ORGANIC LETTERS

2000
Vol. 2, No. 6
743−745

A New Type of Amido-Substituted *p-tert*-Butylcalix[6]arene: Double Diamide Bridges on the Lower Rim

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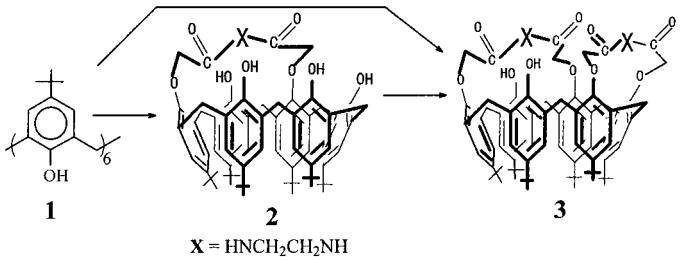
Received December 6, 1999

ABSTRACT



A convenient method for the synthesis of intramolecularly bridged calix[6]arenes by bis(chloroacetyl)amide was reported. A 1,3-singly bridged derivative and an asymmertical 1,3–4,5 doubly bridged derivative were obtained, respectively.

Calixarenes are macrocyclic molecules in which phenolic units are linked via methylene bridges.[1] At the lower rim of calixarenes, the cyclic hydroxyl groups provide excellent sites for bridged modification by bifunctional or polyfunctional reagents. In recent years, amido-substituted calix[4]arenes have been investigated extensively,[2,3] and results show that those compounds can selectively recognize alkali metal cations (specially Na^+) or anions[4] (via hydrogen bonds). As the study of these compounds approaches maturity, the easy accessibility of *p-tert*-butylcalix[6]arene with a larger cavity makes it the next candidate for close scrutiny. However, the conformational flexibility of *p-tert*-butylcalix[6]arenes is the prime disturbance. In 1992, Gustche and co-workers first synthesized a lower-rim-1,4-bridged *p-tert*-butylcalix[6]arene using succinic chloride as the bridging reagent[5] and found that intramolecular bridging chains can effectively reduce the conformational freedom of *p-tert*-butylcalix[6]arene. Following this line, similar 1,4-bridged *p-tert*-butylcalix[6]-arenes[6] as well as the 1,2- and 1,3-*p-tert*-butylcalix[6]arenes have been prepared.[7,8] It is reasonable to assume that intramolecular double bridges can restrict the conformation reversion of *p-tert*-butylcalix[6]arenes more efficiently. Until now, little is known about doubly bridged *p-tert*-butylcalix-[6]arenes.

In this paper, we report the first synthesis of intramolecular doubly bridged *p-tert*-butylcalix[6]arene. Reacting *p-tert*-butylcalix[6]arene **1** with bis(chloroacetyl)amide in refluxing CH_3CN in the presence of K_2CO_3 and KI yielded 1,3-bridged derivative **2** in 35% yield, Further treatment of **2** with bis-(chloroacetyl)amide in THF−DMF in the presence of K_2-

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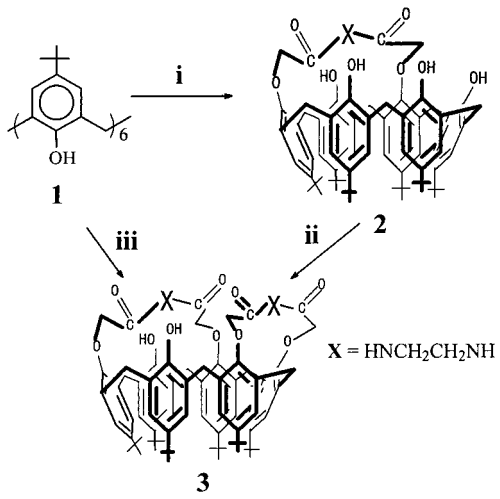
10.1021/ol9903887 CCC: $19.00
Published on Web 03/01/2000

CO_3 and KI resulted in the incorporation of another bridge to afford doubly bridged 1,3−4,5-calix[6]bis-diamide **3** in 67% yield. **3** could be also obtained directly by treatment of *p-tert*-butylcalix[6]arene **1** with 1.5 equiv of bis(chloroacetyl)-amide in the presence of a large excess of K_2CO_3 in 40% yield, which is stable as a cone (u,u,u,u,u,u) conformation at ambient temperature[6b] (see Scheme 1).

