The metal template effect on *O*-alkylation of hexahomotrioxacalix[3]arene with 4-(chloromethyl)pyridine to afford tris[(4-pyridylmethyl)oxy]hexahomotrioxacalix[3]arenes and their conformational studies

J. Chem. Research (S), 2000, 10–12
J. Chem. Research (M), 2000, 0159–0172

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O-Alkylation of the flexible macrocycle **1** with 4-(chloromethyl)pyridine gave di- and tri-*O*-alkylated products with cone or partial-cone conformation which ratio was affected by NaH or alkali metal carbonates used as a base.

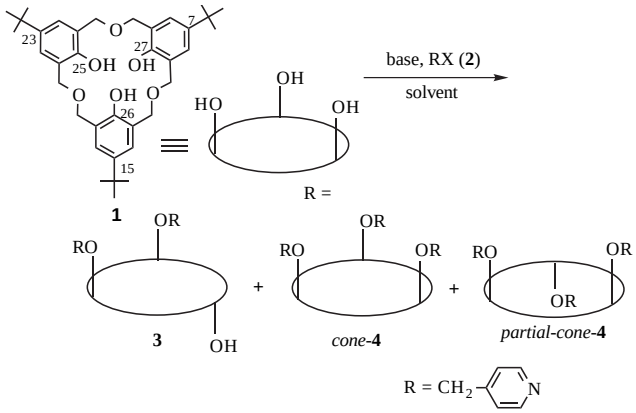
Calixarene and related macrocycles have received considerable attention for their host-guest chemistry as ionophoric receptors and potential enzyme mimics in biology.[1] Chemical modification of calixarene represents an effective and versatile way of producing receptors with high selective cation binding properties. Even minor changes in the regioselective functionalization or conformation of the chemically modified calixarene can be associated with drastic changes in the complexation properties.[1c]

Recently, we have reported the synthesis, conformational studies and inclusion properties of tris[(2-pyridylmethyl)oxy]-hexahomotrioxacalix[3]arenes derived from hexahomotrioxacalix- [3]arene,[13] which show strong Ag^+ ion and *n*-butylammonium ion affinity. ^{1}H-NMR Titration with $AgSO_3CF_3$ clearly demonstrated that a 1:1 complex is formed with retention of the original symmetry. Interestingly, the conformational changes of pyridine moiety from the original outward orientation of the ring nitrogen to the inside orientation toward the cyclophane cavity were observed in the process of Ag^+ complexation. On the other hand, Reinhoudt *et al.*[14b] also reported the well-defined hydrogen-bonded calix[4]arene duplex between tetrakis[(4-pyridyl-methyl)-oxy]calix[4]arene and calix[4]arene tetracarboxylic acid. Independently, Shinkai *et al.* have extended this kind of upper-rim functionalization to larger calixarenes.[15b] Thus there is substantial interest in investigating the synthesis and structures of tris[(4-pyridylmethyl)oxy]-hexahomotrioxacalix[3]arenes with *cone*- and *partial-cone*-conformation, in which the former compounds are supposed to have the property to construct the hydrogen-bonded C_3 symmetrical calix[3]arene duplex with calix[3]arene tricarboxylic acid.

In this paper we describe the metal template effect on *O*-alkylation of hexahomotrioxacalix-[3]arene with 4-(chloromethyl)pyridine to afford tris[(4-pyridylmethyl)oxy]-hexahomotrioxa-calix[3]arenes with *cone*- and *partial-cone*-conformation and their conformational studies.

