570 **RESEARCH PAPER** SEPTEMBER, 570–573 JOURNAL OF CHEMICAL RESEARCH 2009

Synthesis and structures of 8-(tolylmethyl)[2.2]metacyclophanes and 8,8'-(ethane-1,2-diyl)bis(16-methoxy[2.2]metacyclophane)

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A convenient preparation of 8-(tolylmethyl)[2.2]metacyclophanes and 8,8'-(ethane-1,2-diyl)bis(16-methoxy[2.2]metacyclophane) using a cross-coupling reaction of 8-bromomethyl[2.2]metacyclophanes with tolylmagnesium bromides is described. The structures of these novel [2.2]metacyclophanes in solution are also discussed.

Keywords: cyclophanes, Grignard cross coupling reaction, strain, ring current effect

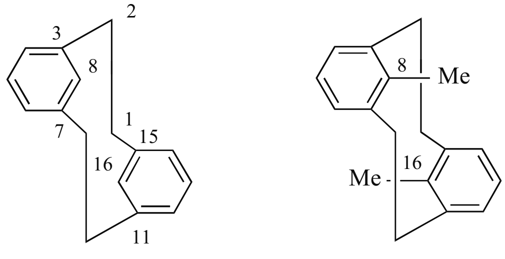
The geometry of the [2.2]MCP ([2.2]MCP = [2.2] metacyclophane) skeleton is known in detail from an X-ray structural analysis.[1] The crystal consists of discrete molecules each of which has a centre of symmetry. The two halves of the molecule form a stepped system. It is interesting to note that the benzene rings are not planar, but have a boat conformation, with the result that the molecule evidently avoids the steric interaction of the central carbon atoms C-8 and C-16 and of the attached hydrogen atoms. The C(8)– C(16) distance is 2.689 Å. The average length of the aromatic C–C bond was found to be 1.386 Å, and that of the aliphatic bond 1.543 Å. It is remarkable that the normally hexagonal, planar benzene ring suffers such a pronounced deformation with no appreciable change in the interatomic distances.[2]

The X-ray structural analysis of 8,16-dimethyl[2.2]MCP **2** confirms the results obtained for the parent compound.[3] The increased strain in the molecule **2** as compared with that in the parent hydrocarbon **1** can be seen in particular in the distance between C-1 and C-2 (1.573 Å). It is also remarkable that the two methyl carbon atoms lie in one plane together with the carbon atoms 8, 7 and 3 and 16, 11 and 15. The C(8)–(16) distance is increased from 2.689 Å in **1** to 2.819 Å in **2**. The rotation of the methyl groups (which are fixed above the aromatic rings) about their axes appears to be hindered, if not blocked. However, proton resonance measurements down to –20 °C show no rotation barrier for the molecule in solution.[4–15]

Thus introduction of methyl substituted benzyl groups to the 8-position of [2.2]MCP might increase the rotation barrier around the [2.2]MCP-*CH₂*–Ar for the molecule in solution. It is surprising that there are no reports on the preparation of 8-(tolylmethyl)[2.2]MCPs despite the fact that the chemical shift of the 2, 3, and 4-methyl substituent provides a convenient probe for ^{1}H NMR studies of any possible conformational changes. Therefore, there is substantial interest to investigate the structures of 8-(tolylmethyl)[2.2]MCPs. We report here the convenient preparation of 8-(tolylmethyl)[2.2]MCPs and 8,8'-(ethane-1,2-diyl)bis(16-methoxy[2.2]MCP) using cross coupling reaction of 8-bromomethyl[2.2]MCPs with tolylmagnesium bromides.