Scheme 1[a]



[a] Reagents and conditions: (**i**) $(ClCH_2CONHCH_2)_2$, K_2CO_3 (2 equiv)/ KI, CH_3CN, reflux, 24 h; (**ii**) $(ClCH_2CONHCH_2)_2$, K_2CO_3 (6 equiv)/KI, THF−DMF (10:1, V/V), reflux; 3 days; (**iii**) $(ClCH_2CONHCH_2)_2$ (1.5 equiv), K_2CO_3 (10 equiv)/KI, CH_3CN, reflux, 3 days.

The structures of **2** and **3** were characterized by FAB-MS spectra, elemental analyses, and ^{1}H NMR spectra;[9] the structure of compound **3** was also supported by ^{13}C NMR and 2D COSY spectra. The ^{1}H NMR ($CDCl_3$) spectrum of **2** shows four singlets at δ 1.304, 1.286, 1.231, and 1.148 (ratio 2:1:2:1) for the *tert*-butyl groups, two pairs of doublets at δ 4.65 and 4.34 (4H, J = 14.1 Hz) and 3.45 and 3.80 (8H, J = 13.8 Hz, two pairs of doublets coincide) for the $ArCH_2Ar$ groups , two singlets at δ 7.0 and 7.2 (12H) in a 1:2 ratio for the aromatic protons, one singlet at δ 7.26 (4H) for the phenolic hydroxyl proton, one singlet at δ 8.4 (2H) for the -CONH- group, multiplets near δ 3.60 (4H) for the NCH_2CH_2N group, and a pair of doublets at δ 4.48 and 4.40 (4H, J = 7.2 Hz) associated with the $-OCH_2CO-$ moieties in which the CH_2 hydrogens bear a diastereotopic relationship (AB system) to one another. These assignments indicate that the calix[6]arene moiety is intramolecularly bridged by a bis-acetylamide spacer at the 1,3-position and that compound **2** adopts a cone (or *syn*) conformation at ambient temperature.

Using a similar process to that used to confirm the structure of precursor **2**, the structure of compound **3** could be assigned as one of the four possible isomers (1,3−4,6 position, 1,3−4,5 position, 1,3−2,4 position, 1,3−2,5 position). The five singlets at δ 1.306 and 1.303 (overlapped), 1.336, 1.322, 1.270, and 0.828 (ratio 2:1:1:1:1) for the *tert*-butyl groups are not compatible with that of the symmetrical 1,3−4,6 and 1,3−2,6 doubly bridged structure. Thus, the 1,3−4,6 and 1,3−2,6 substituted isomers can be ruled out (Figure 1).

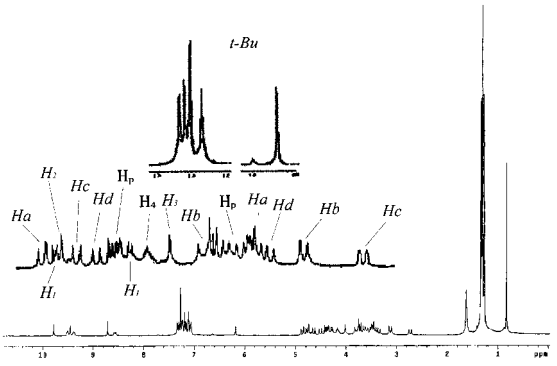


Figure 1. ^{1}H NMR spectrum of compound **3** in $CDCl_3$, 25 °C, 300 MHz: H_{a-d} for the $ArCH_2Ar$ protons, H_{1-4} for the OCH_2 protons, H_p for the NCH_2CH_2N proton.

