Tetrahedron Vol 45, No 7, pp 2177 to 2182, 1989
Printed in Great Britain

0040-4020/89 $3 00+ 00

CHLOROMETHYLATION OF CALIXARENES AND SYNTHESIS OF NEW WATER SOLUBLE MACROCYCLIC HOSTS

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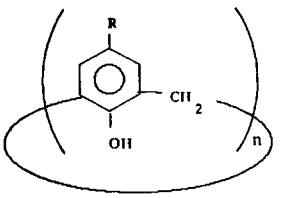
(*Received in UK* 30 *December* 1988)

Abstract - The chloromethylation of calix[4]arene **1a** and of the methyl ethers of calix[6]arene **1b** and calix[8]arene **1c**, using chloromethyl n-octyl ether and $SnCl_4$ in chloroform at room temperature has been performed in good yield for the first time. The chloromethylated products **2a-c** have been used as intermediates to introduce on calixarenes phosphonic acid groups which render these macrocycles water soluble and potentially useful in Host Guest Chemistry.

The functionalization of calixarenes (I) both at the phenolic oxygen and on the aromatic nucleus have attracted our attention and that of several research groups because of the possibility of easily obtaining new host molecules for the complexation of ions and neutral molecules.[1]



(I)

n= 4-8

A particular type of functionalization is that which leads to water soluble calixarenes, because it allows to study in solution the inclusion behaviour of these macrocycles toward organic neutral molecules which has been well documented in the solid state.[2]

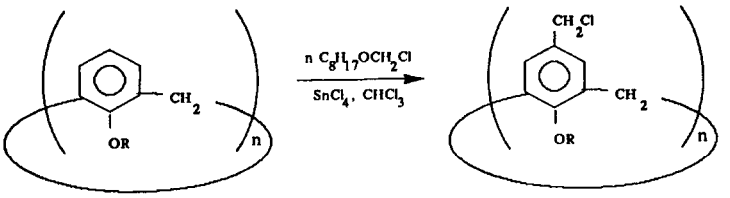
We have first synthesized a water soluble calixarene[3] by introducing four carboxy methyl groups on the phenolic oxygens of p-t-butylcalix[4]arene, then Shinkai[4] and Gutsche[5] have reported on the synthesis and complexing properties of different types of water soluble calixarenes.

In view of this general interest we have explored new synthetic procedures for the functionalization of calixarenes which eventually could allow the easy introduction of ionizable functional groups. We report in this paper the chloromethylation of calixarenes (tetramer, hexamer, octamer) and the synthesis of water soluble calixarene-p-phosphonates *via* chloromethylated compounds.

Chloromethylation of calixarenes

Gutsche and co workers[5-7] have extensively studied the problem of functionalization of calixarenes on the "upper rim" which allows to introduce useful functional groups at this position but nobody has attempted so far the chloromethylation of these macrocycles, a reaction which is rather common in the chemistry of aromatic compounds and could lead to very useful intermediates.

The starting materials, calix[n]arenes, were easily obtained by de-butylation of p-t-butylcalix[n]arenes by known methods.[6,8] Calix[4]arene (1a, n=4, R=H) was used as such whereas the calix[6]- and calix[8]arene, which are very poorly soluble[8] in most organic solvents, were used as their methyl ether derivatives (1b, n=6, R=CH_3) and (1c, n=8, R=CH_3).[6]



(1 a–c)

a n=4, R=H
b· n=6; R=CH_3
c n=8, R=CH_3

(2 a–c)

In order to avoid the use of the dangerous chloromethyl-methyl ether a procedure introduced by Warshawsky[9] for the chloromethylation of styrene-divinyl benzene polymers, was used. The yields of chloromethylated products 2 is reported in the Table.

The reaction conditions are very mild and this allows the obtainement of chloromethylated calix[4]arene 2a in good yields, without protecting the phenolic OH groups. Longer reaction times or higher temperatures lower considerably the yield of compound 2a. This compound exists mainly in the cone conformation in $CDCl_3$ at room temperature as inferred from the ^1H NMR spectrum which shows two broad signals centered at 3.54 and δ 4.17 ppm ($ArCH_2Ar$) and from the sharp OH absorption at δ 10.1 ppm which indicates intramolecular H bonding.[1]

Compound 2a is very reactive, expecially under basic conditions, because it easily looses HCl to give the correspondent p-quinone methide which eventually undergoes several transformations.[7,10]

Analytically pure samples of 2a, obtained by preparative HPLC on a C18 column, could not be chromatographed without decomposition on silica gel or alumina and did not give the correct mass spectrum under electron impact or chemical ionization.