Results and discussion

Hexahomotrioxacalix[3]arene **1**[16a] was *O*-alkylated with 4-(chloromethyl)pyridine **2** in the presence of Cs_2CO_3 gave only one pure stereoisomer *partial-cone*-**4** in 89% yield, while the other possible isomer *cone*-**4** was not observed. When NaH is used in this reaction, a mixture of two conformers of tri-*O*-alkylated product **4** was obtained in 9% (*cone*-**4**:*partial-cone*-**4**, 78:22) along with the recovery of the starting compound **1** in 91% yield. The yield of *cone*- and *partial-cone*-**4** increased in the presence of K_2CO_3 to 93% and the *cone*-to-*partial-cone* ratio of **4** was 15:85 (*cone*-**4**:*partial-cone*-**4**). In contrast, a significant amount of *O*-disubstituted product **3** was produced in 52% yield when Na_2CO_3 was used as a base along with the recovery of the starting compound **1** in 48% yield. The ratio of the products *cone*-**4** and *partial-cone*-**4** is governed by the nature of alkali metal carbonates or NaH used as a base. Thus, when Cs_2CO_3 is used in this reaction, *partial-cone*-**4** was obtained as a major product in 89% yield. On the other hand, when K_2CO_3 is employed, the increased formation of cone-coformer was observed. Unfortunately, a significant recovery of starting compound **1** was observed in spite of the condition of large excess of 4-(chloromethyl)pyridine **2a**, which was quite different from the result that *O*-benzylation of triol **1** with benzyl bromide in the presence of NaH afforded a mixture of *cone*- and *partial-cone*-tri-*O*-alkylated product **5** in a ratio of 75:25 in quantitative yield. When Cs_2CO_3 is used in this reaction, *partial-cone*-**5** was exclusively obtained.[13b] Because the much larger contribution of Cs^+ to the template effect than Na^+ as reported by Harrowfield[17] can



Scheme 1

Table 1 O-Substitution reaction of hexahomotrioxacalix[3]arene **1** with 4-(chloromethyl)pyridine **2**

Run	Base	Distribution (%)[a,b] **3**	*Cone*-**4**	*Partial-cone*-**4**	Recovd. **1**
1	NaH	0	7	2	91
2	Na_2CO_3	52 (42)	0	0	48
3	K_2CO_3	0	14 (8)	79 (68)	7
4	Cs_2CO_3	0	0	89 (75)	11

[a]Relative yields determined by HPLC. [b]Isolated yields are shown in parentheses.

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be expected, the larger Cs^+ might enlarge the cyclophane ring, (*e.g.* the intermediate **B**) to form a sufficient space for ring inversion to afford thermodynamically stable partial-cone conformer in the *O*-alkylation with 4-(chloromethyl)pyridine and benzyl bromide. In contrast, the smaller Na^+ or K^+ might increase the contribution of the metal template effect, which can hold the 4-pyridylmethyl group(s) and the oxide group(s) on the same side of the hexahomotrioxacalix[3]arene through the cation-O^- and cation-π-interaction similar to the *O*-benzylation, but this effect might be smaller due to the decreased π-density of pyridine ring than that of benzene ring (Fig. 1 **A**). The decreased formation of *cone*-conformer in the reaction of the triol **1** with 4-(chloromethyl)pyridine than that with 2-(chloromethyl)pyridine in the presence of NaH or K_2CO_3 might be attributable to the absence of contribution derived from cation-N-interaction.[13b]

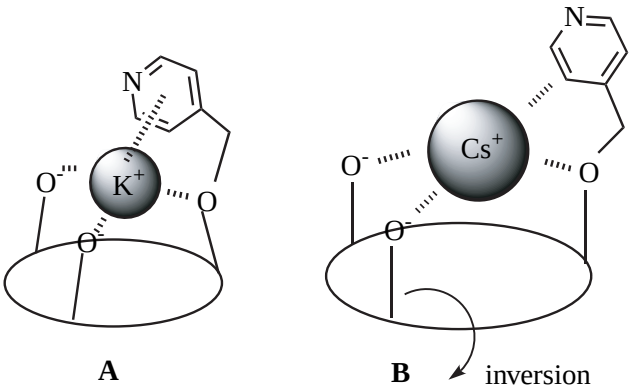

Fig. 1 Ring inversion of *O*-alkylation intermediate of triol **1** and immobilization by metal template.

