Synthesis and Conformational Properties of Monoesters of Calix[4]arene

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Two synthetic procedures were developed for the preparation of monoesters of calix[4]arene, one *via* dibenzylation the other *via* monobenzylation route. Dibenzylation pathway can provide specifically monobenzoester of calix[4]arene, but monobenzylation method could produce a series of monoesters of calix[4]arene such as acetyl, isobutyryl, and benzoesters. Conformational properties were discussed on the basis of ^{1}H and ^{13}C NMR data.

Introduction

Selective derivatization of calixarene has greatly widened the area of calixarenes in host-guest chemistry.[1~3] Several synthetic procedures for selective alkylation have been developed such as 1,3-dialkylation,[4] 1,2-dialkylation,[5] monoalkylation,[6] and trialkylation.[7] Also a few selective acylation techniques has been reported.[8] Unlike alkyl moiety, acyl groups at the lower rim of calixarenes not only can control the reactivity of the *para* position of upper rim, but can be utilized as useful protecting groups. Thus selective acylation can provide quite useful intermediate compounds for the development of important calixarene host. Gutsche *et al.*[8a] found that calix[4]arene is only tribenzoylated when it is treated with excess benzoyl chloride in pyridine. They also reported[8b,8c] that when *t*-butylcalix[4]arene treated with 3,5-dinitrobenzoyl chloride in the presence of bases, various substitution pattern was observed such as triester, 1,3-diester, 1,2-diester, and monoester compounds depending on reaction conditions. But these substitution was only applied to *t*-butylcalix[4]arene with 3,5-dinitrobenzoyl chloride and 3,5-dinitrobenzoyl group was sometimes too labile for further reaction. Recently we reported[9] an indirect acylation procedure providing specifically 1,2-dibenzoester by removing benzyl group selectively from trisubstituted calix[4]arene. Trisubstituted calix[4]arene was obtained from benzoylation of monobenzylcalix[4]arene in pyridine. In a series of developing the esters of calix[4]arenes, here we report two step acylation procedures providing specifically monoesters of calix[4]arene starting from the benzyl substituted calix[4]arenes. Since the benzyl substituted calix[4]arenes are easily available from the selective functionalization,[5,6] this simple method could provide the efficient synthetic method for the preparation of monoesters of calix[4]arene. Monoesters of calix[4]arene such as benzoyl, acetyl, and isobutyryl have not been prepared and it could provide the excellent building block for the useful host calix[4]arenes.

Results and Discussion

Synthesis of monobenzoester calix[4]arene *via* dibenzylation route. Direct monosubstitution of calix[4]arene with benzoyl group was carried out by varying the reaction conditions, but failed to obtain any significant amounts of monobenzoester products. Always 1,3-dibenzoylated calix[4]arene and/or tribenzoylated calix[4]arene was obtained as major products depending on the reaction conditions.[8] After direct monobenzoylation failed, three step procedure was sought. It is known[8] that calix[4]arene **1** produces only tribenzoylated products in pyridine when treated with excess benzoyl chloride. If this selective benzoylation occurred with dialkylcalix[4]arenes, it is possible to get monobenzoester from this reaction. Thus, we treated easily available 1,3-dibenzyl ether calix[4]arene **2**[5] with excess benzoyl chloride in pyridine to obtain the trisubstituted calix[4]arene **3**. As expected, only one benzoyl group was introduced exclusively to give so called ABAH type[11] calix[4]arenes as shown in Scheme 1. The ^{1}H NMR spectrum of **3** shows the typical ABAH type calix[4]arene characteristics such as two pairs of doublets at δ 3.2-4.1 for the eight bridge methylene protons and the complicated aromatic signals around δ 6.2-7.4. The diastereotopic protons of four benzylic methylene appear as a pair of doublets at δ 5.09 and 5.05 as expected.