However the high reactivity of this compound has been exploited for the synthesis of several new p-substituted calix[4]arenes,[11] through a procedure which can be considered complementary to the p-quinone methide route to functionalized calixarenes, recently reported by Gutsche and co-workers.[7]

For example by treating compound 2a with $LiAlH_4$ in THF, p-methylcalix[4]arene 3 could be isolated in 80% yield, whereas the yield of compound 3 was much lower with Gutsche's procedure.[7]

Table. Yields of chloromethylated calixarenes 2 and calixarene-p-phosphonic acids 6[+]

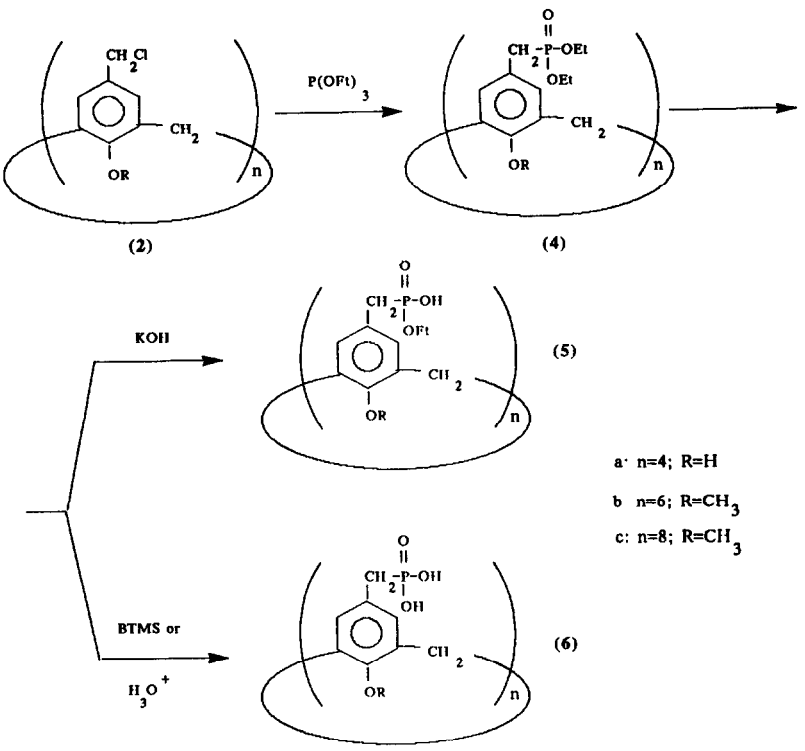
Starting materials	Yield of 2 %	Yield of 6 %
1a (n=4, R=H)	80 (2a)	64 (6a)
1b (n=6, R=CH_3)	90 (2b)	75 (6b)
1c (n=8, R=CH_3)	92 (2c)	73 (6c)

[+] The yield is based on the starting compounds 1a-c.

The protected chloromethyl derivatives of calix[6]- 2b and calix[8]arene 2c are more stable and, as most ethers of these two macrocycles,[8,12] show only singlets in their ^1H NMR spectra indicating a higher degree of conformational mobility in solution compared with 2a.

Calixarene-p-phosphonates

The reaction of chloromethylated calixarenes 2 with triethyl phosphite in the classical conditions of the Arbuzov reaction[13] followed by treatment of the crude diesters 4 with strong acids or with bromotrimethylsilane (BTMS)[14] gives the phosphonic diacids 6 in good yields (see Table).



Basic hydrolysis affords easily the monoacid monoesters 5. By titration with the proper base the phosphonic acids 5 and 6 are transformed in their alkali metal salts which are soluble in water up to about 10^{-1} M concentration. The ^{1}H NMR spectra of the sodium salts of compounds 6 in D_2O shows broad singlets for the bridging methylene groups ($ArCH_2Ar$) in the region of δ 3.9-4.2 ppm which indicate mobile structures for these compounds at room temperature.

