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SYNTHESIS OF *p*-ALKYLCALIXARENES BY FRIEDEL-CRAFTS ALKYLATION

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Abstract: Calix[n]arenes **1** - **3** (n = 4, 6 and 8) were alkylated with alkyl chlorides in the presence of anhydrous aluminium chloride in chloroform by Friedel-Crafts reaction to give *p*-alkylcalix[n]arenes **5** - **7** (n = 4, 6 and 8) in good to excellent yields.

Calixarenes are cavity containing macrocyclic compounds which are attracting increasing interest because of their potential for forming host-guest complexes and acting as enzyme mimics. Calixarenes with different *p*-alkyl groups will change their cavity structure, and the inclusion properties of *p*-alkylcalixarenes may be changed or improved. Calixarenes can be synthesized by both one-step, base induced synthesis and by multi-step synthesis. The latter method is tedious and the overall yield is quite low. The one-step synthesis by base-induced condensation of *p*-alkylphenol with formaldehyde has been widely investigated [1-7], but only a few *p*-alkylphenols , such as *p-tert*-butylphenol, give satisfactory results.

By the proper choice of reaction conditions *p-tert*-alkylcalix[n]arenes (n = 4, 6 and 8) can be easily prepared in good yields by the base-induced condensation of *p-tert*-butylphenol with formaldehyde [1,8]. As aluminium chloride-catalyzed removal of the *tert*-butyl group proceeds in excellent yields [9,10], calixarenes **1** - **3** are readily available starting materials for the introduction of alkyl groups into the

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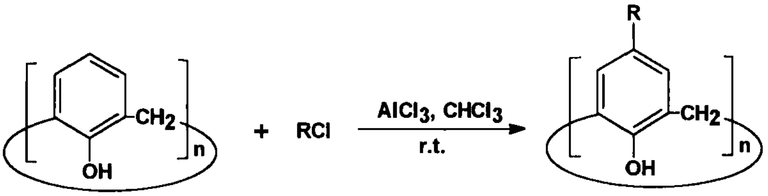
calixarene framework. The synthesis of *p*-alkylcalixarenes starting from **1** through chloromethylation then with methyllithium [11] or starting from **1** - **3** through acylation then reduction [12] has been reported. Herein, we wish to report a more facile method for synthesis of *p*-alkylcalixarenes by Friedel-Crafts alkylation.

Calixarenes **1** and **2** were readily reacted with alkyl chlorides in the presence of anhydrous aluminium chloride in chloroform to give *p*-alkylcalixarenes **5** and **6** in good to excellent yields. However, calixarene **3** showed some difference, i.e. **3** reacted sluggishly with primary alkyl chloride **4b**, and with **4a** , only a lower yield of **7a** was obtained. This may be due to the poor solubility of **3** in chloroform. When *n*-butyl (**4b**) or *sec*-butyl chloride (**4c**) was used as alkylating agent, the *p*-positions of calixarenes were substituted with *sec*-butyl or *tert*-butyl group,



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1, n = 4 **5**, n = 4

2, n = 6 **6**, n = 6

3, n = 8 7, n = 8

4	**a**	**b**	**c**	**d**
R	$(CH_3)_2CH$	$CH_3(CH_2)_3$	$CH_3CH_2(CH_3)CH$	$CH_3CH_2(CH_3)_2C$
4	**e**	**f**	**g**	
R	$CH_3(CH_2)_3(CH_3)_2C$	$CH_3(CH_2)_5(CH_3)_2C$	$CH_3(CH_2)_9(CH_3)_2C$	
5 - 7	**a**	**b**	**c**	**d**
R′	$(CH_3)_2CH$	$CH_3CH_2(CH_3)CH$	$(CH_3)_3C$	$CH_3CH_2(CH_3)_2C$
5 - 7	**e**	**f**	**g**	
R′	$CH_3(CH_2)_3(CH_3)_2C$	$CH_3(CH_2)_5(CH_3)_2C$	$CH_3(CH_2)_9(CH_3)_2C$	

which could be obviously demonstrated by the ^{1}H-NMR spectrum. It is easily realized that the first formed primary or secondary carbonium cation is isomerized to the more stable secondary or tertiary carbonium cation, respectively.

