Medium-sized Cyclophanes. Part 49.[1] *O*-Alkylation of 8,16-Dihydroxy[2.2]-metacyclophane†

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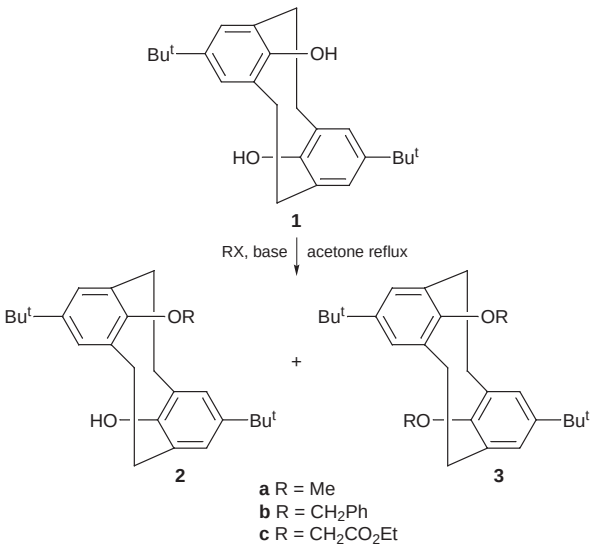
O-Alkylation of 8,16-dihydroxy[2.2]metacyclophane **1** with alkyl halides in the presence of K_2CO_3 affords the mono-*O*-alkylated product **2**; similar reaction in the presence of Cs_2CO_3 or NaH affords dialkylated product **3** in almost quantitative yield.

Previously, we reported[2,3] that the demethylation of 8,16-dimethoxy[2.2]metacyclophane (MCP = metacyclophane) **3a** with BBr_3 in CH_2Cl_2 or $SiMe_3I$ in MeCN solution afforded the desired completely demethylated product, 8,16-dihydroxy[2.2]MCP **1** in good yield. However, attempted selective demethylation of one of the methoxy groups in 8,16-dimethoxy[2.2]MCP **3a** failed. Only a mixture of demethylated products, **1** and **2a** were obtained in 51 and 42% yields, respectively. On the other hand, regioselective *O*-alkylation of hydroxy groups in calixarenes is important for many purposes, in particular for the construction of multiple binding receptors or larger molecules starting from several calixarene building units.[4] Shinkai and coworkers reported the specific synthesis of calix[4]arene derivatives in a given conformation using benzyl residues as protecting groups.[5] Here, we report on selective *O*-monoalkylation of dihydroxy[2.2]MCP **1** under various basic conditions.

O-Alkylation of dihydroxy[2.2]MCP **1** with methyl iodide carried out using NaH as a base exclusively afforded the corresponding dialkylated product **3a**. No formation of monomethoxy[2.2]MCP **2a** was observed. On the other hand, when sodium carbonate is employed, only the monomethylated product **2a** is formed (in 3.6% yield) along with recovery of the starting compound in spite of the presence of a large excess of sodium carbonate. Interestingly, when K_2CO_3 is used in this reaction, the desired monomethylated product was obtained in 30% yield with recovery of the starting compound. Prolonging the reaction time for 12 h led to preferential formation of the monoalkylated product **2a** in 93% yield. Thus, for K_2CO_3 selective monomethylation was observed. By contrast, when Cs_2CO_3 was employed, the reaction was completed within 3 h and the exclusive formation of dimethylated product **3a** was observed (Scheme 1). Similar results were observed in *O*-alkylation of **1** with benzyl bromide or ethyl bromoacetate. These results indicate that the alkali metal cation plays an important role in determining the degree of *O*-alkylation as previously observed in the *O*-alkylation of calix[4]arenes.[7] However, the question remains as to why the *O*-alkylation of dihydroxy[2.2]MCP **1** in the presence of K_2CO_3 mainly affords monoalkylated product **2** rather than dialkylated product **3** despite the large excess of K_2CO_3? The template effect of an alkali metal cation plays an important role in the *O*-alkylation of calixarenes to afford conformational isomers[7] and a similar metal template effect appears to operate in the *O*-alkylation of dihydroxy[2.2]MCP **1**. The present template effect was also confirmed by the observation of *O*-methylation of monomethoxy[2.2]MCP **2a** by use of NaH or Cs_2CO_3 as a base to exclusively give the dimethylated product. However, in the case of K_2CO_3 only recovery of starting compound **2a** was observed.