The results reported in this paper open new perspectives in calixarene functionalization. In particular via the key chloromethyl intermediates 2 several interesting new host macrocycles with extended hydrophobic cavities can be synthesized.[11]

Moreover a new type of water soluble macrocycles of different sizes, bearing phosphonic acid groups on the "upper rim" of calixarenes and potentially useful in Host Guest Chemistry, have been synthesized.

EXPERIMENTAL

Mass spectra were recorded on a Finnigan MAT 8400 spectrometer using DCI technique (isobutane) either positive (DCI+) or negative (DCI-).[15]

^{1}H NMR spectra were recorded at 200 Hz (CXP200 Bruker) or at 100 Hz (AC100 Bruker) in $CDCl_3$ with TMS as internal standard. Chemical shifts (δ) are expressed in ppm. IR spectra were recorded on a Perkin Elmer Mod. 298 instrument. HPLC analyses were performed on a Waters Associates Model 440 using a μ-Bondapak C18 column and the conditions reported in literature.[16] Analytical TLC was carried out on precoated Merck silica gel plates. Column chromatography was performed using silica gel 60 (Merck, 230-400 mesh ASTM).

Elemental analyses were performed at the Istituto di Chimica Farmaceutica of the University of Parma. The chlorine content in compounds (2) was established by argentometric titration after combustion of the samples in an oxygen flask.[17]

The phosphorous content of compounds (6) was established using known methods.[17,18] The nomenclature proposed by Gutsche[19] for calixarenes have been used.

Chemicals. ACS grade reagents were used without further purification.[9] Chloromethyl-n-octyl ether was prepared according to literature methods.[7] Methyl ethers of calix[6]arene (1b) and calix[8]arene (1c) were prepared according to Gutsche's procedure.[7]

5,11,17,23-Tetrachloromethyl-25,26,27,28-tetrahydroxycalix[4]arene (2a). To a solution of 1.0 g (2.4 mmol) of calix[4]arene (1a) and 14.4 g (81 mmol) of chloromethyl-n-octyl ether in 100 ml of $CHCl_3$, cooled at -10°C, 4.7 ml (40.3 mmol) of $SnCl_4$ were added dropwise in about 15 min. The cooling bath was removed and the reaction mixture stored at room temperature for additional 50 min, when all the starting compound (1a) has reacted (TLC, hexane:ethyl acetate = 4:3). Water was then added slowly and the two phases separated.

The organic layer was washed twice with distilled water, dried over Na_2SO_4 and evaporated to give a residue which was treated with n-hexane and filtered to give 1.23 g (80%) of a compound which shows a good degree of purity on HPLC (95%). An analytically pure sample could be obtained by preparative HPLC in the same conditions. The compound decomposes before melting.

IR (KBr) 3200 (OH), 1300 and 710 cm^{-1} (CH_2Cl); ^{1}H NMR ($CDCl_3$) δ 3.54 (bs, 4H, $ArCH_2Ar$), 4.17 (bs, 4H, $ArCH_2Ar$), 4.40 (8H, s, $ArCH_2Cl$), 7.09 (s, 8H, ArH), 10.12 (4H, s, OH). ^{13}C NMR ($CDCl_3$) 31.6 (t, $ArCH_2Ar$), 45.8 (t, $ArCH_2Cl$), 128.3 (s, Ar-ortho), 129.5 (d, Ar-meta), 131.4 (s, Ar-para), 148.9 (s, ArO). Anal Calcd for $C_{32}H_{28}O_4Cl_4$: C, 62.12; H, 4.56; Cl, 22.94. Found C, 62.60; H, 5.00; Cl, 22.35.

5,11,17,23-Tetramethyl-25,26,27,28-Tetrahydroxycalix[4]arene (3). 1.23 g (2 mmol) of (2a) were dissolved in dry THF (100 ml) under a nitrogen atmosphere, treated with 0.19 g (5 mmol) of $LiAlH_4$ stirred at room temperature for 2 h.

