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REMARKABLE METAL TEMPLATE EFFECTS ON SELECTIVE SYNTHESES OF p-t-BUTYLCALIX[4]ARENE CONFORMERS

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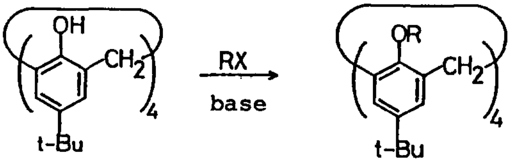
Abstract: It was found that the conformer distribution in tetra-O-substitution of p-t-butylcalix[4]arene is remarkably affected by metal species in base: in particular, 100% "cone" selectivity in the presence of Na_2CO_3 is changed to 100% "partial cone" selectivity in the presence of Cs_2CO_3 in the reaction with ethyl bromoacetate.

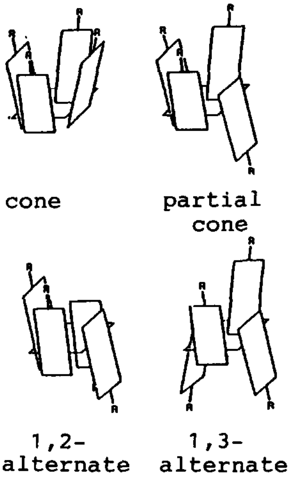
Calix[4]arenes favorably adopt a cone conformation because of strong intramolecular hydrogen-bonding interactions,[1-3] but introduction of bulky alkyl or acyl groups into the OH groups suppresses the oxygen-through-the-annulus rotation and thus results in conformational isomers.[4,5] In conformationally immobile calix[4]arenes there exist four different conformers: that is, cone, partial cone, 1,2-alternate, and 1,3-alternate. To the best of our knowledge, however, considerable confusion still exists in the conformer distribution. For example, tetra-O-propylation of p-t-butylcalix[4]arene (**1**) in the presence of NaH (the most typical method for tetra-O-substitution) affords "cone" and "partial cone" in a 1:1 ratio[5] whereas tetra-O-ethoxycarbonylmethylation under the similar reaction conditions affords only "cone".[6-9] The reason for this difference has never been explained. We carefully compared various reaction conditions and finally reached a conclusion that metal cations in base play a crucial role as a template in determining the conformer distribution. In this paper, we report several synthetic methods for new conformational isomers and discuss a possible correlation between the metal template effect and the conformer distribution.

Compound **1** (1.0 g; 1.54 mmol) in 40 ml of solvent was treated with excess RX (50 equiv.) in the presence of appropriate base. The conformer distribution of **2** was estimated by h.p.l.c. analysis. In a separate study



1

2a: R=n-Pr
2b: R=EtOCOCH$_2$



each conformer was isolated by a preparative t.l.c. method and the structures were determined from the split pattern of the ArCH$_2$Ar protons in ^{1}H n.m.r. spectroscopy.[2] Since the n-Pr and EtOCOCH$_2$ groups are bulky enough to inhibit the oxygen-through-the-annulus rotation,[5,6] 2 is conformationally immobile at room temperature. The results are summarized in Tables 1 and 2.

We used alkali carbonates as base because Li$^+$, Na$^+$, K$^+$, and Cs$^+$ salts are commercially-available. The reaction of 1 and n-PrBr in DMF in the presence of Li$_2$CO$_3$, Na$_2$CO$_3$, or K$_2$CO$_3$ did not yield 2a. The reaction product recovered from these systems was di-O-propylated 1 (identified by ^{1}H n.m.r. and elemental analysis). On the other hand, the reaction of 1 and n-PrBr in the presence of Cs$_2$CO$_3$ gave 2a in 100% yield. The yield of cone-2a is slightly higher than that obtained in the presence of NaH. Interestingly, we isolated 1,2-alternate-2a in 9% yield.[10] To the best of our knowledge, this is the first example for the synthesis of a 1,2-alternate conformer by direct O-alkylation of 1.[10]

Ba(OH)$_2$ has been used for the synthesis of tri-O-alkylcalix[4]arenes.[4] In the reaction of 1 and n-PrBr, we unexpectedly obtained "cone-shaped" tri-O-propyl-p-t-butylcalix[4]arene in the quantitative yield. O-Propylation of "cone-shaped" tri-O-propyl-p-t-butylcalix[4]arene in the presence of NaH gave cone-2a in 100% yield. This is a two-step synthetic method for cone-2a. As shown in Table 1, a trace amount of cone-2a resulted from this reaction system when the reaction was continued for a long period (70 h). This is a one-step synthetic method for cone-2a but not practical because of the low yield.