From the experimental facts, it is clearly indicated that the reactivity of alkyl chlorides is in the following order: tertiary alkyl chloride > secondary alkyl chloride > primary alkyl chloride. Somewhat low reactivity of tertiary long chain alkyl chlorides is due to steric factors.

From the ^{1}H-NMR data, *p*-alkyl substitution is indicated by the singlet of two aromatic protons of all the **5** - **7**. For **5**, a pair of doublets of methylene protons indicate that the calix[4]arenes **5** are in the cone conformation. A singlet for methylene protons of *p*-alkylcalix[6]arene **6** and a pair of doublets for methylene protons of *p*-alkylcalix[8]arenes **7** at room temperature are also recorded in early literature [1]. A comparable lower field shift of the OH group in the ^{1}H-NMR spectra of calix[4]arenes **5** and calix[6]arenes **6** (10.28 - 10.48 ppm) than that of calix[8]arenes **7** (9.43 - 9.64 ppm) and the lower frequency of stretching vibration of the OH group in the IR spectra of **5** and **6** (3142 - 3160 cm^{-1}) than that of **7** (3200 - 3220 cm^{-1}) may be due to the stronger intramolecular hydrogen bond in **5** and **6** than that of **8**.

Experimental

Melting points are uncorrected. ^{1}H-NMR spectra were recorded with a Varian Unity 200 spectrometer. IR spectra were recorded on a Perkin- Elmer 782 spectrometer for KBr tablets. Elemental analyses were performed by the Analytical Laboratory of the Institute. Due to solvent inclusion, satisfactory elemental analysis is always difficult for calixarenes, and the samples should be treated by heating under vaccum for some time, even at 180°C as long as 48h for some calix[4]arenes and calix[6]arenes. Calixarenes **1** - **3** were prepared according to the literature. Alkyl chlorides **4e** - **4g** were prepared by the reaction of the corresponding alcohols with concentrated hydrochloride acid.

General Procedure for the Synthesis of p-Alkylcalixarenes **5 - 7**.

To a solution of 0.20 g of **1 - 3** (1.89 mili-equivalent of phenol-methylene unit) and 1.5 - 3 mmol of alkyl chloride **4** in 6 ml of dried chloroform was added 0.20 g (1.5 mmol) of anhydrous aluminium chloride. The reaction mixture was stirred at room temperature for a given time and monitored by TLC. Then it was worked up by addition of water (10 ml) and the organic layer was washed with water. After removal of the solvent to ca. 1 ml, methanol (20 ml) was added to give a powder product. The crude product was purified by recrystallization from chloroform-methanol, if no other purification procedure is indicated.

25,26,27,28-Tetrahydroxy-5,11,17,23-tetrakis(1-methylethyl)calix[4]arene (**5a**)[6].

Reaction time, 4h. Yield, 87%. M.p. > 300°C. IR (KBr): ν = 3145 (OH), 1598, 1470 cm^{-1}. ^{1}H-NMR (CDCl$_3$): δ = 10.28 (4H, s), 6.89 (8H, s), 4.22 (4H, d), 3.47 (4H, d), 2.71 (4H, sep), 1.14 ppm (24H, d). Anal. calcd. for $C_{40}H_{48}O_4$ (592.8): C 81.04, H 8.16; found C 80.62, H 8.39.

25,26,27,28-Tetrahydroxy-5,11,17,23-tetrakis(1-methylpropyl)calix[4]arene (**5b**).

Reaction time, 10h. Yield, 78%. M.P. > 300°C. IR (KBr): ν = 3142 (OH), 1592, 1464 cm^{-1}. ^{1}H-NMR (CDCl$_3$): δ = 10.32 (4H, s), 6.84 (8H, s), 4.22 (4H, d), 3.50 (4H, d), 2.40 (4H, sex), 1.47 (8H, quin), 1.12 (12H, d), 0.78 ppm (12H, t). Anal. calcd. for $C_{44}H_{56}O_4$ (648.9): C 81.44, H 8.70; found C 81.43, H 8.69.