After the addition of ethyl acetate to destroy the excess of $LiAlH_4$, and treatment with diluite HCl, the reaction mixture was extracted with CH_2Cl_2, the solvent evaporated and the solid residue submitted to column chromatography (Silica gel, CH_2Cl_2) to give compound (3) which showed the same spectral data reported in literature.[7,20]

5,11,17,23-Tetrakis(Dihydroxyphosphonoyl)methyl-25,26,27,28-Tetrahydroxycalix[4]arene (6a). 1g (1.6 mmol) of (2a) was refluxed for 6 h with 20 ml of $P(OEt)_3$. The triethyl phosphite in excess was then distilled and the solid residue dried under vacuum for 8 h. 60 ml of 20% HCl were added and the reaction mixture refluxed for 20 h, then most of the solvent was evaporated and the precipitate filtered, whashed with methanol and subsequently with $CHCl_3$ and dried under vacuum to give 1.11 g (80%) of a white solid: m.p. 360°C. Anal Calcd for $C_{32}H_{36}O_{16}P_4$: C, 48.02; H, 4.53; P, 15.47. Found C, 48.10; H, 4.62; P, 15.00.

The dry solid was suspended in water and potentiometrically titrated with 0.05 N NaOH solution until the first equivalence point was observed and the pH reached the value of 7.5 which resulted in the salification of the first OH group of the phosphonic acid (6a) and in the complete dissolution of the suspended solid.

The solvent was then removed completely and the solid residue dried under vacuum for 24 h. m.p. 360°C, ^1H NMR (D_2O) δ 2.64 (d, 8H, $-CH_2P$, J_{HP} = 18 Hz), 3.60 (bs, 8H, $ArCH_2Ar$), 6.80 (bs, 8H, ArH).

5,11,17,23,29,35-Hexachloromethyl-37,38,39,40,41,42-Hexamethoxycalix[6]arene (2b). Via the procedure described for (2a), 1.9 g (2.64 mmol) of hexamethoxycalix[6]arene was treated with 32 g (180 mmol) of chloromethyl-n-octyl ether and 8 ml (67.2 mmol) of $SnCl_4$ and reacted for 1 h. After crystallization from $CHCl_3$-MeOH 2.3 g (90%) of pure compound (2b) was obtained as white powder: m.p. 273-275°C, IR (KBr) 1290 and 710 cm^{-1} (CH_2Cl); ^1H NMR ($CDCl_3$ δ 3.69 (18H, s, OCH_3), 3.93 and 3.96 (24H, two s, $ArCH_2Ar$ and $ArCH_2Cl$); 6.76 (12H, s, ArH); ^{13}C NMR ($CDCl_3$) δ 30.1 (t, $ArCH_2Ar$), 45.9 (t, $ArCH_2Cl$), 61.0 (q, OCH_3), 129.36 (d, Ar-meta), 133.4 (s, Ar-ortho), 134.3 (Ar-para), 156.2 (ArO); DCI-MS(-) m/e 1008 (M^-, 86%), 1010 (M+2, 100%), 1012 (M+4, 70%). Anal. Calcd. for $C_{54}H_{54}O_6Cl_6$: C, 64.11; H, 5.38; Cl, 21.02. Found C, 64.35; H, 5.04; Cl, 20.55.

5,11,17,23,29,35-Hexakis (Dihydroxyphosphonoyl methyl)-37,38,39,40,41,42-Hexamethoxycalix[6]arene (6b). 1.0 g (1 mmol) of (2b) was refluxed for 5 h with 20 ml of $P(OEt)_3$. After the complete removal of the triethyl phosphite in excess under vacuum, the solid residue was treated under a nitrogen athmosphere with 5 ml of bromotrimethylsilane (BTMS) and stirred at room temperature for 5 h. Most of the BTMS was there removed under vacuum and water was added slowly to the reaction mixture. The precipitate which forms is filtered, whashed with water, methanol and $CHCl_3$ and finally dried under vacuum, to give 1.06 g/83%) of a white solid: m.p. > 360°C. Anal. Calcd. for $C_{54}H_{66}O_{24}P_6$: C, 50.47; H, 5.18; P, 14.46. Found: C, 50.20; H, 5.10; P, 14.10.

The dry solid was suspended in water and potentiometrically titrated with 0.05 N NaOH solution until the first equivalence point was observed and the pH reached the value of 7.5.

The solvent was then removed completely and the solid residue dried under vacuum for 24 h. m.p. 350°C; ^1H NMR (D_2O) δ 2.84 (12H, d, CH_2P, J_{HP} = 19.6 Hz), 3.15 (18H, s, $ArOCH_3$); 3.95 (12H, s, $ArCH_2Ar$), 6.98 (12H, s, ArH).