Results and discussion

We have prepared 8-bromomethyl[2.2]MCPs **3** by bromination of the corresponding 8-methy[2.2]MCPs with *N*-bromosuccinimide (NBS) in the presence of benzoyl peroxide under CCl_4 reflux for 3 h in 80 and 70% yields, respectively, as following our previous reported procedure.[16–18] The Grignard coupling reaction of 8-bromomethyl[2.2]MCP **3** with tolylmagnesium bromides **4** was carried out under the various conditions and the results are compiled in Table 1. The Grignard coupling reaction of **3a** with a large excess of (2-methylphenyl)magnesium bromide **4a** under THF reflux for 90 min afforded a desired 8-(2-methylbenzyl)[2.2]MCP **5a** in 52% yield. Similar results were obtained in the case of the coupling reaction of **3a** with (3-methylphenyl) (**4b**) and (4-methylphenyl)magnesium bromide (**4c**) to afford the corresponding coupling products **5b** and **5c** in 46 and 40% yields, respectively. On the other hand, the coupling reaction of **3b** with **4a** under the same reaction conditions described above afforded the coupling product **5d** in 42% yield along with the reduction product **6b** and 8,8'-(ethane-1,2-diyl)bis(16-methoxy[2.2]MCP) **7** in 14 and 2% yields, respectively. Interestingly, the present coupling reaction was carried out in the presence of almost 2 equivalents of (2-methylphenyl)magnesium bromide **4a** to increase the yield of bis[2.2]MCP **7** to 43%. In contrast, compounds **5e** and **5f** were obtained only in 5 and 10% yields in spite of using a



1 **2**

Fig. 1 Structure and numbering of [2.2]MCP and 8,16-dimethyl[2.2]MCP.

Table 1 Grignard coupling reaction of 8-bromomethyl[2.2]metacyclophanes (3) with tolylmagnesium bromides (4)[a]

Run	Substrate	Grignard reagent	Products yield/%[b]		
1	**3a**	**4a**	**5a** (52)	**6a** (0)	
2	**3a**	**4b**	**5b** (46)	**6a** (0)	
3	**3a**	**4c**	**5c** (40)	**6a** (0)	
4[c]	**3b**	**4a**	**5d** (0)	**6b** (0)	**7** (43)
5	**3b**	**4a**	**5d** (42)	**6b** (14)	**7** (2)
6	**3b**	**4b**	**5e** (5)	**6b** (5)	**7** (4)
7	**3b**	**4c**	**5f** (10)	**6b** (17)	

[a]Reaction conditions: [substrate]: [bromotoluene]:[Mg] = 1:10:20 (mol mol^{-1}); reaction time was 90 min otherwise indicate. [b]Isolated yields are shown. [c][substrate]: [bromotoluene]:[Mg] = 1:5:2.4 (mol/mol); reaction time was 6 h.

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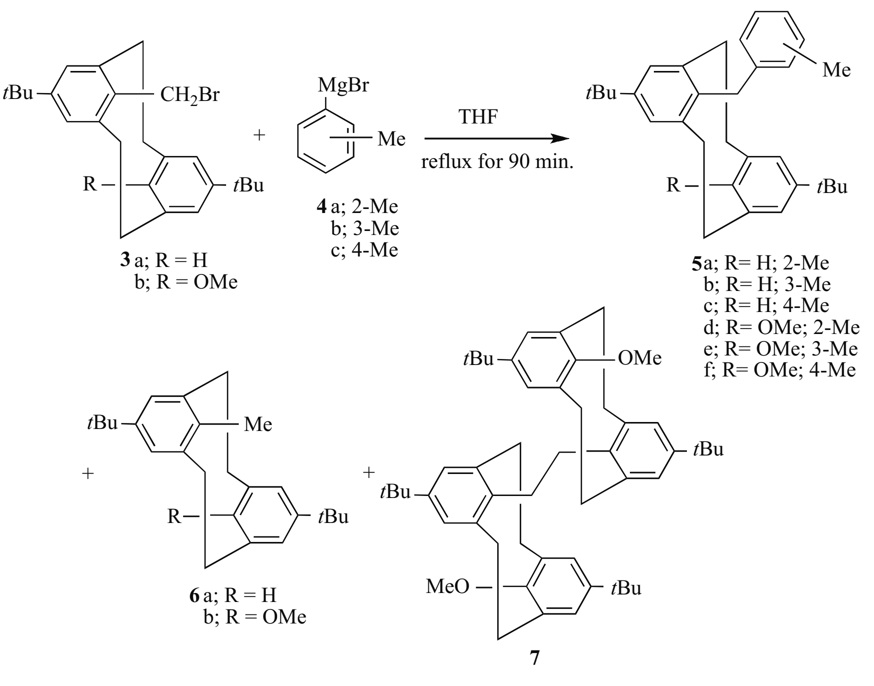
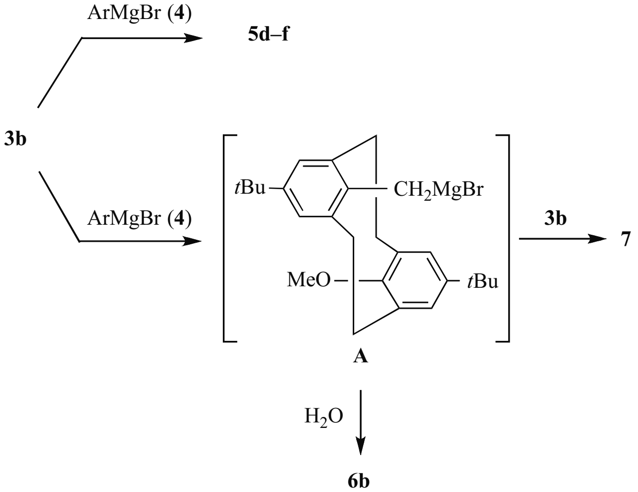