The ^{1}H NMR spectrum of *cone*-**4** shows a singlet for the *tert*-butyl protons at δ 1.17 and a singlet for ArO*CH*$_2$Py and the aromatic protons at δ 4.44 and 7.32, respectively, indicating a C_3-symmetric structure of *cone*-**4**. Interestingly, the heteroaromatic protons of the pyridine rings in *cone*-**4** are exposed to the ring current shielding effect operated by the opposing pyridine ring among the dibenzylether linkage, and resonate at higher fields with respect to those of the reference compound **7**, which was prepared by *O*-alkylation of 4-*tert*-butyl-2,6-dimethylphenol **6** with 4-(chloromethyl)pyridine **2** in the presence of NaH in 63% yield.

The magnitude of this shielding, computed as the difference between pertinent pyridine protons of *cone*-**4** and reference compound **7**, increases significantly on H_2 and H_3 protons. The remarkable shielding effect experienced by H_3 (–0.63 ppm) protons of the pyridine ring suggests that these protons are located in much closer enviroment toward the opposing pyridine ring than H_2 (–0.37 ppm) protons due to the repulsion among the nitrogen atoms in the pyridine rings between the dibenzylether linkage. Thus, nitrogens in all of the pyridine rings were oriented outwards the cyclophane cavity as shown in Fig. 2.

In contrast, the ^{1}H NMR spectrum of *partial-cone*-**4** shows two singlets for the *tert*-butyl protons at δ 0.90, 1.20 (relative intensity 2:1), a singlet and a pair of doublets at δ 7.40 and 7.17, 7.19 for the aromatic protons. Furthermore, the resonance for the ArO*CH*$_2$Py methylene protons appeared as a singlet at δ 4.23 and a pair of doublets at δ 4.80, 4.84 (J_{AB} = 10.3 Hz). Upfield shifts for the inverted pyridine ring protons were observed, especially at δ 6.73 for H_3, proton. These signals correspond to C_2-symmetric structure. On the basis of the ^{1}H-NMR studies and the consideration of CPK model of *partial-cone*-**4**, two (4-pyridylmethyl)oxy groups in the compound point upwards and the another one folded into the π-cavity

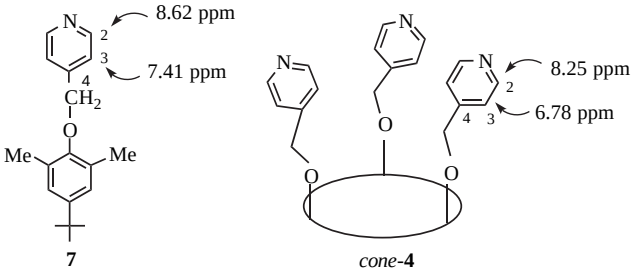

Fig. 2 Reference compound **7** and orientation of the pyridine in *cone*-**4**.

formed by two calix benzene rings and are thus shifted stronger upfield. Furthermore, upfield shifts for two *tert*-butyl groups are observed attributable to being located on the pyridine ring of the inverted picolyl group in spite of the sterically crowded environment. This finding might be attributed to the C-H-π-interaction[20a] between methyl groups of the *tert*-butyl group and the pyridine ring.

It was also found that ring inversion by oxygen-through-the-annulus rotation is inhibited for tris[(4-pyridylmethyl)oxy] derivatives *cone*-**4** and *partial-cone*-**4** because of the observation of no change of spectrum pattern for the ArC*H*$_2$OC*H*$_2$Ar methylene protons below 130°C in $CDBr_3$.

The structure of di-*O*-substitution product **3** has been elucidated on the basis of its elemental analyses and spectral data. For instance, the mass spectral data for **3** (M^+ = 758) strongly supports di-*O*-substitution product. ^{1}H NMR spectrum of **3** shows resonances for the *tert*-butyl protons at δ 1.08 and 1.09 (relative intensity, 2:1) as a singlet, for the aromatic protons at δ 7.00 as a singlet and at δ 7.29, 7.37 as a doublet (*J* 2.4 Hz), and the hydroxy proton at δ 7.42 as a singlet indicating a di-*O*-substituted structure.