Scheme 1

In order to study the template effect of an alkali metal cation on *O*-alkylation of **1** in more detail, we examined *O*-alkylation of the reference compound **4**. Thus, *O*-methylation of 1,2-bis(2-hydroxy-3-methylphenyl)ethane **4** with methyl iodide in the presence of K_2CO_3 afforded the fully *O*-alkylated product 1,2-bis(2-methoxy-3-methylphenyl)ethane **5** in quantitative yield within 3 h under the same conditions.

Apparently, the present selective mono-*O*-alkylation of diol **1** in the presence of K_2CO_3 is attributable to the cyclophane structure.[6] Probably, the smaller Na^+ or K^+ are included very strongly in a sufficient space around the cyclophane benzene ring, which increases the strength of the cation–π-interaction[8] between K^+ and the opposite benzene ring (Fig. 1, **A**). Thus, intermediate **A** might be much stabilized so as to decrease the nucleophilicity of phenolic O^- anions by cation–π-interaction, resulting in the formation of only a monoalkylated product **2**. By contrast, Cs^+ is too large enough to form a similar intermediate **A**, and will generate two O^- anions at different sides of the ring (intermediate **B**) resulting in much faster alkylation to form the dialkylation product **3**.

The present template effect of K^+ on *O*-alkylation was also confirmed by the competitive, *O*-alkylation of unsymmetrically substituted 8,16-dihydroxy[2.2]MCP. *O*-Methylation of 5-bromo-13-*tert*-butyl-8,16-dihydroxy-[2.2]MCP **6** with methyl iodide in the presence of K_2CO_3 led to a mixture of monomethylation products 5-bromo-13-

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Table 1 *O*-Alkylation of 8,16-dihydroxy[2.2]MCP **1** with alkyl halides in the presence of M_2CO_3 or NaH

Run	RX	Base	*t*/h	Product yields(%)[a,b] **2**	**3**	Recovered **1** (%)
1	MeI	NaH[c]	3	0	100 (88)	0
2	MeI	Na_2CO_3	12	3.6	0	96.4
3	MeI	K_2CO_3	3	30.5	0	69.5
4	MeI	K_2CO_3	12	92.7 (83)	4.7	2.6
5	MeI	Cs_2CO_3	3	2.2	94.2 (85)	0
6	$PhCH_2Br$	K_2CO_3	12	89.1 (80)	6.1	4.8
7	$PhCH_2Br$	Cs_2CO_3	3	18.6	81.4 (70)	0
8	$EtOOCCH_2Br$	K_2CO_3	12	81.9 (72)	0	18.1
9	$EtOOCCH_2Br$	Cs_2CO_3	3	1.4	98.6 (90)	0

[a]Yields were determined by GLC analyses. [b]Isolated yields are given in parentheses. [c]Solvent THF–DMF (4:1 v/v).

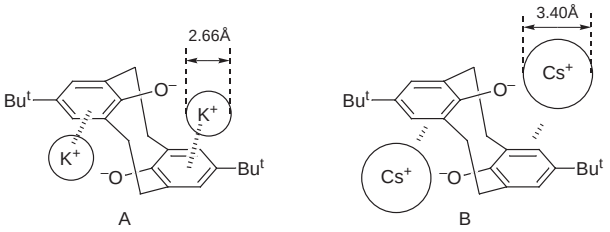

Fig. 1 Possible intermediates for *O*-alkylation of diol **1** on the basis of a template effect.

tert-butyl-8-hydroxy-16-methoxy[2.2]MCP **7** and 5-bromo-13-*tert*-butyl-8-methoxy[2.2]MCP **8** in 95% total yield, ^{1}H NMR analyses of the reaction mixture indicated a mixture of **7** and **8** in the ratio of 80:20, *i.e.* preferential formation of monomethylation product **7** was observed. This finding strongly supports the involvement of intermediate **A** described above, in which the contribution of the cation–π-interaction between K^+ and the opposing benzene ring might be decreased by the electron withdrawing Br group, and thus a higher nucleophilicity of phenolic O^- anion than that of the other might be observed.

Experimental

All mps and bps 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 on 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^{-1}; carrier gas nitrogen, 25 cm^3 min^{-1}.