Scheme 1

large excess of (3-methylphenyl)magnesium bromide **4b** and (4-methylphenyl)magnesium bromide **4c**, respectively. Quite different results from the coupling reaction of **3a** with tolylmagnesium bromides **4** were observed by the introduction of methoxy group at the 18-position.

The formation of **6b** in the reaction of **3b** with **4** suggests the occurrence of an exchange reaction between **3b** and **4** to generate the intermediate [2.2]MCP-8-methylmagnesium bromide **A**, which could react with **3b** to afford bis[2.2]MCP **7**. The exchange reaction would occur competitively with the C–C-coupling reaction of **3b** with **4a–c**, which would give the product **5d–f**. The intermediate **A** is so stable in the reaction mixture that compound **6** might be formed when the reaction mixture is quenched with water. Thus the methoxy group at 16-position could contribute the stability of the intermediate **A** by through-space electronic interaction between two benzene rings.

The structures of **5a–f** and **7** were determined on the basis of their elemental analyses and spectral data. The ^{1}H NMR spectrum of **5a** in $CDCl_3$ shows a singlet at δ 2.08 ppm for methylene protons of benzyl group at the 8-position which is in a strongly shielding region of opposite *meta*-bridged benzene ring and δ 3.68 ppm for the internal aromatic proton at the 16-position, respectively. Similar findings were observed in compounds **5b–f**. The mass spectral data for **7** (M^+ = 726) strongly support bis[2.2]-MCP structure. The ^{1}H NMR spectrum of bis[2.2]MCP **7** shows the protons of the central ethano-bridge at δ 0.34 ppm, indicating that it is shielded by the ring current of the both opposing aromatic rings. It was also found that the one of the *tert*-butyl groups appeared at higher field δ 0.92 ppm due to the ring current effect of the other MCP benzene ring.



Scheme 2

The benzyl protons of the above-prepared 8-(tolylmethyl)[2.2]MCPs **5** are observed as a singlet in ^{1}H NMR spectra at 25 °C. The conformation of **5** has been evaluated by dynamic ^{1}H NMR spectroscopy. However, for instance, the methylene protons of the 8-(2-methylbenzyl)[2.2]MCP **5a** appear each as a singlet even below –60 °C ($CDCl_3/CS_2$ 1/3), and the rate of the rotation around the [2.2]MCP-*CH₂*–Ar of **5a** is faster than the NMR time scale above this temperature. Similar findings were obtained in other 8-(tolylmethyl)[2.2]MCPs **5b–f**. These results indicate that the rotation barrier around the [2.2]MCP-*CH₂*–Ar **5a** and **5d** are still quite low in spite of the introduction of the methyl group at the *ortho* position of the 8-benzyl group.

