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Synthesis and characterization of new symmetrical 3,6-bis[(25,26,27- tripropoxy-28-(3-(4-iodophenyl) propoxy)-p-tert-butyl calix[4]arene ethynyl]-9H- fluoren-9-one by Sonogashira coupling as a novel precursor for synthesis of quinodimethane (QDM)

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Synthesis and characterization of new symmetrical 3,6-bis[(25,26,27-tripropoxy-28-(3-(4-iodophenyl) propoxy)-*p*-*tert*-butyl calix[4]arene ethynyl]-9H-fluoren-9-one by Sonogashira coupling as a novel precursor for synthesis of quinodimethane (QDM)

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Novel symmetrical 3,6-bis[(25,26,27-tripropoxy-28-(3-(4-iodophenyl)propoxy)-*p*-*tert*-butyl calix[4]arene ethynyl]-9H-fluoren-9-one with a cone conformation was synthesized by palladium-catalyzed coupling of (25,26,27-tripropoxy-28-(3-(4-iodophenyl)propoxy)-*p*-*tert*-butyl calix[4]arene and 3,6-diethynyl-9H-fluoren-9-one. Its structure was confirmed by FT-IR, ^{1}H-NMR, and ^{13}C-NMR spectroscopy, and elemental analysis and positive ion FAB mass spectrometry.

Key Words: Synthesis, 3,6-diethynyl-9H-fluoren-9-one, *p*-*tert*-butyl calix[4]arene, FAB mass, palladium-catalyzed

Introduction

The development of methods for the synthesis of macromolecules such as dendrimers, supramolecules, and nanostructures with specific functions has increasingly become the center of attention in recent years.[1,2] Calixarenes, which are phenol-formaldehyde cyclic oligomers, are receiving increasing attention in the field of supramolecular chemistry. Calix[4]arenes can be selectively functionalized easily, both at the phenolic OH

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groups (lower rim)[3] and at the *para* positions of the phenol rings (upper rim). Consequently, they are useful building blocks for host molecules with different properties.[4] To date, various calixarenes that possess ester,[5,6a] amide,[7] or other functional groups have been synthesized for separation,[8] recognition,[9] discrimination,[10] and catalysis.[11] Lower-rim ethers,[6] and esters,[6a,12] show strong complexation with cations. Lower-rim esters are more effective than simple ethers in complexation with cations.[6]

In recent years, the chemistry of quinodimethanes (QDM) has attracted increasing interest.[13,14] The QDM derivative assembles itself into a spherical cyclic by the 4 weak C_{sp3}–C_{sp3} bonds between the fluorene units (compound **8**) that are formed during tetramerization. The unstable and reactive QDMs are commonly generated in situ from a suitable precursor. QDM derivatives are of considerable interest, both from a theoretical point of view and for their potential in organic synthesis,[13] as useful dienes in Diels-Alder reactions.[14] The inter- and intramolecular Diels-Alder reactions of these compounds form the basis of the synthesis of a wide range of target molecules.[13]

In this work, we reported the synthesis and characterization of a novel symmetrical "double calix[4]arene"[6]-substituted bis ethynyl fluorenone. Compound **8** is the key compound for the synthesis of QDM with a calix[4]arene substitute.

Experimental

The melting points of all compounds were recorded on a Philip Harris C4954718 apparatus (Birmingham, UK) without calibration. IR spectra were determined on a Thermo Nicolet 610 Nexus FT-IR spectrometer (Waltham, MA, USA) with KBr disks. Ultraviolet spectra were recorded on a Shimadzu UV-2401/PC spectrometer (Columbia, MD, USA). ^{1}H-NMR (400 MHz) and ^{13}C-NMR (50 and 100 MHz) measurements were recorded on a Bruker AM-400 spectrometer (Ettlingen, Germany) in $CDCl_3$ using TMS as the internal reference. Elemental analyses were performed using a Heraeus CHN-O-Rapid analyzer (Austin, TX, USA). Positive ion FAB mass spectra were recorded using a JEOL AX505HA spectrometer (Tokyo, Japan) with *m*−nitro benzyl alcohol as the matrix. Thin layer chromatography (TLC) analyses were carried out on silica gel plates. All chemicals were purchased from Merck (Tehran, Iran) and used as received by standard procedures, such as compound **5**. All reactions were carried out under an argon atmosphere. All of the instruments, chemicals, and solvents were dried according to standard methods. Freshly distilled solvents were used throughout, and anhydrous solvents were dried according to the method of Perrin and Armarego.[15]

p-*tert*-Butyl calix[4]arene (1): prepared according to Gutsche's method[16] as white crystals.

