl*. However, the attempted separation of these isomers of **2** pure failed. The preparation of the TosMIC adduct **2c** of 2,6-bis(bromomethyl)-4-*tert*-butylanisole (**1c**) has already been described in earlier paper.[12] *syn*-9-Methoxy(1,4)naphthaleno[3.3]MCP-2,11-dione (**4a**) was obtained in 12% yield by the coupling reaction of 2,6-bis[2-cyano-2-(toluenesulfony)ethyl]anisole (**2a**) and **3** in dimethylformamide (DMF) with an excess of sodium hydride according to the reported procedure.[12] Similarly, in the case of 2,6-bis[2-cyano-2-(toluenesulfony)ethyl]-4-methylanisole (**2b**) and 4-bromoanisole (**2d**) *syn*-isomers (**4b**) and (**4d**) were predominantly obtained in 36 and 21%

Table 1 *Anti*-to-*syn* Ratios in TosMIC cyclisation of **2** with **3**

Substrate			Product yield/%[a]	Isomer distribution/%[b]	
	R			*anti*	*syn*
2a	H	**4a**	(12)	0	100
2b	Me	**4b**	(36)	0	100
2c	*t*Bu	**4c**	(45)	22 (10)	78 (35)
2d	Br	**4d**	(21)	0	100

[a]Isolated yields. [b]*anti*-to-*syn* Ratios determined by ^{1}H NMR spectroscopy at 20°C.

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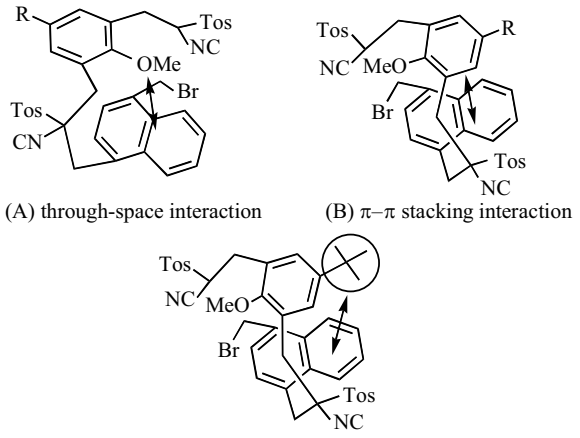
yields, respectively. No *anti*-product was obtained under the conditions used. In contrast, similar reaction of 2,6-bis [2-cyano-2-(toluenesulfony)ethyl]-4-*tert*-butylanisole (**2c**) with **3** afforded a mixture of *syn*-(*syn*-**4c**) and *anti*-9-metho xy(1,4)naphthaleno[3.3]MCP-2,11-dione (*anti*-**4c**) in a ratio of 78: 22 in 45% yield. Thus, depending on the substituents at position 4 on the 2,6-bis[2-cyano-2-(toluenesulfony)ethyl] anisoles **2**, different yields of *anti*-**4** and *syn*-**4** were achieved.

The structures of **4** have been elucidated by elemental analyses and spectral data. For instance, the mass spectral data for *anti*-**4c** (M^+ = 400) strongly supports cyclic dimeric structure. The IR spectrum of *anti*-**4c** shows the absorption of the carbonyl stretching vibration around 1688 cm^{-1}. The ^1H NMR spectrum (in $CDCl_3$) of *anti*-**4c** exhibits two sets of doublets at δ 3.16, 3.81 ppm (J = 11.0 Hz) and 3.52, 3.81 ppm (J = 14.0 Hz) for the ArCH_2COCH_2Ar methylene protons and a singlet for the methoxy protons at an upfield shift δ 2.77 ppm from 4-*tert*-butyl-2,6-dimethylanisole (δ 3.83 ppm) due to the ring current of the opposing aromatic ring.[4] The same upfield shift of the inner naphthalene protons (H_{21}, H_{22}) was observed at δ_{MCP}[21,22] 6.36 ppm in *anti*-**4c** [Δδ = 0.81 ppm from 1,4-dimethylnaphthalene, δ_{BMX}[2,3] 7.17 ppm] due to the ring current effect by the opposing benzene ring. These observations strongly suggest that compound *anti*-**4c** adopts the *anti*-conformation.

In contrast, the methoxy protons of *syn*-**4c** are observed at δ 3.33 ppm. Further, the benzene protons (H_5, H_7) can clearly be seen to be shielded at δ_{MCP}[5,7] 6.45 ppm by the adjacent naphthalene ring, a common consequence of face-to-face aryl rings.[4] Also the *tert*-butyl proton was observed at higher field, δ 0.86 ppm compared to that of the *anti*-**4c** at δ 1.29 ppm due to the strong shielding effect of the naphthalene ring. These observations strongly suggest that compound *syn*-**4c** adopts *syn*-conformation. Similarly, the assignments of structures for other *syn* conformers *syn*-**4a**, *syn*-**4b** and *syn*-**4d** were readily apparent from their ^1H NMR spectra.