The values of the chemical shifts of the methylene protons, methyl protons and aromatic protons of the 8-benzyl group in [2.2]MCPs **5** are summarised in Table 2.[18–20] As shown in Table 2, the chemical shifts of the methylene protons in **5a–c** (δ 2.08–2.11 ppm) are upper field than those (δ 2.29–2.31 ppm) in 16-methoxy analogues **5d–f**.

Considering the molecular model, it is concluded that the conformation of the 8-(tolylmethyl)[2.2]MCPs should be strongly affected by the size of the substituents at the position 16. The interaction between the methylene protons and opposite benzene ring might be much more favourable for unsubstituted [2.2]MCP **5a–5c** than the 16-methoxy one **5d–f**. Thus, the steric repulsion of 16-substituent for the opposite benzene ring could make the distance between the methylene protons and the opposite benzene ring longer, whereas the H–π interaction at the 16-position could shorten

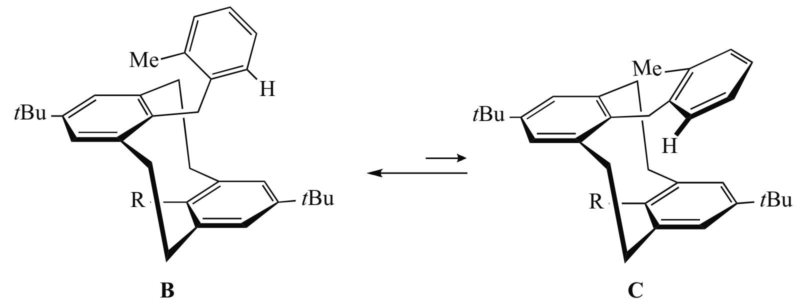


Fig. 2 Structure of 8-(2-methylbenzyl)[2.2]MCPs.

Table 2 Chemical shifts of the methylene protons, methyl protons and aromatic protons of 8-benzyl group in 8-(tolylmethyl)[2.2]MCPs **5**[a]

Substrate		δCH_2	δMe	δAr*H*
5a	2-Me	2.08	1.94	6.39, 6.87[b]
5b	3-Me	2.11	2.16	6.42, 6.87[b]
5c	4-Me	2.10	2.19	6.51
5d	2-Me	2.29	1.95	6.23, 6.84[b]
5e	3-Me	2.31	2.13	6.32, 6.94[b]
5f	4-Me	2.31	2.16	6.62

[a]Determined in $CDCl_3$ using $SiMe_4$ as a reference.
[b]The midpoint value of multiplets

this distance. Interestingly, the chemical shifts of the methyl protons and *ortho* aromatic protons benzyl group in **5a**–**f** shifted upper field in order of 2-methyl-, 3-methyl- and 4-methylbenzyl group. From these findings, it is concluded that 8-(tolylmethyl)[2.2]MCPs **5** have the conformers **B** and **C** and that 8-(2-methylbenzyl) analogues **5a** and **5d** might exist in conformer **B** because of steric repulsion between the 2-methyl group and the bridged ethylene bonds. Accordingly, the 2-methyl protons of the benzene rings of **5a** and **5d** might be slightly affected by the ring current of the aromatic rings on the same side rather than that of the opposite aromatic rings.

Conclusions

We have developed a convenient preparation of 8-(tolylmethyl)[2.2]MCPs and 8,8'-(ethane-1,2-diyl)bis-(16-methoxy [2.2]MCP) using a cross-coupling reaction of 8-bromomethyl [2.2]MCPs with tolylmagnesium bromides. The rotation barrier around the 8-(2-methylbenzyl)[2.2]MCPs **5a** and **5d** are still quite low in spite of the introduction of methyl group at the *ortho* position of the 8-benzyl group. Interestingly, the 2-methyl protons of the benzene rings of **5a** and **5d** might be slightly affected by the ring current of the aromatic rings on the same side rather than that of the opposite aromatic rings. Further studies on the chemical properties of the 8-(tolylmethyl)[2.2]MCPs **5** are now in progress.

Experiment

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.

Materials

Preparations of 5,13-di-*tert*-butyl-8-bromomethyl[2.2]metacyclophane **3a** and 5,13-di-*tert*-butyl-8-bromomethyl-16-methoxy[2.2]metacyclophane **3b**[17,18] were previously described.