The cone conformer of 25,26,27-tripropoxy-28-hydroxy-p-*tert*-butyl calix[4]arene (2): prepared by the previously reported method[17] as white crystals.

25,26,27-Tripropoxy-28-(3-bromopropoxy)-p-*tert*-butyl calix[4]arene (3): prepared with a cone conformation according to the literature procedure.[18]

3,6-Bis[(trimethyl-silyl)ethynyl]-9H-fluoren-9-one (6): prepared by Sonogashira coupling procedure.[19]

3,6-Bis ethynyl-9H-fluoren-9-one (7): prepared according to the published procedure.[19]

25,26,27-Tripropoxy-28-(3-(4-iodophenyl)propoxy)-p-*tert*-butyl calix[4]arene (4):

To a solution of 480 mg (2.4 mmol) of 4-iodophenol in DMF (35 mL), 18 mg (3 mmol) of NaH (60%

dispersion in oil) was added, and the reaction mixture was stirred at 55 °C for 1 h. Then 0.9 g (1.05 mmol) of compound **3** was added and the mixture was stirred for 24 h at the same temperature. The solvent was removed under reduced pressure. The residue was dissolved in CH_2Cl_2 and washed with NaOH solution (10%). The organic layer was washed with water and dried with $MgSO_4$. The solvent was evaporated and the residue was submitted to column chromatography (SiO_2, CH_2Cl_2-petrolium ether, 30-50 °C, 1:5). The expanded structure of this compound is shown in Figure 1. Yield 77% (0.8 g), mp 91-92 °C. Anal. calcd. (%) for $C_{62}H_{83}O_5I$ (1035.0): C, 71.93, H, 8.08; found: C, 72.08, H, 8.09. ^{1}H-NMR (400 MHz, $CDCl_3$)δ (ppm): 0.97 (t, 9H, J = 7.4 Hz, H-14, 17), 1.02 (s, 18H, H-6), 1.13 (s, 9H, H-1 or 11), 1.14 (s, 9H, H-11 or 1), 1.95-2.08 (m, 6H, H-13, 16), 2.25 (quint., 2H, H-19), 3.13 (d, 2H, J = 12.5 Hz, H-3 or 8), 3.14 (d, 2H, J = 12.5 Hz, H-8 or 3), 3.73-3.84 (m, 4H, H-12), 3.86 (t, 2H, J = 7.8 Hz, H-15), 4.08 (t, 2H, J = 7.3 Hz, H-18), 4.12 (t, 2H, J = 6.3 Hz, H-20), 4.40 (d, 2H, J = 12.5 Hz, H-4 or 9), 4.43 (d, 2H, J = 12.5 Hz, H-9 or 4), 6.65-6.75 (m, 6H, H-2, 10, 22), 6.85 (s, 4H, H-5, 7), 7.56 (d, 2H, J = 9 Hz, H-21); ^{13}C-NMR (100 MHz, $CDCl_3$)δ (ppm): 10.26, 10.40, 23.26, 23.36, 30.06, 31.09, 31.12, 31.39, 31.51, 31.53, 33.75, 33.85, 33.88, 65.87, 71.83, 76.68, 77.31, 82.46, 116.94, 124.77, 124.89, 125.03, 125.13, 133.25, 133.42, 134.22, 138.19, 144.20, 144.30, 144.66, 153.38, 153.67, 153.94, 159.13.