5,11,17,23-Tetrakis(1,1-dimethylethyl)-25,26,27,28-tetrahydroxycalix[4]arene (**5c**)[1].

Reaction time, 30 min, the product could be directly filtered from the reaction mixture. Yield, 92%. M.p. > 300°C. IR (KBr): ν = 3160 (OH), 1600, 1478 cm^{-1}. ^{1}H-NMR (CDCl$_3$): δ = 10.35 (4H, s), 7.05 (8H, s), 4.25 (4H, d), 3.50 (4H, d), 1.21 ppm (36H, s). Anal. calcd. for $C_{44}H_{56}O_4$ (648.9): C 81.44, H 8.70; found C 81.30, H 8.69.

5,11,17,23-Tetrakis(1,1-dimethylpropyl)-25,26,27,28-tetrahydroxycalix[4]arene **(5d)**[4,6].

Reaction time, 15 min. Yield, 95%. M.p. > 300°C. IR (KBr): ν = 3160 (OH), 1598, 1476 cm^{-1}. ^1H-NMR ($CDCl_3$): δ = 10.37 (4H, s), 7.04 (8H, s), 4.25 (4H, d), 3.50 (4H, d), 1.54 (8H, q), 1.21 (24H, s), 0.67 ppm (12H, t). Anal. calcd. for $C_{48}H_{64}O_4$ (705.0): C 81.77, H 9.15; found C 81.48, H 9.14.

5,11,17,23-Tetrakis(1,1-dimethylpentyl)-25,26,27,28-tetrahydroxycalix[4]arene **(5e)**.

Reaction time, 2h. Yield, 75%. M.p. 76-77°C. IR (KBr): ν = 3160 (OH), 1599, 1460 cm^{-1}. ^1H-NMR ($CDCl_3$): δ = 10.33 (4H, s), 6.98 (8H, s), 4.24 (4H, d), 3.50 (4H, d), 1.16 (24H, s), 0.60 - 1.60 ppm (36H, m). Anal. calcd. for $C_{56}H_{80}O_4$ (817.2): C 82.30, H 9.87; found C 82.14, H 9.48.

5,11,17,23-Tetrakis(1,1-dimethylheptyl)-25,26,27,28-tetrahydroxycalix[4]arene **(5f)**.

Reaction time, 2h. Yield, 74%. M.p. 53-54°C. IR (KBr): ν = 3155 (OH), 1598, 1460 cm^{-1}. ^1H-NMR ($CDCl_3$): δ = 10.32 (4H, s), 6.97 (8H, s), 4.21 (4H, d), 3.52 (4H, d), 1.12 (24H, s), 0.62 - 1.56 ppm (52H, m). Anal. calcd. for $C_{64}H_{96}O_4$ (929.4): C 82.70, H 10.41; found C 82.25, H 9.37.

5,11,17,23-Tetrakis(1,1-dimethylundecyl)-25,26,27,28-tetrahydroxycalix[4]arene **(5g)**.

Reaction time, 2h, the crude product was recrystllized from chloroform-butanol. Yield, 89%. M.p. 57-58°C. IR (KBr): ν = 3155 (OH), 1598, 1460 cm^{-1}. ^1H-NMR ($CDCl_3$): δ = 10.40 (4H, s), 6.98 (8H, s), 4.24 (4H, d), 3.50 (4H, d), 1.15 (24H, s), 0.67 - 1.60ppm (84H, m). Anal. calcd. for $C_{80}H_{128}O_4$ (1153.8): C 83.27, H 11.18; found C 83.33, H 11.35.

37,38,39,40,41,42-Hexahydroxy-5,11,17,23,29,35-hexakis(1-methylethyl)-calix[6]arene (**6a**)[6].

Reaction time, 4h. Yield, 81%. M.p. > 300°C. IR (KBr): ν = 3150 (OH), 1602, 1585, 1465 cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ = 10.47 (6H, s), 6.99 (12H, s), 3.84 (12H, s), 2.78 (6H, sep), 1.20 ppm (36H, d). Anal. calcd. for $C_{60}H_{72}O_6$ (889.2): C 81.04, H 8.16; found C 81.07, H 8.44.