Grignard coupling reaction of **3** *with (tolyl)magnesium bromide* **4**; *typical procedure*

A solution of **3b** (100 mg, 0.23 mmol) in THF (2 mL) was added to a solution of (2-methylphenyl)magnesium bromide [prepared from 2-bromotoluene (400 mg, 2.3 mmol) and magnesium (112 mg, 4.6 mg-atom)] in refluxing THF (3 mL) was added. After the reaction mixture had been refluxed for 90 min, it was quenched with 10% aqueous ammonium chloride and extracted with methylene dichloride; the extract was dried (Na_2SO_4) and concentrated under reduced pressure. The residue was subjected to silica-gel (Wako, C-300; 100 g) column chromatography using as eluent hexane to give **6** (12 mg, 14%) and **5d** (44 mg, 42%), respectively.

8-*Methoxy*-16-*methyl*-5,13-di-*tert-buyl*[2.2]*metacyclophane*(**6**): Prisms (hexane); m.p. 215–216 °C (lit.[17] 215–216 °C).

5,13-Di-tert-butyl-8-(2-*methylbenzyl*)-16-*methoxy*[2.2]*metacyclophane* (**5d**): Prisms (from hexane); m.p. 136 °C; ν_{max}(KBr)/cm^{-1} 2960, 2864, 1601, 1478, 1461, 1361, 1242, 1027 and 742; δ_H ($CDCl_3$) 1.32 (9H, s, *t*Bu), 1.34 (9H, s, *t*Bu), 1.95 (3H, s, *Me*), 2.29 (2H, s, *CH_2*), 2.64–2.82 (8H, m, *CH_2*), 2.89 (3H, s, O*Me*), 6.21–6.24 (1H, m, Ar*H*), 6.80–6.90 (3H, m, *ArH*), 7.06 (2H, s, *ArH*) and 7.17 (2H, s, *ArH*); *m*/*z* 454 (M^+) (Found: C, 87.18; H, 9.93. $C_{33}H_{42}O$ (454.7) requires C, 87.17; H, 9.31%).

Reaction of **3** with various Grignard reagents was carried out using the same procedure as described above and details of the products and yields are compiled in Table 1.

5,13-*Di-tert-butyl*-8-(2-*methylbenzyl*)[2.2]*metacyclophane* (**5a**): Prisms (from hexane); m.p. 136–137 °C; ν_{max}(KBr)/cm^{-1} 2959, 2864, 1502, 1460, 1358, 1178 and 870; δ_H ($CDCl_3$) 1.34 (9H, s, *t*Bu), 1.38 (9H, s, *t*Bu), 1.94 (3H, s, *Me*), 2.08 (2H, s, *CH_2*), 2.20–3.05 (8H, m, *CH_2*), 3.68 (1H, s, *ArH*), 6.38–6.40 (1H, m, Ar*H*), 6.80–6.95 (3H, m, *ArH*), 7.09 (2H, s, *ArH*) and 7.18 (2H, s, *ArH*); *m*/*z* 424 (M^+) (Found: C, 90.66; H, 9.51. $C_{32}H_{40}$ (424.68) requires C, 90.51; H, 9.49%).

5,13-*Di-tert-butyl*-8-(3-*methylbenzyl*)[2.2]*metacyclophane* (**5b**): Prisms (from hexane); m.p. 136–138 °C; ν_{max}(KBr)/cm^{-1} 2960, 2860, 1502, 1358, 1380 and 840; δ_H ($CDCl_3$) 1.36 (18H, s, *t*Bu), 2.11 (2H, s, *CH_2*), 2.16 (3H, s, *Me*), 2.69–3.00 (8H, m, *CH_2*), 3.70 (1H, s, *ArH*), 6.41–6.43 (1H, m, ArH), 6.80–6.95 (3H, m, *ArH*), 7.07 (2H, s, *ArH*) and 7.18 (2H, s, *ArH*); *m*/*z* 424 (M^{+}) (Found: C, 90.73; H, 9.41. $C_{32}H_{40}$ (424.68) requires C, 90.51; H, 9.49%).