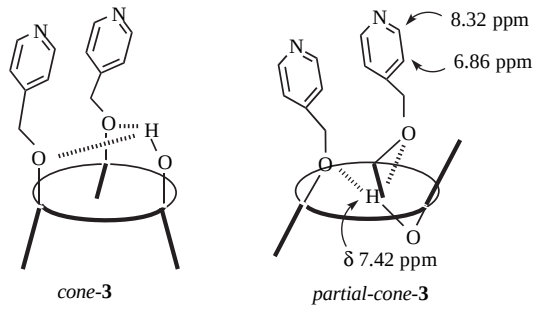

Fig. 3 Intramolecular hydrogen bonding in **3**.

Furthermore, the resonance for the benzyl methylene protons of the ArO*CH*$_2$Py appeared as a pair of doublets (δ 4.58 and 4.69, J_{AB} = 12.7 Hz) (relative intensity 1:1) and do not coalesce below 130°C in $CDBr_3$. The AB systems from the ArO*CH*$_2$Py methylene protons are a consequence of the rigid cyclophane conformation which makes the CH_2 protons diastereotopic. The calixarenes show concentration-independent hydroxyl stretching bands in the 3200 cm^{-1} region of the infrared spectrum and a signal at δ 9–10 in the ^{1}H-NMR spectrum, indicative of very strong intramolecular hydrogen bonding and the cyclic nature of calixarenes.[1] The IR (KBr) spectrum of **3** shows the absorption for the hydroxyl stretching vibration around 3370 cm^{-1}. These data show the existence of the intramolecular hydrogen bonding between the hydroxy group and (4-pyridylmethyl)oxy groups of **3**. Although these signals for ^{1}H NMR spectrum also correspond to cone or partial-cone conformer, the υ_{OH} (3370 cm^{-1}) and δ_{OH} (7.42 ppm) values in **3** in which two (4-pyridylmethyl)oxy groups are located in the

same side, show a same frequency and a slightly upper-field shift, which implies that a weaker hydrogen bond does exist than that in the parent triol **1** (υ_{OH} = 3369 cm^{-1} and δ_{OH} = 8.57).[21] Although the signal for hydroxyl groups around δ 7.42 might strongly suggest cone-coformation, only a slightly lower-upfield shifts for the pyridyl protons of **3** at δ 6.86 and 8.32 than those of *cone*-**4** at δ 6.78 and 8.25 were observed. Therefore, di-*O*-substitution product **3** might adopt "partial-cone" conformation (Figure 3).

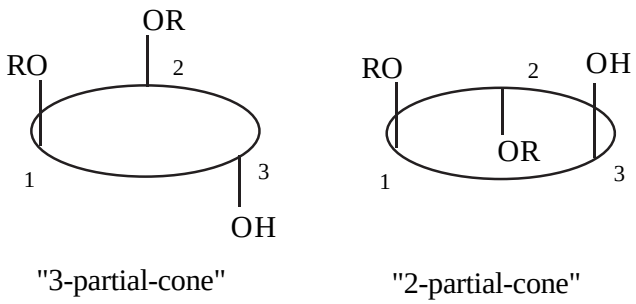

Fig. 4 Conformers possible for *partial-cone*-**3**.

Although 2-partial-cone or 3-partial-cone conformer are possible in the *partial-cone*-**3**, ^{1}H NMR spectrum of macrocycle **3** presents a set of doublet for methylene protons and pyridine protons of ArO*CH*$_2$Py. These patterns correspond to the former conformer because the methylene protons and the heteroaromatic protons of the pyridine rings of two *CH*$_2$Py groups are all in same environment, but the latter conformer should exhibit two set of doublets for these protons due to the unsymmetric structure (Figure 4). Thus, the (4-pyridylmethyl)oxy compound **3** is fixed to form a symmetric "3-partial-cone" conformation at room temperature by the observation of a set of doublets for the methylene protons and pyridine protons. Therefore, in this conformation the two (4-pyridylmethyl)oxy groups in the compound should be located in the same side of cyclophane ring, while the hydroxy group inverted into the calix cavity in favor to form intramolecular hydrogen bonding. Further studies of the structural and chemical properties of **3** and **4** are in progress.

Received 31 August 1999; accepted 26 October 1999
Paper 9/06991G

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Figs: 4

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