5,11,17,23,29,35,41,47-Octachloromethyl-49,50,51,52,53,54,55,56- Octamethoxycalix[8]arene (2c). Via the procedure described for (2a), 1.15 g (1.2 mmol) of octamethoxycalix[8]arene was treated with 17.0 g (95 mmol) of chloromethyl octyl ether and 4.5 ml (38 mmol) of $SnCl_4$ and stirred for 1 h. Recrystallization of the crude product from acetonitrile gave 1.554 g (92%) of (2c): m.p. 230°C dec., IR (KBr) 1295 and 710 cm^{-1} (CH_2Cl); ^1H NMR ($CDCl_3$) 3.55 (24H, s, OCH_3), 4.0 (16H, s, $ArCH_2Ar$); 4.3 (16H, $ArCH_2Cl$), 6.9 (s, 16H, ArH); ^{13}C NMR ($CDCl_3$) δ 30.3 (t, $ArCH_2Ar$), 46.3 (t, $ArCH_2Cl$), 61.1 (q, OCH_3), 129.6 (d, Ar-meta), 133.3 (Ar-ortho), 134.5 (Ar-para), 158.9 (ArO); DCI-MS(-) m/e 1344(M, 26%), 1346(M+2, 78%), 1348(M+4, 100%), 1350(M+6, 84%). Anal. Calcd. for $C_{72}H_{72}O_8Cl_8$: C, 64.11; H, 5.38; Cl, 21.02. Found: C, 64.40; H, 5.15; Cl, 20.80.

5,11,17,23,29,35,41,47-Octakis (ethoxyhydroxyphosphonoyl)methyl-49,50,51,52,53,54,55,56-Octamethoxycalix[8]arene (5c). 1.0g (0.7 mmol) of compound (2c), in 20 ml of $P(OEt)_3$ was refluxed for 5 h. The solid residue which was obtained after evaporation of the triethyl phosphite under vacuum was suspended in 15 ml of NaOH 10% and refluxed for 5 h. The solution was made acidic with HCl and extracted with methylene chloride.

The combined organic extracts were washed with water and reduced to a volume of about 10 ml. This CH_2Cl_2 solution was then poured with stirring, in 100 ml of n-hexane which causes the precipitation of a solid compound. Recrystallization from $CHCl_3$-hexane gave 0.97 g (72%) of a white powder: m.p. > 350°C; ^{1}H NMR ($CDCl_3$) δ 1.2 (24H, t, $OCH_2\underline{CH_3}$), 2.9 (16H, d, $ArCH_2P$, J_{HP} = 20 Hz); 3.5 (24H, s, OCH_3), 3.6-4.2 (32H, m, $ArCH_2Ar$ + $O\underline{CH_2}CH_3$), 6.8 (16H, bs, ArH), 8.0 (8H, bs, OH). Anal Calcd. for $C_{88}H_{120}O_{32}P_8$: C, 54.55; H, 6.24; P, 12.79. Found: C, 54.30; H, 6.35; P, 12.10.

Titration of the monoacid (5a) with 0.05 N NaOH solution up to pH 7.5 and evaporation of the solvent gave the sodium salt of (5) which is water soluble. M.p. > 350°C, ^{1}H NMR (D_2O) δ 1.0 (24H, t, $OCH_2\underline{CH_3}$), 2.8 (16H, d, CH_2P, J_{HP} = 20 Hz), 3.30 (24H, s, OCH_3), 3.65 (16H, bq, $\underline{OCH_2}CH_3$), 3.9 (16H, s, $ArCH_2Ar$), 6.9 (16H, s, ArH).

5,11,17,23,29,35,41,47-Octakis (dihydrophosphonoyl)methyl- 49,50,51,52,53,54,55,56-Octamethoxycalix[8]arene (6c). Via the procedure described for (6b) compound (6c) was obtained from (2c) in 80% yield. m.p.> 350°C. The monosodium salt prepared as described for (6b) is water soluble.

^{1}H NMR (D_2O) δ 2.9 (16H, d, $ArCH_2P$, J_{HP} = 10 Hz), 3.5 (24H, s, OCH_3); 4.0 (16H, s, $ArCH_2Ar$), 7.0 (16H, s, ArH).

Acknowledgements - We are grateful to Consiglio Nazionale delle Ricerche (C.N.R., Roma) and to Ministero della Pubblica Istruzione for financial support. We thanks also Mrs. Paola Pedretti for typing the manuscript and Mr. Bruno Bottarelli for the drawings.

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