37,38,39,40,41,42-Hexahydroxy-5,11,17,23,29,35-hexakis(1-methylpropyl)-calix[6] arene (**6b**).

Reaction time, 15h. Yield, 74%. M.p. > 300°C. IR (KBr): ν = 3160 (OH), 1600, 1585, 1465 cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ = 10.48 (6H, s), 6.94 (12H, s), 3.86 (12H, s), 2.47 (6H, sex), 1.50 (12H, quin), 1.14 (18H, d), 0.80 ppm (18H, t). Anal. calcd. for $C_{66}H_{84}O_6$ (973.3): C 81.44, H 8.70; found C 81.09, H 8.51.

5,11,17,23,29,35-Hexakis(1,1-dimethylethyl)-37,38,39,40,41,42-hexahydroxy-calix[6] arene (**6c**)[1].

Reaction time, 20min. Yield, 90%. M.p. > 300°C. IR (KBr): ν = 3160 (OH), 1598, 1475 cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ = 10.43 (6H, s), 7.13 (12H, s), 3.90 (12H, s), 1.27 ppm (54H, s). Anal. calcd. for $C_{66}H_{84}O_6$ (973.3): C 81.44, H 8.70; found C 80.97, H 8.47.

5,11,17,23,29,35-Hexakis(1,1-dimethylpropyl)-37,38,39,40,41,42-hexahydroxy-calix[6]arene (**6d**)[4].

Reaction time, 10min. Yield, 93%. M.p. > 300°C. IR (KBr): ν = 3150 (OH), 1600, 1478 cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ = 10.48 (6H, s), 7.10 (12H, s), 3.90 (12H, s), 1.58 (12H, q), 1.20 (36H, s), 0.66 ppm (18H, t). Anal. calcd. for $C_{72}H_{96}O_6$ (1057.5): C 81.77, H 9.15; found C 81.35, H 8.99.

5,11,17,23;29,35-Hexakis(1,1-dimethylpentyl)-37,38,39,40,41,42-hexahydroxy-calix[6]arene (**6e**).

Reaction time, 2h. Yield, 73%. M.p. 167-168°C. IR (KBr): ν = 3145 (OH), 1600, 1585, 1460 cm^{-1}. ^{1}H-NMR (CDCl$_3$): δ = 10.43 (6H, s), 7.12 (12H, s), 3.92 (12H, s), 1.26 (36H, s), 0.65 - 1.70 ppm (54H, m). Anal. calcd. for $C_{84}H_{120}O_6$ (1225.8): C 82.30, H 9.87; found C 82.27, H 10.51.

5,11,17,23,29,35-Hexakis(1,1-dimethylheptyl)-37,38,39,40,41,42-hexahydroxy-calix[6]arene (**6f**).

Reaction time, 2h. Yield, 65%. M.p. 63-64°C. IR (KBr): ν = 3145 (OH), 1600, 1582, 1480 cm^{-1}. ^{1}H-NMR (CDCl$_3$): δ = 10.48 (6H, s), 7.10 (12H, s), 3.92 (12H, s), 1.19 (36H, s), 0.62 - 1.64 ppm (78H, m). Anal. calcd. for $C_{96}H_{144}O_6$ (1394.1): C 82.70, H 10.41; found C 82.48, H 10.44.

5,11,17,23,29,35-Hexakis(1,1-dimethylundecyl)-37,38,39,40,41,42-hexahydroxy-calix[6]arene (**6g**).

Reaction time, 2h. Yield, 66%. M.p. 58-59°C. IR (KBr): ν = 3145 (OH), 1600, 1585, 1480 cm^{-1}. ^{1}H-NMR (CDCl$_3$): δ = 10.46 (6H, s), 7.08 (12H, s), 3.90 (12H, s), 1.20 (36H, s), 0.63 - 1.65 ppm (126H, m). Anal. calcd. for $C_{120}H_{192}O_6$ (1730.8): C 83.27, H 11.18; found C 83.10, H 10.93.