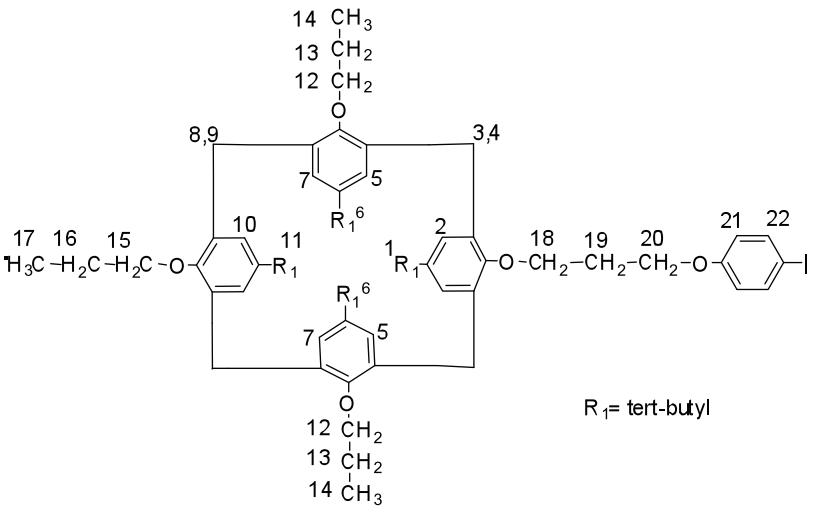


Figure 1. The numbering system for ^{1}H-NMR spectrum of compound **4**.

3,6-Bis-(25,26,27-tripropoxy-28-(3-(4-iodophenyl)propoxy)-p-*tert*-butyl calix[4]arene ethynyl)9H-fluoren-9-one (8):

To a 2-necked, 250-mL flask, 228 mg (1 mmol) of compound **7**, 2.2 g (2.1 mmol) of compound **4**, 28 mg (0.04 mmol) of $Pd(PPh_3)_2Cl_2$, and 15 mg (0.08 mmol) of CuI were added. DMF (50 mL) and Et_3N (25 mL) were then added and stirred under argon at 80 °C for 24 h. Solvents were evaporated under reduced pressure. The residue was dissolved in CH_2Cl_2 (200 mL) and washed with water. The organic layer was separated and rotary evaporated. The residue was submitted to column chromatography (SiO_2.CH_2Cl_2). The expanded structure of this compound is shown in Figure 2. Yield 58% (1.18 g), mp 170-172 °C. Anal. calcd. (%) for $C_{141}H_{172}O_{11}$ (2042.5): C, 82.89, H, 8.49; found: C, 82.52, H, 8.84. IR (KBr, ν, cm^{-1}): 2206 (C $\equiv$ C), 1714 (C=O); ^{1}H-NMR (400 MHz, $CDCl_3$)δ (ppm): 0.99 (t, 18H, J = 7.5 Hz, H-14, 17), 1.02 (s, 36H, H-6), 1.14 (s, 36H, H-1, 11), 1.95-2.05 (m, 12H, H-13, 16), 2.6 (quint., 4H, H-19), 3.14 (d, 4H, J = 12.5 Hz, H-3 or 8),

3.16 (d, 4H, J = 12.5 Hz, H-3 or 8), 3.74-3.86 (m, 8H, H-12), 3.90 (t, 4H, J = 7.7 Hz, H-15), 4.1 (t, 4H, J = 7.2 Hz, H-18), 4.2 (t, 4H, J = 6.2 Hz, H-20), 4.41 (d, 4H, J = 12.5 Hz, H-4 or 9), 4.44 (d, 4H, J = 12.5 Hz, H-4 or 9), 6.65-6.75 (m, 8H, H-2, 10), 6.86 (s, 8H, H-5, 7), 6.95 (d, 4H, J = 8.7 Hz, H-22), 7.46 (dd, 2H, J_{orto} = 7.7 Hz, J_{meta} = 1 Hz, H-24), 7.52 (d, 4H, J = 8.7 Hz, H-21), 7.66 (d, 2H, J = 7.7 Hz, H-23), 7.68 (s, 2H, H-26); ^{13}C-NMR (50 MHz, $CDCl_3$)δ (ppm): 10.44, 23.31, 23.42, 30.17, 31.20, 31.43, 33.79, 33.89, 66.01, 71.84, 76.37, 77.63, 88.00, 94.00, 114.78, 123.19, 124.83, 124.96, 125.08, 125.20, 130.34, 133.29, 133.39, 133.46, 134.25, 144.26, 144.74, 153.45, 153.98.