The signal pattern in the diarylmethylene region is the criterion to confirm the structure of calix[6]arene. It is well know that the hydrogen atoms of a methylene group connecting two neighboring aryl groups of calix[6]arene appear as a pairs of AB doublets in the ^{1}H NMR spectrum if the aryl groups are *syn* to one another.[10] On the other hand, a singlet for the methylene hydrogen atoms indicates that the aryl groups are *anti* to one another. With the aid of COSY experiments, all signals of the ^{1}H NMR spectrum of **3** have

(9) Compound **2** and compound **3**: the eluent for column chromatography was dichloromethane:methanol (50:1), recrystallized from CH_2Cl_2/MeOH as colorless crystals and a white power, respectively. Compound **2**: mp 251 °C (dec); MS(FAB) m/z = 1112 [M^+]. Anal. Calcd for $C_{72}H_{92}O_8N_2$: C, 77.66; H, 8.32. Found: C, 77.56; H, 8.30. ^{1}H NMR ($CDCl_3$): 1.148 (s, 9H, $C(CH_3)_3$, 1.231 (s, 18H, $C(CH_3)_3$), 1.286 (s, 9H, $C(CH_3)_3$), 1.304 (s, 18H, $C(CH_3)_3$), 3.45 (d, 4H, $ArCH_2Ar$, J = 13.8 Hz), 3.60 (m, 4H, NCH_2CH_2N), 3.80 (d, 4H, $ArCH_2Ar$, J = 13.8 Hz), 4.34 (d, 2H, $ArCH_2Ar$, J = 14.1 Hz), 4.40 (d, 2H, OCH_2, J = 7.2 Hz), 4.48 (d, 2H, OCH_2, J = 7.2 Hz), 4.65 (d, 2H, $ArCH_2Ar$, J = 14.1 Hz), 7.01 (s, 4H, ArH), 7.20 (s, 8H, ArH), 7.26 (s, 4H, ArOH), 8.40 (bs, 2H, NH). Compound **3**: mp 234 °C (dec); MS(FAB) m/z = 1252 [M^+]. Anal. Calcd for $C_{78}H_{100}O_{10}N_4$: C, 74.23; H, 8.04. Found: C, 74.76; H, 7.92. ^{1}H NMR ($CDCl_3$): δ 0.828 (s, 9H, $C(CH_3)_3$), 1.270 (s, 9H, $C(CH_3)_3$), 1.322 (s, 9H, $C(CH_3)_3$), 1.306 (s, 18H, $C(CH_3)_3$), 1.336 (s, 9H, $C(CH_3)_3$), 2.72 (d, 1H, $ArCH_2Ar$, J = 14.7 Hz), 3.10 (d, 2H, $ArCH_2Ar$, J = 13.8 Hz), 3.38 (d, 1H, $ArCH_2Ar$, J = 14.7 Hz), 3.43(d, 2H, $ArCH_2Ar$, J = 13.8 Hz), 3.56 (m, 4H, NCH_2CH_2N), 3.79 (d, 2H, $ArCH_2Ar$, J = 13.8 Hz), 4.01 (s, 2H, OCH_2), 4.16 (bs, 2H, OCH_2), 4.28 (d, 1H, OCH_2, J = 5.1 Hz), 4.35 (m, 4H, NCH_2CH_2N), 4.52 (d, 1H, $ArCH_2Ar$, J = 14.7 Hz), 4.64 (d, 1H, $ArCH_2Ar$, J = 14.7 Hz), 4.70 (s, 2H, OCH_2), 4.75 (d, 1H, OCH_2, J = 5.1 Hz), 4.84 (d, 2H, $ArCH_2Ar$, J = 13.8 Hz), 6.202 (d, 1H, ArH, J = 2.1 Hz), 7.053 (d, 1H, ArH, J = 1.8 Hz), 7.070 (d, 1H, ArH, J = 2.4 Hz), 7.108 (s, 2H, ArH), 7.155 (d, 1H, ArH, J = 2.1 Hz), 7.183 (s, 2H, ArH,), 7.226 (d, 1H, ArH, J = 2.1 Hz) 7.242 (d, 1H, ArH, J = 2.4 Hz), 7.305 (d, 1H, ArH, J = 1.8 Hz), 7.336 (d, 1H, ArH, J = 2.1 Hz), 8.71 and 9.42 (s, 2H, ArOH), 8.56, 9.42, and 9.68 (bs, 4H, NH). ^{13}CNMR (50 MHz,$CDCl_3$): δ 28.53, 29.80, 31.30, 31.56, 31.73, 31.81, 32.37, 32.71, 33.20, 34.24, 34.61, 34.67, 36.85, 40.30, 41.89, 52.03, 55.86 for CH_2 and CH_3/71.67 × 3C, 73.04 for OCH_2/124.04, 124.38, 125.66 × 2C, 125.99 × 2C, 126.25 × 4C, 126.68, 126.80, 127.93, 128.14, 128.40, 128.59, 128.72, 128.90, 131.70, 131.96, 132.87 × 2C, 133.02, 134.34, 143.81, 143.95, 144.06, 146.40, 147.26, 147.47, 148.55, 148.73, 148.97, 149.37, 149.89, 151.868 for Ar carbons/168.39, 169.17, 171.15, 172.45 for C═O.

