THE FIRST SYNTHESIS AND PROPERTIES OF HEXAHOMOTRIAZACALIX[3]ARENE

Hiroyuki Takemura,^{*a} Kazuhisa Yoshimura,^a Islam Ullah Khan,^b Teruo Shinmyozu,^b and Takahiko Inazu^{*b}

a Laboratory of Chemistry, College of General Education, Kyushu University, Ropponmatsu 4-2-1, Chuo-ku, Fukuoka, 810 Japan. b Department of Chemistry, Faculty of Science, Kyushu University, Hakozaki 6-10-1, Higashi-ku, Fukuoka, 812 Japan.

Summary: The reaction between 2,6-bis(hydroxylmethyl)-4-methylphenol and benzylamine afforded N,N',N''-tribenzyl-6,15,24-trimethyl-9,18,27-trihydroxy-2,11,20-triaza[3.3.3]metacyclophanes.

In the present communication, we describe a new cyclization procedure leading to a predominant synthesis of trihydroxytriaza[3.3.3]metacyclophane (<u>1a</u>: hexahomotriazacalix[3]arene). The compound is an aza analog of oxacalixarene. Oxacalixarene was first reported in 1962,¹ as a reaction product of the condensation of *p*-alkylphenol and formaldehyde. Characterization and conformational properties have also been described in detail.² Condensation reaction between 2,6-bis(hydroxylmethyl)-4-methylphenol and

benzylamine has been reported to give dihydrobenzoxazine derivative. Besides this compound, the isomeric cyclic structure (Figure 1) was also considered.³ But the possibility of the cyclic structure was not confirmed. By reinvestigating the reaction and identifying the product, we found that the product has triaza[3.3.3]cyclophane structure.

Synthesis: A mixture of 2,6-bis(hydroxymethyl)-4-methylphenol (12.0 g, 71.3 mmol) and benzylamine (7.7 g, 72 mmol) in 500 mL of toluene was refluxed for 24 hr, water generated being removed during the course of the reaction. After evaporating toluene, the residual oily material was heated at



Scheme I.



135 °C for additional 24 hr. After cooling the reaction mixture, it was dissolved in 200 mL of methanolacetone mixture (4:1) and left to stand overnight. The precipitate was washed with acetone-methanol mixture. Recrystallization of the resulting yellow powder from benzene-methanol mixture (5:1) afforded <u>1a</u> CH₃OH as pale yellow powder (6.77 g, 38 %).

The cyclophane <u>1a</u> (hexahomotriazacalix[3]arene) was identified by means of ¹H-NMR, FD-Mass and elemental analysis.⁴ FD mass spectrum of this material showed characteristic parent ion peak (M⁺), and the peak which shows the monomeric structure (Figure 1) was not detected. Starting from 2,6-bis-(hydroxymethyl)-*p*-tert-butylphenol, or linear bishydroxymethyl compounds, <u>4</u>, <u>5</u>, analogous azacalixarenes <u>1b</u>, <u>2</u> and <u>3</u> were obtained in satisfactory yields, respectively.⁵

The phenolic OH group which activates the hydroxymethyl group is essential for carbon nitrogen bond formation as in the case of calixarene formation. Actually, the reaction between 2,6-bis(hydroxylmethyl)-p-tert-butylbenzene and benzylamine was also attempted, but only the starting materials were recovered. Predominant trimer formation occurs by template effect of the hydrogen bonding among three OH groups in nonpolar solvent such as toluene. To confirm this speculation, we carried out the reaction in a mixture of toluene/pyridine (70/30), in which the hydrogen bonding among OH groups is completely broken. Resultant viscous oil was a mixture of the starting materials and acyclic compounds. Cyclic trimer formation was not observed. From a space filling model consideration, the cavity size of 1a is ca. 2.0 Å

 Table I. IR and NMR data of hydroxyl group.

 a-- CHCl₃ or CDCl₃ solution; cited from

Ref.2c

b-- KBr disk(IR) and CDCl₃ solution.

	ν _{OH} (cm ⁻¹)	δ(ppm)
Calix[4]arene ^a	3160	10.2
Calix[6]arene ^a	3150	10.5
Calix[8]arene ^a	3230	9.6
Oxacalixarene ^a	3410	8.5
Azacalixarene ^b <u>1a</u>	2800	11.1
<u>1b</u>	2800	11.2
<u>2</u>	3000	10.7
<u>3</u>	2700	11.6

and almost the same as that of calix[5]arene. Three phenolic OH groups are oriented toward the center of the cavity and the molecule is flexible enough to provide a planar or a bowl shape structure. In ¹H-NMR spectrum, the OH signal appears at 11.1 ppm as a broad singlet (CDCl₃). In the IR spectrum, the O-H vibrational mode appears in the region of 3000-2600 cm⁻¹ as a very broad band. The spectral data of the phenolic hydroxyl groups of calixarenes and hexahomotrioxacalix[3]arene are summarized in Table I together with those of <u>1a</u>, <u>1b</u>, <u>2</u> and <u>3</u>. The spectra show that the hydrogen bonds in azacalixarenes are stronger than those in calix[n]arene or oxacalixarene series.^{2c} The nitrogen atom is a good proton accepter. Thus, in the case of azacalixarenes, the hydrogen bonds in the cavity exist not only between OH groups but also among OH and nitrogens.