In order to synthesize the monoester of calix[4]arene, two benzyl groups were removed. Treatment of **3** with H_2 in the presence of palladium catalyst produced a clean monobenzoester calix[4]arene **4a** in 74% yield. The ^{1}H NMR spectrum of **4a** showed one upfield shifted triplet at δ 6.42 for the *para* hydrogens of calixarene aromatic rings as characteristic signals[12,13] of monosubstituted calix[4]arenes, and the bridge methylene protons appear as two pairs of doublets at δ 4.1-3.7. The difference in the chemical shifts among two pairs of doublets is small ($\Delta\delta$=0.25 ppm). According to Gutsche,[7,14] the $\Delta\delta$ becomes smaller when the phenol unit is flattened and this result is consistent with the ^{13}C NMR observation. The conformation of calix[4]arene can be determined by the ^{13}C NMR spectrum. Particularly diagnostic were the chemical shifts for the methylene carbons[15] of calix[4]arene which showed peaks at about δ 32 for the *syn* oriented phenol rings or δ 37 for the *anti* oriented phenol rings. Interestingly the ^{13}C NMR spectrum of **4a** showed two signals at δ 34.44 and 31.35 for the bridge carbons as shown in Figure 1, that is, one *syn* oriented phenol ring, but peak at δ 34.44 could not be assigned as *syn* or *anti* on the basis of previous analysis method,[14] but rather be interpreted as signal of flatten oriented phenol ring. To accommodate these spectral characteristics it is suggested that **4a** exists in a "flatten" conformation[7,12] as shown in Figure 2. These flatten conformation was observed previously

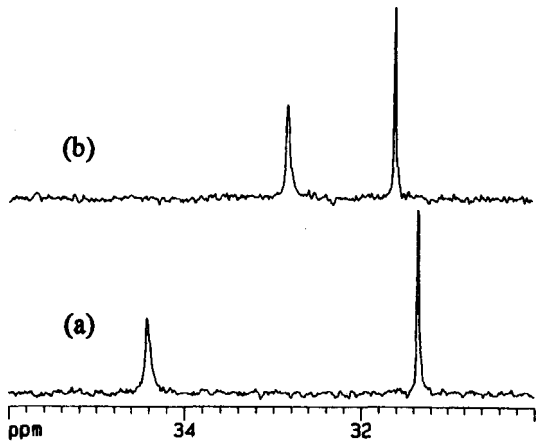


Figure 1. The partial ^{13}C NMR spectra of **4** in $CDCl_3$. (a) the partial ^{13}C NMR spectrum of **4a**, (b) the partial ^{13}C NMR spectrum of **4b**.

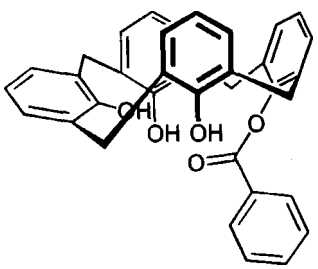
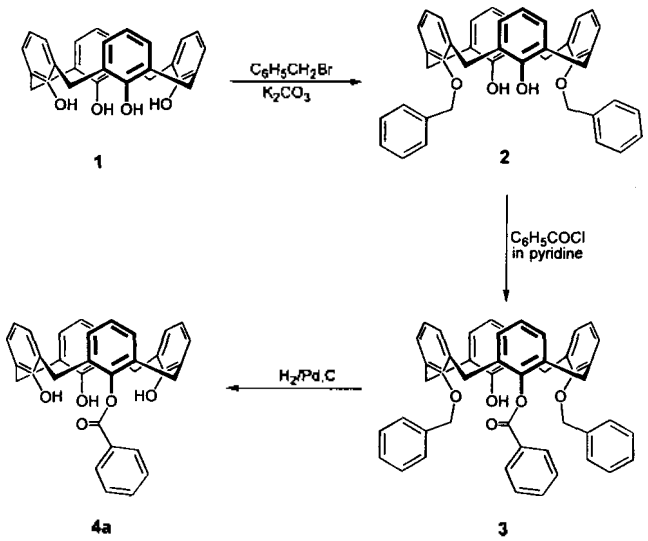


Figure 2. The proposed flatten conformation of **4a**.