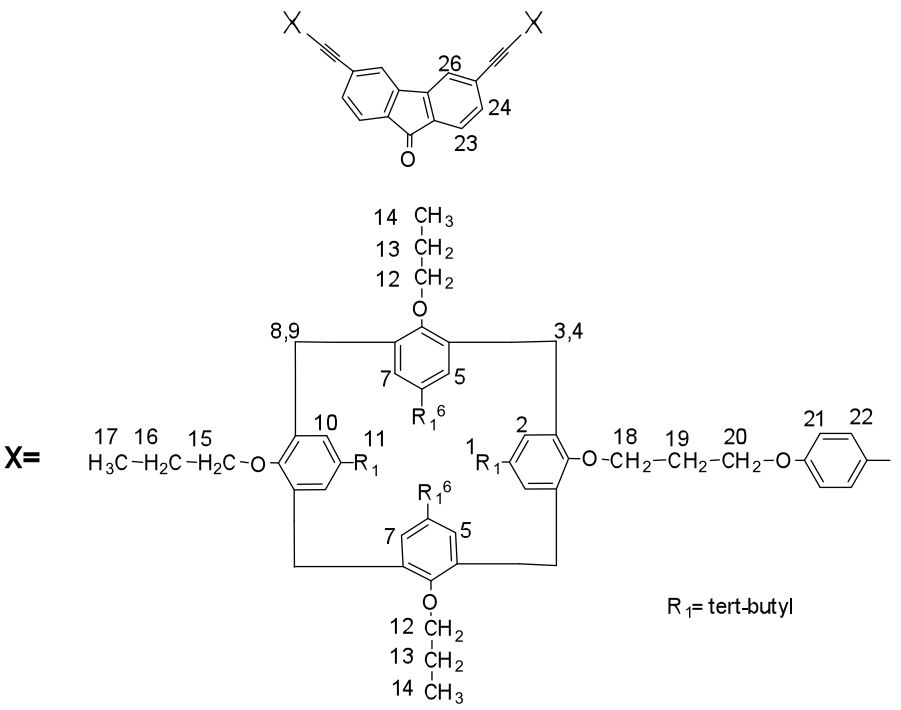


Figure 2. The numbering system for ^{1}H-NMR spectrum of compound **8**.

Analytical procedure (M^+ extraction)

The organic phase (5 mL of CH_2Cl_2), containing compound **4** or **8** (2.50 mmol L^{-1}), and the aqueous phase (5 mL), containing M^+Pic^- (0.25 mmol L^{-1}), NaOH (0.10 mol L^{-1}), and NaCl (0.50 mol L^{-1}), were mixed and shaken for 12 h at 25 °C. Extraction percentage values were determined spectrophotometrically at 357 nm. Blank experiments showed that no picrate extraction occurred in the absence of calixarene.

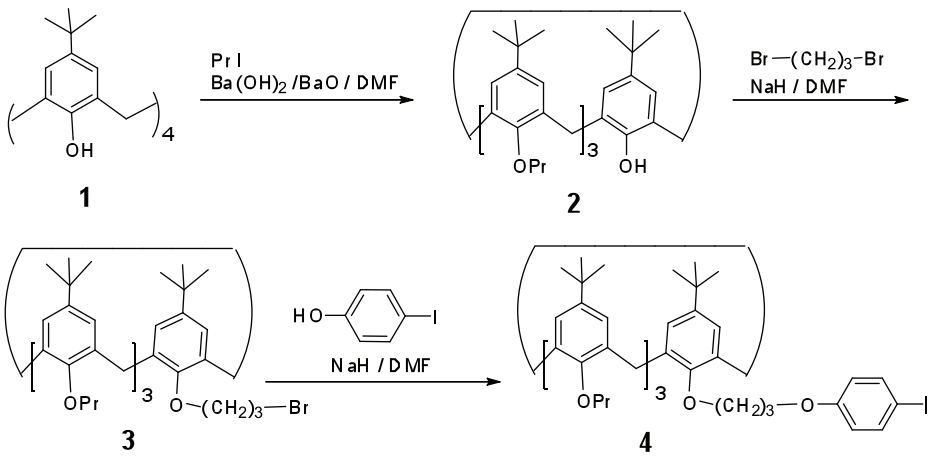
Results and discussion

It was recognized by Cornforth et al.[20] that a calix[4]arene can exist in 4 main conformations: cone, partial cone, 1,2-alternate, and 1,3-altemate. The structures of these conformers can be easily distinguished by their characteristic ^{1}H-NMR patterns arising from the $ArCH_2Ar$ methylene protons.[21–23] The conformations of

calix[4]arenes can be deduced from the ^{13}C-NMR chemical shifts of the methylene groups connecting each pair of aromatic rings.[24] An inspection of the proton-decoupled ^{l3}C-NMR spectra of all of the series revealed that the methylene carbon chemical shifts always ranged around 2 values: δ 31 and 37 ppm. In cone conformations, adjacent phenol rings are in a *syn* (δ 31 ppm) orientation only, while in the other conformations, adjacent phenol rings are in both *syn* and *anti* (δ 37 ppm) orientations.