Materials.—The preparation of 5,13-di-*tert*-butyl-8,16-dihydroxy[2.2]metacyclophane **1** has been previously described.[2]

Methylation of 5,13-*Di*-tert-*butyl*-8,16-*dihydroxy[2.2]metacyclophane* **1** *in the Presence of Alkali–metal Carbonates.—Typical procedure.* A mixture of **1** (88 mg, 0.25 mmol) and K_2CO_3 (86.4 mg, 1.25 mmol) in dry acetone (16 cm^3) was heated at reflux for 1.5 h under nitrogen. Then MeI (0.16 cm^3, 2.5 mmol) was added and the mixture heated at reflux for 6 h. After cooling of the reaction mixture to room temperature, it was filtered. The filtrate was concentrated to give a colourless oil, which was then chromatographed over silica gel (Wako, C-300; 100 g) with hexane–benzene (1:1) as eluent to give a colorless solid, which was recrystallized from hexane to afford 5,13-di-*tert*-butyl-8-hydroxy-16-methoxy[2.2]metacyclophane **2a** as prisms (76 mg, 83%), mp 183–185 °C (lit.[3] 182–183 °C); ν_{max} (KBr) 3550, 3040, 2960, 1480, 1360, 1285, 1190, 1025, 890, 860 cm^{-1}; δ_H($CDCl_3$) 1.30 (9 H, s), 1.32 (9 H, s), 1.94 (1 H, s, exchanged by D_2O), 2.6–2.8 (8 H, m), 2.95, (3 H, s), 6.99 (2 H, s) and 7.16 (2 H, s); *m/z* 366 (M^+) (Found: C, 82.02; H, 9.32. $C_{25}H_{34}O_2$ requires C, 81.92; H, 9.35%).

Similarly, *O*-alkylation of **1** with alkyl halides was carried out in the same manner as described above. The yields are given in Table 1.

5,13-*Di*-tert-*butyl*-8-*benzyloxy*-16-*hydroxy*[2.2]*metacyclophane* **2b**. Prepared as prisms, mp 147–149 °C (MeOH); ν_{max} (KBr) 3473, 2958, 1478, 1186, 1018 cm^{-1}; δ_H($CDCl_3$) 1.13 (9 H, s), 1.33 (9 H, s), 2.06 (1 H, s, exchanged by D_2O), 2.65–2.8 (8 H, m), 4.11 (2 H, s), 6.95 (2 H, s), 6.96–7.03 (2 H, m), 7.19 (2 H, s) and 7.16–7.30 (3 H, m); *m/z* 442 (M^+) (Found: C, 84.26; H, 8.54. $C_{31}H_{38}O_2$ requires C, 84.12; H, 8.65%).

5,13-*Di*-tert-*butyl*-8,16-*dibenzyloxy*[2.2]*metacyclophane* **3b**. Prepared as prisms, mp 178–179 °C (MeOH); δ_H($CDCl_3$) 1.13 (9 H, s), 1.33 (9 H, s), 2.63–2.73 (8 H, m), 4.07 (4 H, s), 7.01 (4 H, s), 6.96–7.05 (4 H, m) and 7.18–7.26 (6 H, m); *m/z* 532 (M^+) (Found: C, 85.70; H, 8.43. $C_{38}H_{44}O_2$ requires C, 85.67; H, 8.32%).

5,13-*Di*-tert-*butyl*-8-*(ethoxycarbonyl)methoxy*-16-*hydroxy*[2.2]-*metacyclophane* **2c**. Prepared as prisms, mp 61–62 °C (MeOH); ν_{max}(KBr) 3452, 2952, 2932, 1748, 1736, 1480, 1437, 1361, 1288, 1217, 1184, 1116 cm^{-1}; δ_H($CDCl_3$) 1.16 (3 H, t, *J* 6.8), 1.28 (9 H, s), 1.30 (9 H, s), 2.06 (1 H, s, exchanged by D_2O), 2.7–2.9 (8 H, m), 3.75 (2 H, s), 4.03 (2 H, q, *J* 6.8), 7.01 (2 H, s), 7.15 (2 H, s); *m/z* 438 (M^+) (Found: C, 76.91; H, 8.79, $C_{28}H_{38}O_4$ requires C, 76.68; H, 8.73%).

5,13-*Di*-tert-*butyl*-8,16-*bis*(*ethoxycarbonyl*)*methoxy*[2.2]*metacyclophane* **3c**. Prepared as prisms, mp 178–179 °C (MeOH); ν_{max}(KBr) 1764 (C=O), 1181 cm^{-1}; δ_H($CDCl_3$) 1.16 (6 H, t, *J* 7.3), 1.26 (18 H, s), 2.7–2.85 (8 H, m), 3.72 (4 H, s), 4.01 (2 H, *J* 7.3), 7.01 (2 H, s) and 7.04 (4 H, s); *m/z* 524 (M^+) (Found: C, 73.21; H, 8.43. $C_{32}H_{44}O_6$ requires C, 73.25; H, 8.45%).

Similarly, *O*-methylation of **6** was carried out in the same manner as described above. The assignment of **7** and **8** was carried out by comparison with authentic samples.

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