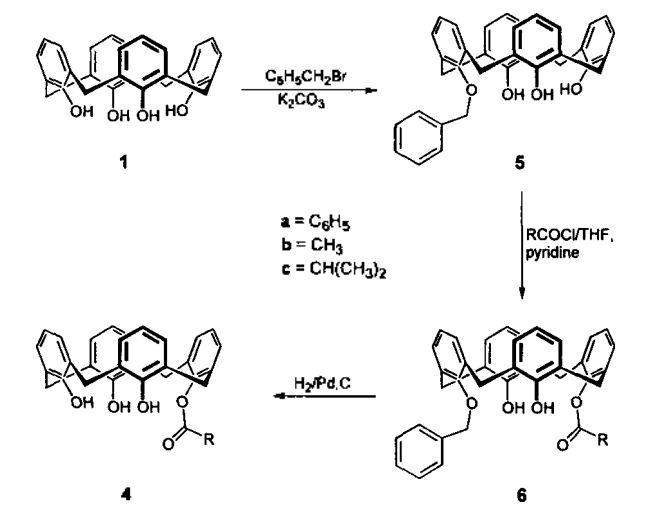
for the 1,2-dibenzoester calix[4]arene[15] and is consistent with the observation of chemical shift difference of bridge methylene protons.

Synthesis of monoesters of calix[4]arene *via* monobenzylation route. Even though Scheme 1 could provide the efficient synthetic procedure for the preparation of monobenzoester calix[4]arene **4a**, it can only produce the benzoester **4a**. For the purpose of developing synthetic procedure of general monoesters of calix[4]arene, we utilized the selective acylation technique starting from monobenzylcalix[4]arene **5** in Scheme 2. Since monobenzylcalix[4] arene **5** can be obtained easily[6] and the benzyl group can be removed selectively, this approach can provide the several monoesters of calix[4]arene. By controlling the acylation reaction carefully, we developed the selective acylation procedure of monoalkylcalix[4]arenes and prepared the series of monoacylated calix[4]arenes **6** in high yield. When **5** was treated with 1.2 equivalent of acyl halide such as benzoyl chloride, acetyl chloride, and isobutyryl chloride in the presence of pyridine, monoacylated calix[4]arenes **6** were obtained exclusively. Substitution of acyl groups was occurred only at the opposite side of the existing benzyl group with a cone conformation. In these reactions, the present benzyl group obviously controlled the position of incoming acyl group.

Substitution pattern and conformation of disubstituted calix[4]arenes **6** were confirmed by the NMR spectra. The ^1H NMR spectrum of **6a** showed two pairs of doublets at 3.52-3.94 ppm arising from the bridged methylene protons and a singlet at 4.94 ppm for the two benzylic protons, in-



Scheme 1. Synthesis of monobenzoester calix[4]arene *via* dibenzylation.



Scheme 2. Synthesis of monoesters calix[4]arene *via* monobenzylation.

dicating that second substitution was occurred at the opposite side of the benzyl group of calix[4]arene **5**. The IR absorption band of **6a** showed at 3500 cm^{-1} as a sharp singlet for the OH and at 1740 cm^{-1} for the C=O stretching band, indicating that two hydroxy groups are not hydrogen bonded each other. The ^1H NMR spectrum of **6b** and **6c** showed the similar pattern as described above such as two pairs of doublets at 3.45-4.02 ppm for the methylene protons and a singlet at δ 4.8-4.9 for the two benzylic protons. The IR absorption band of **6b** and **6c** also showed the similar pattern as observed for **6a**. The conformation of disubstituted calix[4]arenes **6a-6c** was deduced from the ^{13}C NMR chemical shifts of the bridge methylene carbons. All of those disubstituted calix[4]arenes show two peaks at around 31 ppm, indicating that they exist as a cone conformation.