The cone conformer of compound **2** (1HPr$_3$) has only one hydroxyl group in the lower rim; therefore, its reactions with di-bromo alkyl reagents are more selective and do not produce any other by-products. Because of the lower acidity of the proton of the OH group in compound **2**, it was activated by using NaH as a strong base; the small size of NaH is also very useful for this type of reaction.

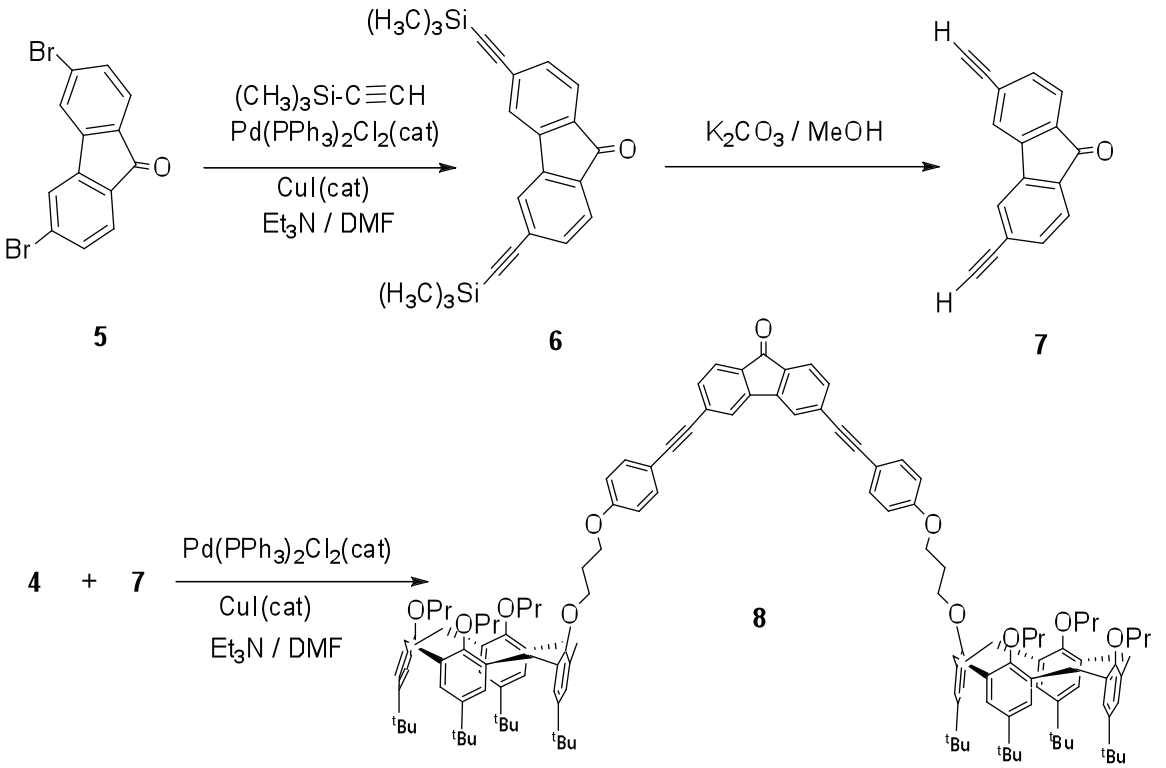
The cone conformer of 25,26,27-tripropoxy-28-(3-iodophenyl)propoxy)-*p*-*tert*-butyl calix[4]arene **4** was synthesized by the reaction of appropriate mono-bromo alkyl calix[4]arene derivative **3** with 2 eq of 4-iodophenol in DMF at an elevated temperature and in the presence of NaH. Under these conditions, compound **4** was synthesized in a yield of 77%. The sole by-product found in the reaction mixture was a mono-alkyl derivative, the product of the β-elimination reaction of the starting –O-(CH$_2$)$_3$-Br group in **3** (Scheme 1).