49,50,51,52,53,54,55,56-Octahydroxy-5,11,17,23,29,35,.41,47-octakis-(1-methylethyl)calix[8]arene (**7a**)[6].

Reaction time, 12h, the crude product was purified by silical gel column chromatography. Yield, 45%. M.p. > 300°C. IR (KBr): ν = 3200 (OH), 1580, 1548, 1478 cm^{-1}. ^{1}H-NMR (CDCl$_3$): δ = 9.43 (8H, s), 7.00 (16H, s), 4.33 (8H, d), 3.48 (8H, d), 2.78 (8H, sep), 1.17 ppm (48H, d). Anal. calcd. for $C_{80}H_{96}O_8$ (1185.6): C 81.04, H 8.16; found C 80.83, H 8.09.

5,11,17,23,29,35,41,47-Octakis(1,1-dimethylethyl)-49,50,51,52,53,54,55,56-octahydroxycalix[8]arene (**7c**)[1].

Reaction time, 30min. Yield, 91%. M.p. > 300°C. IR (KBr): ν = 3210 (OH), 1575, 1480 cm^{-1}. ^{1}H-NMR (CDCl$_3$): δ = 9.62 (8H, s), 7.17 (16H, s), 4.37 (8H, d), 3.50 (8H, d), 1.25 ppm (72H, d). Anal. calcd. for $C_{88}H_{112}O_8$ (1297.8): C 81.44, H 8.70; found C 81.11, H 8.80.

5,11,17,23,29,35,41,47-Octakis(1,1-dimethylpropyl)-49,50,51,52,53,54,55,56-octahydroxycalix[8]arene (**7d**)[4,6].

Reaction time, 20min. Yield, 85%. M.p. > 300°C. IR (KBr): ν = 3220 (OH), 1595, 1480 cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ = 9.64 (8H, s), 7.16 (16H, s), 4.38 (8H, d), 3.50 (8H, d), 1.60 (16H, q), 1.24 (48H, s), 0.64 ppm (24H, t). Anal. calcd. for $C_{96}H_{128}O_8$ (1410.0): C 81.77, H 9.15; found C 81.54, H 9.13.

5,11,17,23,29,35,41,47-Octakis(1,1-dimethylpentyl)-49,50,51,52,53,54,55,56-octahydroxycalix[8]arene (**7e**).

Reaction time, 40min. Yield, 72%. M.p. 241-242°C. IR (KBr): ν = 3205 (OH), 1592, 1478 cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ = 9.60 (8H, s), 7.10 (16H, s), 4.38 (8H, d), 3.50 (8H, d), 1.23 (48H, s), 0.63 - 1.60 ppm (72H, m). Anal. calcd. for $C_{112}H_{160}O_8$ (1634.4): C 82.30, H 9.87; found C 81.80, H 9.71.

5,11,17,23,29,35,41,47-Octakis(1,1-dimethylheptyl)-49,50,51,52,53,54,55,56-octahydroxycalix[8]arene (**7f**).

Reaction time, 40min. Yield, 68%. M.p. 181-182°C. IR (KBr): ν = 3200 (OH), 1594, 1478 cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ = 9.58 (8H, s), 7.10 (16H, s), 4.38 (8H, d), 3.50 (8H, d), 1.20 (48H, s), 0.64 - 1.60 ppm (104H, m). Anal. calcd. for $C_{128}H_{192}O_8$ (1858.8): C 82.70, H 10.41; found C 82.28, H 10.55.

5,11,17,23,29,35,41,47-Octakis(1,1-dimethylundecyl)-49,50,51,52,53,54,55,56-octahydroxycalix[8]arene (**7g**).

Reaction time, 40min. Yield, 74%. M.p. 131-132°C. IR (KBr): ν = 3200 (OH), 1594, 1478 cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ = 9.55 (8H, s), 7.10 (16H, s), 4.38 (8H, d), 3.50 (8H, d), 1.24 (48H, s), 0.62 - 1.65 ppm (168H, m). Anal. calcd. for $C_{160}H_{256}O_8$ (2307.7): C 83.27, H 11.18; found C 83.27, H 11.85.

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