The 9-methoxy analogues are exclusively formed as the *syn*-conformers except the *tert*-butyl group. These findings suggest that the through-space interaction between the non-bonding electron pairs of the oxygen atom of the methoxy group and the opposite naphthalene π-electrons of the *anti*-conformer may disfavour the formation of the latter (Fig. 1A). The exclusive formation of *syn*-conformer might be also governed by π–π-stacking charge-transfer-type interactions[13] between the substituted benzene ring and naphtahalene ring as shown in Fig. 1B. In the case of the 6-*tert*-butyl analogue the formation of *anti*-[3.3]MCP-2,11-dione *anti*-**4c** was observed



(A) through-space interaction (B) π–π stacking interaction

(C) steric interaction

Fig. 1 Reaction intermediate for the cyclisation to form 9-methoxy(1,4)naphthaleno[3.3]MCP-2, 11-diones (**4**).

(*syn*-to-*anti* ratio; 78: 22). This result might be attributed to the bulkiness of the *tert*-butyl group which would inhibit the formation of *syn*-**4c** (Fig. 1C).

In conclusion, the cyclisation reaction of 2,6-bis[2-cyano-2-(toluenesulfony)ethyl]anisoles (**2**) and 1,4-bis(bromomethyl) naphthalene **(3)** in DMF with an excess of sodium hydride exclusively afforded *syn*-(1,4)naphthaleno[3.3]MCP-2,11-diones **4**. The effect of the bulkiness of the 4-substituents of **2** such as *tert*-butyl group on the ratio of *syn*-to-*anti* conformers was observed. Further studies on the chemical properties of the two conformers *syn*- and *anti*-**4** are now in progress.

Experiment

All melting points are uncorrected. ^1H 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.

Materials

2,6-Bis(bromomethyl)anisoles (**1a**–**1d**) and 2,6-bis[2-cyano-2-(toluenesulfony)ethyl]-4-*tert*-butylanisole (**2c**) were prepared according to the literature.[11,12]

Preparation of the TosMIC adduct **2**. *Typical procedure*

To a mixture of 20% aqueous NaOH (25 cm^3) and CH_2Cl_2 (30 cm^3) was added *n*-Bu_4NI (440 mg, 1.2 mmol) followed by a solution of TosMIC (4.45 g, 25 mmol) in CH_2Cl_2 (30 cm^3). After the reaction mixture was stirred at room temperature for 30 min, a solution of 2,6-bis(bromomethyl)anisole (**1a**) (3.0 g, 8 mmol) in CH_2Cl_2 (30 cm^3) was added. The reaction mixture was stirred at room temperature for 2 h, quenched with water (50 cm^3), and was extracted with CH_2Cl_2 (50 cm^3 × 3). It was washed with water (50 cm^3), dried with Na_2SO_4, and concentrated *in vacuo* to leave a residue. To this residue methanol (50 cm^3) was added and left overnight in the refrigerator to give 2,6-bis[2-cyano-2-(toluenesulfony)ethyl]anisole (**2a**) (1.64 g, 34%) as pale brown prisms; m.p. 104–106°C; ν_{max}(KBr)/cm^{-1}: 2136 (CN); δ_H($CDCl_3$): 2.49 (6 H, s, *Me*), 3.05 (2 H, m, CH_2), 3.67 (2 H, dd, J = 2.9, 2.8, CH_2), 3.79 (3 H, s, O*Me*), 4.75 (2 H, dd, J = 3.1, 3.1, *CH*), 7.09 (1 H, d, J = 7.0, Ar–*H*), 7.19 (1 H, d, J = 7.0, Ar–*H*), 7.24 (1 H, t, J = 6.2, Ar–*H*), 7.44 (4 H, d, J = 7.9, Ar–*H*), 7.90 (4 H, d, J = 8.3, Ar–*H*); *m*/*z*: 522 (M^+). Anal. calcd. for $C_{27}H_{26}N_2O_5S_2$ (522.6): 62.05; H, 5.01; N, 5.36. Found C, 62.08; H, 5.02; N, 5.21.

Compounds **2b** and **2d** were similarly prepared in 53 and 34% yields as shown in Scheme 1.