5,13-*Di-tert-butyl*-8-(4-*methylbenzyl*)[2.2]*metacyclophane* (**5c**): Prisms (from hexane); m.p. 140–141 °C; ν_{max}(KBr)/cm^{-1} 2961, 2860, 1504, 1450, 1360, 1180 and 860; δ_H ($CDCl_3$) 1.35 (18H, s, *t*Bu), 2.10 (2H, s, *CH_2*), 2.19 (3H, s, *Me*), 2.64–3.05 (8H, m, *CH_2*), 3.70 (1H, s, *ArH*), 6.51 (2H, d, J = 7.8 Hz, Ar*H*), 6.87 (2H, d, J = 7.8 Hz, Ar*H*), 7.06 (2H, s, *ArH*) and 7.18 (2H, s, *ArH*); *m*/*z* 424 (M^+) (Found: C, 90.67; H, 9.45. $C_{32}H_{40}$ (424.68) requires C, 90.51; H, 9.49%).

5,13-*Di-tert-butyl*-8-(3-*methylbenzyl*)-16-*methoxy*[2.2]*metacyclophane* (**5e**): Prisms (from hexane); m.p. 145–147 °C; ν_{max}(KBr)/cm^{-1} 2956, 2860, 1478, 1459, 1360, 1276, 1027, 1185, 885, 796 and 479; δ_H ($CDCl_3$) 1.31 (9H, s, *t*Bu), 1.36 (9H, s, *t*Bu), 2.13 (3H, s, *Me*), 2.31 (2H, s, *CH_2*), 2.65–2.84 (8H, m, *CH_2*), 2.89 (3H, s, O*Me*), 6.31–6.33 (1H, m, Ar*H*), 6.85–6.98 (3H, m, *ArH*), 7.04 (2H, s, *ArH*) and 7.16 (2H, s, *ArH*); *m*/*z* 454 (M^+) (Found: C, 87.07; H, 9.83. $C_{33}H_{42}O$ (454.7) requires C, 87.17; H, 9.31%).

5,13-*Di-tert-butyl*-8-(4-*methylbenzyl*)-16-*methoxy*[2.2]*metacyclophane* (**5f**): Prisms (from hexane); m.p. 144–145 °C; ν_{max}(KBr)/cm^{-1} 2960, 2864, 1597, 1483, 1455, 1290 and 980; δ_H ($CDCl_3$) 1.31 (9H, s, *t*Bu), 1.36 (9H, s, *t*Bu), 2.16 (3H, s, *Me*), 2.31 (2H, s, *CH_2*), 2.64–2.88 (8H, m, *CH_2*), 2.89 (3H, s, O*Me*), 6.62 (2H, d, J = 7.8 Hz, Ar*H*), 6.83 (2H, d, J = 7.8 Hz, Ar*H*), 7.04 (2H, s, *ArH*) and 7.16 (2H, s, *ArH*); *m*/*z* 454 (M^+) (Found: C, 87.26; H, 9.81. $C_{33}H_{42}O$ (454.7) requires C, 87.17; H, 9.31%).

8,8'-(*Ethane*-1,2-*diyl*)*bis*(5,13-*di-tert-butyl*-16-*methoxy*[2.2]*metacyclophane*) (**7**): Prisms (from hexane); m.p. 279 °C (decomp.); ν_{max}(KBr)/cm^{-1} 2954, 2864, 1478, 1460, 1360, 1291, 1278, 1207, 1020 and 864; δ_H ($CDCl_3$) 0.34 (4H, s, *CH$_2$*), 0.92 (18H, s, *t*Bu), 1.27 (18H, s, *t*Bu), 2.46–2.84 (16H, m, *CH$_2$*), 2.77 (6H, s, O*Me*), 6.80 (4H, s, *ArH*) and 6.87 (4H, s, *ArH*); *m*/*z* 726 (M^+) (Found: C, 86.23; H, 9.85. $C_{52}H_{70}O_2$ (727.14) requires C, 85.90; H, 9.70%).

Received 5 May 2009; accepted 8 July 2009
Paper 09/0567 doi: 10.3184/030823409X12508764525015

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