More remarkable metal template effects were observed for the reaction of 1 with ethyl bromoacetate (Table 2). It is known that the standard method using NaH as base affords only cone-2b.[1,2,6-9] The "perfect" cone selectivity was also observed for Li$_2$CO$_3$ (in DMF) and Na$_2$CO$_3$ (in acetone). Surprisingly, partial-cone-2a[12] was isolated from the reaction systems using

Table 1. Reaction of 1 with n-propyl bromide[a)]

Base(equiv. of 1)		Solvent	Temperature /°C	Time /h	Yield /%	Conformer of 2a/%		
						Cone	Partial cone	1,2-Alternate
NaH	(16)	THF	67	1	100	45	55	0
Li_2CO_3	(40)	DMF	70	78	0	0	0	0
Na_2CO_3	(40)	DMF	70	78	0	0	0	0
K_2CO_3	(40)	DMF	70	78	0	0	0	0
Cs_2CO_3	(40)	DMF	70	3	100	58	34	9
$Ba(OH)_2$ $8H_2O$ BaO	(3) (5.8)	DMF	70	70	6	100	0	0
$Ba(OH)_2$ $8H_2O$ BaO	(3) (5.8)	DMF	30	1	100[b)]	100[b)]	0	0

a) For the reaction conditions see the text. In all runs the 1,3-altenate conformer was not detected.

b) The yield of tri-O-propyl-p-t-butylcalix[4]arene.

Table 2. Reaction of 1 with ethyl bromoacetate[a)]

Base(equiv. of 1)		Solvent	Temperature /°C	Time /h	Yield /%	Conformer of 2b/%	
						Cone	Partial cone
NaH	(16)	THF	67	1	96	100	0
Li_2CO_3	(20)	DMF	70	45	22	100	0
Na_2CO_3	(20)	DMF	70	6	100	88	12
K_2CO_3	(20)	DMF	70	8	100	84	16
Cs_2CO_3	(20)	DMF	70	3	100	27	73
Li_2CO_3	(20)	Acetone	56	45	0	0	0
Na_2CO_3	(20)	Acetone	56	22	59	100	0
K_2CO_3	(20)	Acetone	56	22	99	96	3
Cs_2CO_3	(20)	Acetone	56	1	100	0	100

a) For the reaction conditions see the text. In all runs the 1,2- and 1,3-alternate conformers were not detected.

carbonate salts with large alkali metal cations. In particular, the reaction in acetone in the presence of Cs_2CO_3 afforded partial-cone-**2b** in 100% selectivity. This is the first example that a **2b** conformer other than cone is synthesized. The findings indicate that the remarkable change in the conformer distribution from 100% cone to 100% partial cone can be attained only by changing the alkili metal cations.

The foregoing results consistently indicate that the metal template effects play a crucial role in the conformer distribution. The four $EtOCOCH_2O$ groups in cone-**2b** form a closed ionophoric shell and selectively bind Na^+.[6-9] On the other hand, the three $EtOCOCH_2O$ groups in partial-cone-**2b** form an open ionophoric cavity and Cs^+ is more selectively bound to partial-cone-**2b** rather than to cone-**2b**. The difference in the metal affinity is thus reflected by the conformer distribution. The remarkable cone template effect of $Ba(OH)_2$ is explained by the strong interaction between Ba^{2+} and two phenoxide anions in di-O-alkylated **1**, keeping the four phenol units in a cone conformation.

Thus, this paper demonstrated for the first time the importance of metal template effects on the conformer distribution.

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10. Mp 279-280 °C. The ^1H NMR spectrum ($CDCl_3$, 30 °C) for the 1,2-alternate isomer is characterized by one singlet (3.85 ppm) and a pair of doublets (3.10 and 4.17 ppm) for the $ArCH_2Ar$ protons.
11. K. Iwamoto, K. Fujimoto, S. Shinkai, to be submitted.
12. Mp 203-205 °C. The ^1H NMR spectrum ($CDCl_3$, 30 °C) for the partial cone isomer is characterized by two pairs of doublets (3.13 and 4.50 ppm for one pair and 3.85 and 3.91 ppm for another pair) for the $ArCH_2Ar$ protons.

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