Complexation with metal ions: In the case of calixarenes, metal ions bind only under basic conditions.⁶ Azacalixarene <u>la</u> complexed with alkali and alkaline-earth metal ions under neutral conditions, but the

120 к¹ Ba²⁺ 100 Distribution Ratio × 100 80 2 Sr 60 Са Rb⁺ 40 Na 20 Cs¹ 1.0 0.2 2.0 Ionic Radii (Å)

complexation ability was very weak. The results of metal picrate extraction experiments⁷ are shown in Figure 2. Compound <u>1a</u> binds selectively to potassium and barium ions.

Figure 3. Plots of distribution ratio of uranyl ion in CHCl₃ vs. pH. [Host] = 4.9×10^{-4} M, $[UO_2^{2+}] =$ 10 ppm, [NaCl] = 0.50 M, 25 °C. Buffer; HCl/AcOH, AcONa/AcOH, NH₃/NH₄⁺.

Figure 2. Plots of distribution ratios of metal picrates in CHCl₃ vs. ionic radii of alkali and alkaline earth metal ions. [Pic⁻] = 7.0×10^{-4} M, [M⁺] = 0.10 M, [Host] = 1.0×10^{-3} M, pH = 6, 25 °C.

Complexation between uranyl ion $(UO_2^{2^+})$ and <u>1a</u> was also studied because <u>1a</u> has coordination sites and geometry similar to those in calix[5]-, or -[6]arene. The calix[5]- and -[6]arene derivatives are known to be excellent uranophiles. Shinkai et al.⁸ reported that the planar coordinating sites of calix[5]- and -[6]arene derivatives gave high selectivity for uranyl ion. Uranyl ion extraction was carried out from diluted aqueous $UO_2^{2^+}$ solution (10 ppm) in the presence of high concentration of NaCl (0.5 M) at various pH into chloroform.⁹ The results are shown in Figure 3. In the presence of <u>1a</u>, $UO_2^{2^+}$ ion is effectively extracted into organic phase from aqueous phase in a neutral region (pH = 6 ~ 7) but not under acidic and alkaline conditions. Even in the presence of high concentration of sodium ion, pH dependent and relatively strong complexation between uranyl ion and <u>1a</u> was observed. These properties are applicable to liquid-liquid transport of uranyl ion.

References

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- (4) Compound <u>1a</u>: ¹H NMR (270MHz, CDCl₃) δ 11.1(bs, 3H, OH), 7.28(s, 15H, aromatic), 6.86-6.62(m,



6H, aromatic), 3.61(s, 6H, CH_2Ph), 3.48(s, 12H, CH_2N), 2.17(s, 9H, CH_3 -Ar); FD-Mass m/z (rel intensity) 717(M⁺, 100), 628(10), 598(3), 478(3); m.p. 204-206 °C. Anal. Calcd for $C_{48}H_{51}N_3O_3$ •CH₃OH C; 78.46, H; 7.41, N; 5.60. Found C; 78.34, H; 7.11, N; 5.24.

(5) These compounds were identified by means of ¹H NMR, FD-MS spectra and elemental analyses. The details of the data will be described elsewhere.



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(7) Solvent extraction experiments were carried out as follows. Water-saturated chloroform solutions of the ligand $(1.0 \times 10^{-3} \text{ M}, 10 \text{ mL})$ and aqueous solutions of each metal picrate $(7.0 \times 10^{-4} \text{ M}, 10 \text{ mL})$ were introduced into teflon-sealed vials, which were magnetically stirred for 12 hr at 25 ± 0.1 °C. Prolonged time of stirring (24 hr) gave identical results. The resulting mixture were allowed to stand for overnight at the temperature in order to complete the phase separation. Picrate concentration in chloroform was determined spectrophotomecally at the absorption maximum, 374 nm.

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(9) Uranyl ion extraction experiments were carried out as follows. Water-saturated chloroform solutions of the ligand (4.9×10^{-4} M, 10.0 mL) and buffered uranyl solutions (40.0 mL) containing 10 ppm of uranyl ion and 0.5 M of NaCl, were introduced into Erlenmeyer flasks, which were then stoppered and magnetically stirred for 12 hr at 25 ± 0.1 °C. After the complete phase separation (12 hr later), the uranyl concentration in aqueous phase was determined spectrophotometrically with chlorophosphonazo III as a colorling agent.¹⁰

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