Benzyl group in **6** was removed by hydrogenation. Treatment of **6** with H_2 in the presence of palladium catalyst produced clean monoesters of calix[4]arene **4a, 4b**, and **4c** in

high yield. The ^{1}H NMR spectrum of **4b** showed a little different pattern observed as in **4a**, which showed one upfield shifted triplet at δ 6.42 for the *para* hydrogens of calixarene aromatic rings as characteristic signals[11,12] of monosubstituted calix[4]arenes, but here two triplets for the *para* hydrogens of calixarene aromatic rings appear at δ 6.71 and the bridge methylene protons appear as distinct two pairs of doublets at δ 4.12-3.57. The difference ($\Delta\delta$= 0.55 ppm) in the chemical shifts among two pairs of doublets is much large compared to that of **4a**. Contrary to the flatten conformation of **4a**, **4b** exists as a cone conformation and this result is consistent with the ^{13}C NMR observation. The ^{13}C NMR spectrum of **4b** showed two signals at δ 32.80 and 31.58 for the bridge carbons as shown in Figure 1, that is, two *syn* oriented phenol ring, indicating that **4b** exist as a normal cone conformation. It was also found that **4c** existed as a cone conformation based on the ^{13}C NMR analysis. We do not have a good explanation at this moment why **4a** exists as a flatten cone, on the other hand **4b** and **4c** exist as a cone conformation. But this conformational change could be the results of the effective hydrogen bonding among the remaining three hydroxy protons.

In conclusion, the present paper describes the two synthetic pathways for the preparation of monoesters of calix[4]arene, one *via* dibenzylation and the other *via* monobenzylation route. Dibenzylation technique can provide only monobenzoester of calix[4]arene, but monobenzylation method could produce a series of monoesters of calix[4]arene such as acetyl, isobutyryl, and benzoesters. The conformation of monobenzoester of calix[4]arene **4a** was deduced as a flatten conformation, but monoacetyl and monoisobutyrylesters of calix[4]arene **4b** and **4c** exist as a cone conformation on the basis of ^{1}H and ^{13}C NMR analyses.

Experimental

25,26,27,28-Tetrahydroxycalix[4]arene 1. was prepared by the known procedure.[8a] mp 314-316 °C (*lit.*[8a] 313-315 °C).

25,27-Dibenzyloxy-26,28-dihydroxycalix[4]arene 2. was prepared by the known procedure.[5] mp 222-225 °C (*lit.*[5] 220-223 °C).

26,27-Dibenzyloxy-25-benzoyloxy-28-hydroxycalix[4]arene 3. To a solution of 2 g (3.4 mmol) of **2** in 70 mL of pyridine, 10 mL (85 mmol) of benzoyl chloride was added slowly at room temperature. The reaction mixture was stirred for 18 hrs, and then 150 mL $CHCl_3$ and 200 mL H_2O were added. The organic layer was separated and washed with the water three times. After removing the solvents, the residue was triturated with methanol. Recrystallization from chloroform-methanol gave 2.06 g (88%) of colorless crystals **3**. mp 211-214 °C. ^{1}H NMR ($CDCl_3$) δ 7.4-6.6 (m, 24H, ArH and OH), 6.45 (d, 2H, ArH, J=7.2 Hz), 6.16 (t, 2H, ArH, J=7.2 Hz), 5.07 and 4.79 (a pair of d, 4H, -OCH_2Ar), 4.08, 3.95, 3.71, and 3.22, (two pairs of d, 8H, ArCH_2Ar, J=13.2 and 15.9 Hz). ^{13}C NMR ($CDCl_3$) δ 163.68 (-CO_2-), 154.18, 153.28, 148.10, 137.09, 133.43, 133.21, 132.90, 132.57, 132.39, 130.43, 129.65, 129.58, 129.27, 128.34, 128.21, 127.59, 127.28, 127.24, 125.21, 123.98, and 118.75 (Ar), 75.31 (-OCH_2Ar), 37.96 and 31.21 (ArCH_2Ar). IR (KBr) 3343 cm^{-1} (OH), 1724 cm^{-1} (-CO_2-).