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been assigned. The AB doublets of the diarylmethylene protons can be clearly defined from the cross-peaks in the H−H COSY. The four pairs of doublets (δ 4.84 and 3.43 (4H, J = 13.8 Hz), 3.80 and 3.10 (4H, J = 13.8 Hz), 2.72 and 4.64 (2H, J = 14.7 Hz), 4.52 and 3.38 (2H, J = 14.7 Hz), respectively) for the diarylmethylene groups in a 2:2:1:1 ratio (two pairs of doublets coincide) indicate that compound **3** adopts a cone (*syn*) conformation at ambient temperature. Since the splitting pattern of the 1,3−2,5-substituted calix[6]arene in the cone conformation is symmetrical, the signals arising from the *tert*-butyl moiety should be three singlets in a 1:1:1 ratio. Therefore, the unique possibility is that the calix[6]arene moiety of **3** is 1,3−4,5 substituted.

According to the NMR rule, δ 71.67 × 3C, 73.04 can be assigned to the ^{13}C resonances of the OCH_2 groups; with the aid of C−H COSY, one pairs of doublets (δ 4.75 and 4.28 (2H, J = 5.1HZ) and three singlets at δ 4.70, 4.16, and 4.01 (2H each) can be easily assigned for the OCH_2 groups in the ^{1}H NMR spectrum. Furthermore, the ^{1}H NMR signals also show multiplets near δ 3.56 and 4.35 (8H) for the NCH_2-CH_2N group, four pairs of doublets (2H:2H:2H:2H) and two singlets (2H:2H) near 7.0 for the aromatic protons, and six singlets (6H) in the range of δ 7.5−9.0 for the phenolic hydroxyl proton and CONH groups, which confirm that the structure of compound **3** is asymmetrically 1,3−4,5 doubly bridged. On the other hand, the clear assignment of the ^{1}H NMR and the ^{13}CNMR spectrum of **3** indicates that **3** adopts the cone conformation completely.[6b,9]

The high yields of **3** can be explained by the fact that the phenolic hydroxyl proton at the 5 position possesses less steric hindrance to being attack. Therefore, the phenolic hydroxyl proton at the 4 position is the convenient choice to be bridged to form the 1,3−4,5 doubly bridged *p-tert*-butylcalix[6]arene.

Examination of the CPK molecular models reveals that compound **3** is well preorganized to complex cations, which is in accordance with the results of extraction experiments (Table 1). Compounds **3** and **2** show high extraction abilities toward the largest, $Et_2NH_2^+$, and also the smallest, Li^+. Perhaps, the Li^+ is embedded deeply into the cyclic cavity.

Table 1. Percentage Extraction (% E) of Picrate Salts from Water into $CHCl_3$ at 25 °C.[a] Arithmetic Mean of Several Experiments−Standard Deviation of the Mean: $\sigma_{N-1} \leq 1$

	% E					
host	Li^+	Na^+	K^+	NH^+	$Et_2NH_2^+$	n-$PrNH_3^+$
2	5.3	1.2	0.9	1.2	6.5	2.3
3	12.8	1.1	0.8	0.5	12.3	3.5

[a] 1.00 mL of 0.005 mol dm^{-3} receptor solution in $CHCl_3$ was shaken (10 min) with 1.00 mL of 0.005 mol dm^{-3} picrate salt solution in H_2O, and the percentage extraction was measured from the resulting absorption at 380 nm.

Acknowledgment. Financial support from the National Natural Foundation of China is gratefully acknowledged.

OL9903887