2,6-Bis[2-cyano-2-(toluenesulfony)ethyl]-4-methylanisole (**2b**): obtained as pale brown powder (methanol), m.p. 151–153°C (dec.); ν_{max}(KBr)/cm^{-1}: 2133 (CN); δ_H($CDCl_3$): 2.27 (3 H, s, *Me*), 2.49 (6 H, s, *Me*), 2.89 (2 H, dd, J = 11.7, 13.7, CH_2), 3.61 (2 H, dd, J = 2.9, 3.1, CH_2), 3.79 (3 H, s, O*Me*), 4.75, 4.83 (2 H, dd, J = 3.1, 3.1, *CH*), 7.00 (2 H, s, Ar–*H*), 7.43 (4 H, d, J = 7.9, Ar–*H*), 7.90 (4 H, d, J = 8.4, Ar–*H*); *m*/*z*: 536 (M^+). Anal. calcd. for $C_{28}H_{28}O_5N_2S_2$ (536.67): C, 62.67; H, 5.26; N, 5.22. Found: C, 62.48; H, 5.24; N, 5.38.

2,6-Bis[2-cyano-2-(toluenesulfony)ethyl]-4-bromoanisole (**2d**) was obtained as pale brown prisms; m.p. 104–106°C; ν_{max}(KBr)/cm^{-1}: 2132 (CN); δ_H($CDCl_3$): 2.49, 2.50 (6 H, each s, *Me*), 2.89, 3.04 (2 H, each dd, J = 11.2, 13.9, CH_2), 3.66, 3.60, 3.67 (2 H, each dd, J = 2.9, 13.9, CH_2), 3.79, 3.83 (3 H, each s, O*Me*), 4.73, 4.83 (2 H, each dd, J = 2.9, 11.2, *CH*), 7.26, 7.34 (each s, 2 H, Ar–*H*), 7.44, 7.46 (4 H, d, J = 8.3, Ar–*H*), 7.87, 7.93 (4 H, d, J = 8.3, Ar–*H*); *m*/*z*: 600, 602 (M^+). Anal. calcd. for $C_{27}H_{25}BrN_2O_5S_2$ (601.5): C, 53.91; H, 4.19; N, 4.66. Found: C, 53.69; H, 4.20; N, 4.66.

Cyclisation of TosMIC adduct **2c** *and 1,4-bis(bromomethyl)na phthalene* **(3):** To a suspension of NaH (2.1 g, 51 mmol) in DMF (150 cm^3) a solution of **2c** (4.0 g, 6.9 mmol) and 1,4-bis(bromomethyl)naphthalene (**3**) (2.23 g, 6.9 mmol) in DMF (35 cm^3) was added dropwise over a period of 6 h. After the suspension was stirred for an additional 5 h at room temperature, it was quenched with ice water (300 cm^3). The reaction mixture was extracted with CH_2Cl_2 (100 cm^3 × 3), washed with water (200 cm^3), dried with Na_2SO_4, and concentrated *in vacuo* to 30 cm^3. Concentrated HCl (15 cm^3) was added, and the solution was stirred for 15 min. The organic layer was again extracted with CH_2Cl_2 (100 cm^3 × 3), washed with water

(100 $cm^3 \times 2$), dried with Na_2SO_4, and concentrated and condensed under reduced pressure. The residue was chromatographed on silica gel using benzene and benzene-$CHCl_3$ (1: 1) as eluents to give crude *syn*-**4c** (1.02 g, 35%) and *anti*-**4c** (290 mg, 10%) as a colourless solid, respectively. Recrystallisation from hexane afforded *syn*-**4c** (830 mg, 30%) and *anti*-**4c** (230 mg, 8%) as a colourless prisms.

Syn-6-*tert*-*butyl*-9-*methoxy(1,4)naphthaleno[3.3]metacyclophane-2,11-dione* (*syn*-**4c**): Obtained as *prisms* (hexane); m.p. 198–201°C; ν_{max}(KBr)/cm^{-1}: 1699 (C=O); δ_H($CDCl_3$): 0.86 (9 H, s, *t*Bu), 3.33 (3 H, s, O*Me*), 3.12 (2 H, d, *J* = 11.0, CH_2), 3.78 (2 H, d, *J* = 14.0, CH_2), 4.04 (2 H, d, *J* = 11.0, CH_2), 4.30 (2 H, d, *J* = 14.0, CH_2), 6.45 (2 H, s, Ar–$H_{5,7}$), 7.20 (2 H, dd, *J* = 6.5, 3.4, Ar–$H_{16,17}$), 7.43 (2 H, s, Ar–$H_{21,22}$), 7.58 (2 H, dd, *J* = 6.5, 3.4, Ar–$H_{15,18}$); *m*/*z*: 400 (M^+). Anal. calcd. for $C_{27}H_{28}O_2$ (400.52): C, 80.97; H, 7.05. Found: C, 81.26; H, 7.16.