25-Benzoyloxy-26,27,28-trihydroxycalix[4]arene 4a. A mixture of 1.0 g (1.4 mmol) of **3** and 0.05 g of Pd/C in THF was shaken for 7 hrs under H_2 atmosphere at 60 psi. After filtered off the catalyst, the solvents were removed and the residue was triturated with n-hexane. Recrystallization from chloroform-hexane produced 0.55 g (74%) of colorless crystals **4**. mp 228-231 °C. ^{1}H NMR ($CDCl_3$) δ 8.68 and 7.34 (two s, 3H, OH), 7.60-6.78 (m, 15H, ArH), 6.42 (t, 2H, ArH, J=7.50 Hz), 4.00-3.75 (two pairs of d, 8H, ArCH_2Ar, J=15.0 and 14.1 Hz). ^{13}C NMR ($CDCl_3$) δ 164.09 (-CO_2-), 150.81, 149.30, 146.36, 133.32, 132.69, 129.99, 129.95, 128.98, 128.80, 128.60, 128.22, 127.60, 127.32, 126.79, 121.86, and 120.99 (Ar), 34.44, and 31.35 (ArCH_2Ar). IR (KBr) 3431 and 3365 cm^{-1} (OH), 1741 cm^{-1} (-CO_2-).

25-Acetyloxy-26,27,28-trihydroxycalix[4]arene 4b. A mixture of 0.3 g (0.539 mmol) of **6b** and 0.05 g of Pd/C in THF was shaken for 7 hrs under H_2 atmosphere at 60 psi. After filtered off the catalyst, the solvents were removed and the residue was triturated with *n*-hexane. Recrystallization from chloroform-hexane produced 0.21 g (83%) of colorless crystals **4b**. mp 244-247 °C. ^{1}H NMR ($CDCl_3$) δ 9.00 and 8.02 (two s, 3H, OH), 7.15-6.60 (m, 12H, ArH), 4.11-3.58 (two pairs of d, 8H, ArCH_2Ar, J=14.1 and 13.8 Hz), 2.39 (s, 3H, CH_3CO-). ^{13}C NMR ($CDCl_3$) δ 168.05 (-CO_2-), 150.68, 148.99, 144.46, 133.07, 129.51, 129.11, 128.87, 128.57, 128.22, 128.06, 127.54, 127.45, 122.04, and 121.18 (Ar), 32.81 and 31.58 (ArCH_2Ar), 20.47 (CH_3). IR (KBr) 3344 and 3227 cm^{-1} (OH), 1783 cm^{-1} (-CO_2-).

25-Isobutyryloxy-26,27,28-trihydroxycalix[4]arene 4c. A mixture of 0.3 g (0.513 mmol) of **6c** and 0.05 g of Pd/C in THF was shaken for 7 hrs under H_2 atmosphere at 60 psi. After filtered off the catalyst, the solvents were removed and the residue was triturated with hexane. Recrystallization from chloroform-hexane produced 0.17 g (67%) of colorless crystals **4c**. mp 226-228 °C. ^{1}H NMR ($CDCl_3$) δ 9.03 and 8.15 (two s, 3H, OH), 7.14-6.65 (m, 12H, ArH), 4.18-3.54 (two pairs of d, 8H, ArCH_2Ar, J=13.8 Hz), 3.08 (m, 1H, -CH-), 1.47 (d, 6H, -CH_3, J=6.9 Hz). ^{13}C NMR ($CDCl_3$) δ 174.57 (-CO_2-), 151.03, 148.49, 143.84, 132.83, 132.83, 129.42, 129.08, 128.98, 128.59, 128.26, 127.86, 127.54, 127.41, 122.26, and 121.00 (Ar), 34.49 (-CH-), 32.02 and 31.68 (ArCH_2Ar), 19.12 (-CH_3). IR (KBr) 3370 and 3252 cm^{-1} (OH), 1762 cm^{-1} (-CO_2-).

25-Benzyloxy-26,27,28-trihydroxycalix[4]arene 5. was prepared by the known procedure.[6,14] mp 224-225 °C (*lit.*[6,14] 225-226 °C).