Scheme 1. General synthetic pathway for synthesis of compound **4**.

The coupling of the terminal alkynes with aryl or alkenyl halides was reported by Sonogashira[25] in 1975. Sonogashira coupling is carried out in the presence of a catalytic amount of a palladium(II) complex as well as copper(I) iodide by using an amine as the solvent. This coupling is one of the most straightforward methods for the preparation of aryl alkynes and conjugated enynes. Compound **8** was synthesized by the reaction of compound **4** with compound **7** under Sonogashira coupling conditions. The acetylenic hydrogens in compound **7** were easily substituted by the iodo-aryl in compound **4** (Scheme 2). The formation of product **8** can be clearly followed through its ^{1}H-NMR spectrum. Compound **8** was treated with 1,4-di-lithiobenzene and then converted to the QDM derivative with a calix[4]arene substitute.

The splitting pattern for ArCH$_2$Ar protons (a pair of doublets with a typical AX pattern)[21–23] showed that compounds **4** and **8** adopted a cone conformation (Table 1). We used the DEPT-135 technique to distinguish signals relevant to the methylene carbons in compounds **4** and **8**, which did not show a signal at δ 37 ppm, confirming that **4** and **8** adopt a cone conformation.[6] The numbering systems for the ^{1}H-NMR spectra of compounds **4** and **8** are shown in Figures 1 and 2.



Scheme 2. General synthetic pathway for synthesis of compound **8**.

Table 1. Properties of compounds **4** and **8**.

Sample no.	Product type	Mp (°C)	Yield (%)	Conformation	^{1}H-NMR $ArCH_2Ar$ $CDCl_3$ δ (ppm)	Splitting pattern of $ArCH_2Ar$ protons	J (Hz)	FABMS[a] data (me^{-1})
4	mono	91-92	77	cone	3.13 3.14 4.40 4.43	doublet doublet doublet doublet	12.5 12.5 12.5 12.5	1036
8	bis	170-172	58	cone	3.14 3.16 4.41 4.44	doublet doublet doublet doublet	12.5 12.5 12.5 12.5	2044

[a]1036 = $(M+1)^+$ and 2044 = $(M+2)^+$

Solvent extraction of metal salts, mostly picrates, from water into an organic solvent, usually CH_2Cl_2 or $CHCl_3$, was performed at 25 °C. Compounds **4** and **8** were able to encapsulate guest cations, and better selectivity in favor of Na^+ was obtained, especially for compound **8**. Although the cation selectivity of ionophoric calix[4]arenes can be changed by conformation, the cation affinity observed for cone conformers is always the highest among all 4 possible conformers.[17b] The results for the extraction ability of **4** and **8** are summarized in Table 2. The percentage extraction value (Ex %) for **8** was higher than that for **4**; this is attributed to

the existence of 2 bonding sites in **8**. The ratio of metal to ligand for compound **4** was 1:1 in the ML system and 2:1 for compound **8** in M_2L. The induced 3D cavity (size-fitting) of the parent calixarene platform and the attached side arms upon complexation play an important role in cation binding ability and selectivity. A picrate extraction experiment was performed following a modified version of Pedersen's procedure.[26]

Table 2. The percentage extraction value (Ex %) of compounds **4** and **8** for cation picrates.

Sample no.	Ex % of Li^+Pic^-	Ex % of Na^+Pic^-	Ex % of K^+Pic^-	Ex % of Cs^+Pic^-	Ex % of Ag^+Pic^-
4	5.6	26.2	19.1	4.3	18.9
8	10.7	53.6	38.8	6.2	37.4

The conditions necessary for the formation of the complexes and the factors influencing their stability include:

1. The relative sizes of the ion and the hole in the calixarene.
2. The number of oxygen atoms in the molecule.
3. The coplanarity of the oxygen atoms (maximum in cone conformation).
4. The symmetrical placement of the oxygen atoms (maximum in cone conformation).
5. The basicity of the oxygen atoms.
6. Steric hindrance in the hole of the calixarene (minimum in cone conformation).
7. The tendency of the ion to associate with the solvent.
8. The electrical charge of the ion.

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