Anti-6-*tert*-*butyl*-9-*methoxy(1,4)naphthaleno[3.3]metacyclophane-2,11-dione* (*anti*-**4c**): Obtained as *prisms* (hexane); m.p. 175–178°C; ν_{max}(KBr)/cm^{-1}: 1688 (C=O); δ_H($CDCl_3$): 1.29 (9 H, s, *t*Bu), 2.77 (3 H, s, O*Me*), 3.16 (2 H, d, *J* = 11.0, CH_2), 3.52 (2 H, d, *J* = 14.0, CH_2), 3.81 (2 H, d, *J* = 11.0, CH_2), 4.45 (2 H, d, *J* = 14.0, CH_2), 6.36 (2 H, s, Ar–$H_{21,22}$), 6.88 (2 H, s, Ar–$H_{5,7}$), 7.57 (2 H, dd, *J* = 6.5, 3.4, Ar–$H_{16,17}$), 8.07 (2 H, dd, *J* = 6.5, 3.4, Ar–$H_{15,18}$); *m*/*z*: 400 (M^+). Anal. calcd. for $C_{27}H_{28}O_2$ (400.52): C, 80.97; H, 7.05. Found: C, 80.68; H, 6.81.

Compounds *syn*-**4a**, *syn*-**4b** and *syn*-**4d** were similarly prepared in 12, 36 and 21% yields as shown in Table 1.

Syn-9-*methoxy(1,4)naphthaleno[3.3]metacyclophane-2,11-dione* (*syn*-**4a**): Obtained as *prisms* (hexane); m.p. 250–253°C; ν_{max}(KBr)/cm^{-1}: 1694 (C=O); δ_H($CDCl_3$): 3.14 (2 H, d, *J* = 11.6, CH_2), 3.34 (3 H, s, CH_2), 3.77 (2 H, d, *J* = 14.5, CH_2), 4.06 (2 H, d, *J* = 11.6, CH_2), 4.30 (2 H, d, *J* = 14.5, CH_2), 5.83 (1 H, t, *J* = 7.7, Ar–H_6), 6.38 (2 H, d, *J* = 7.7, Ar–$H_{5,7}$), 7.23 (2 H, dd, *J* = 6.5, 3.4, Ar–$H_{15,18}$), 7.40 (2 H, s, Ar–$H_{21,22}$), 7.58 (2 H, dd, *J* = 6.5, 3.4, Ar–$H_{16,17}$); *m*/*z*: 344 (M^+). Anal. calcd. for $C_{23}H_{20}O_3$ (344.41): C, 80.21; H, 5.85. Found: C, 80.37; H, 5.76.

Syn-9-*methoxy*-6-*methyl(1,4)naphthaleno[3.3]metacyclophane-2,11-dione* (*syn*-**4b**): Obtained as *prisms* (hexane); m.p. 245–246°C; ν_{max}(KBr)/cm^{-1}: 1698 (C=O); δ_H($CDCl_3$): 1.52 (3 H, s, *Me*), 3.08 (2 H, d, *J* = 11.7, CH_2), 3.32 (3 H, s, O*Me*), 3.75 (2 H, d, *J* = 14.5, CH_2), 3.99 (2 H, d, *J* = 11.6, CH_2), 4.28 (2 H, d, *J* = 14.5, CH_2), 6.15 (2 H, s, Ar–$H_{5,7}$), 7.27 (2 H, dd, *J* = 6.5, 3.4, Ar–$H_{15,18}$), 7.40 (2 H, s, Ar–$H_{21,22}$), 7.56 (2 H, dd, *J* = 6.5, 3.4, Ar–$H_{16,17}$); *m*/*z*: 458 (M^+). Anal. calcd. for $C_{24}H_{22}O_3$ (358.44): C, 80.42; H, 6.19. Found: C, 80.33; H, 6.17.

Syn-6-*bromo*-9-*methoxy(1,4)naphthaleno[3.3]metacyclophane-2,11-dione* (*syn*-**4d**): Obtained as *prisms* (hexane); m.p. 289–290°C; ν_{max}(KBr)/cm^{-1}: 1699 (C=O); δ_H($CDCl_3$): 3.07 (2 H, d, *J* = 11.7, CH_2), 3.33 (3 H, s, O*Me*), 3.78 (2 H, d, *J* = 14.5, CH_2), 3.99 (2 H, d, *J* = 11.7, CH_2), 4.33 (2 H, d, *J* = 14.5, CH_2), 6.47 (2 H, s, Ar–$H_{5,7}$), 7.39 (2 H, s, Ar–$H_{15,18}$), 7.40 (4 H, dd, *J* = 6.5, 3.4, Ar–$H_{21,22}$), 7.56 (2 H, dd, *J* = 6.5, 3.4, Ar–$H_{16,17}$); *m*/*z*: 422, 424 (M^+). Anal. calcd. for $C_{23}H_{19}O_3Br$ (423.31): C, 65.26; H, 4.52. Found: C, 65.24; H, 4.51.

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