27-Benzoyloxy-25-benzyloxy-26,28-dihydroxycalix[4]arene 6a. To a solution of 0.3 g (0.584 mmol) of **5** in 50 mL of dry THF, 0.1 mL of pyridine and a few drops of DMAP(4-dimethylaminopyridine), 0.085 mL (0.73 mmol) of benzoyl chloride was added at room temp. The mixture was stirred at room temperature for 2 hrs. The solvents were removed and the residue was triturated with methanol. The crude product was recrystallized from chloroform-methanol to give 0.21 g (58%) of colorless fine needles **6a**. mp 265-267 °C. ^{1}H NMR ($CDCl_3$) δ 8.68-7.40 (m, 24H, 22 ArH and 2OH), 5.12 (s, 2H, -OCH_2Ar), 4.20-3.36 (two pairs of d, 8H, ArCH_2Ar). ^{13}C NMR ($CDCl_3$) δ 165.42 (-CO_2-), 153.02, 151.05, 145.22, 136.04, 133.44, 132.71,

132.28, 130.55, 129.53, 129.37, 129.06, 128.93, 128.75, 128.62, 128.57, 127.95, 127.22, 126.17, 126.00, and 119.46 (Ar), 79.02 (-OCH_2Ar), 31.77 ($ArCH_2Ar$).

27-Acetyloxy-25-benzyloxy-26,28-dihydroxycalix[4]arene 6b. To a solution of 0.3 g (0.58 mmol) of **5** in 30 mL of dry THF, 0.1 mL of pyridine, a few drops of DMAP, and 0.1 mL (1.2 mmol) of acetyl chloride was added at room temp. The mixture was stirred at room temperature for 5 hrs. The solvents were removed and the residue was triturated with methanol. The crude product was recrystallized from chloroform-methanol to give 0.3 g (93.8%) of colorless crystals **6b**. mp 256-259 °C. ^{1}H NMR ($CDCl_3$) δ 7.70-6.66 (m, 17H, ArH), 5.10 (s, 2H, -OCH_2Ar), 4.27-3.36 (two pairs of d, 8H, $ArCH_2Ar$, J=13.5 Hz), 2.37 (s, 3H, -CH_3). ^{13}C NMR ($CDCl_3$) δ 169.23 (-CO_2-), 152.77, 151.22, 144.64, 135.88, 133.25, 132.44, 129.48, 128.77, 128.75, 128.70, 128.53, 128.46, 128.22, 127.52, 126.46, 126.12, 119.65 (Ar), 78.69 (-OCH_2-), 31.91 and 31.86 ($ArCH_2$). IR (KBr) 3527 and 3477 cm^{-1} (OH), 1740 cm^{-1} (-CO_2-).

27-Isobutyryloxy-25-benzyloxy-26,28-dihydroxycalix[4]arene 6c. To a solution of 0.5 g (0.97 mmol) of **5** in 40 mL of dry THF, 0.1 mL of pyridine, a few drops of DMAP, and 0.305 mL (2.91 mmol) of isobutyryl chloride was added slowly at room temperature. The mixture was stirred at room temperature for 30 hrs. The solvents were removed and the residue was triturated with methanol. The crude product was recrystallized from chloroform-methanol to give 0.33 g (58.2%) of colorless crystals **6c**. mp 258-260 °C. ^{1}H NMR ($CDCl_3$) δ 7.70-6.65 (m, 19H, 17 ArH and 2 OH protons), 5.08 (s, 2H, -OCH_2Ar), 4.29-3.33 (two pairs of d, 8H, $ArCH_2Ar$, J=13.5 Hz), 2.92 (m, 1H, -CH-), 1.42 (d, 6H, -CH_3, J=6.9 Hz). ^{13}C NMR ($CDCl_3$) δ 175.32 (-CO_2-), 152.98, 151.20, 144.45, 132.97, 132.21, 129.46, 128.81, 128.76, 128.65, 128.53, 128.46, 128.13, 127.33, 126.22, 126.05, and 119.47 (Ar), 78.90 (-OCH_2-), 34.66 (-CH-), 31.70 and 31.58 ($ArCH_2Ar$), 19.19 (-CH_3). IR (KBr) 3483 and 3426 cm^{-1} (OH), 1737 cm^{-1} (-CO_2-).

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