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Synthesis and characterization of new sulfonamide derivatives of Calix[4]arenes in biomolecular recognition

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Abstract: In the present paper, we report novel natural water-soluble calix[4]arenes via Ipso-chlorosulfonation of upper rim and then reaction of these derivatives with aromatic amines to achieve the p-sulfonamid calix[4]arenes. Obtained receptors have been characterized by ^{1}HNMR, ^{13}CNMR, FTIR and MS spectroscopy. These Derivatives can be used as bimolecular receptors.

Keywords: *P*-sulfonamid Calix[4]arenes, Chlorosulfonation, Aqueous solution.

Introduction

Molecular recognition involves the association of molecules through non-covalent interaction that often called host-guest interactions [1]. These interactions are highly selective, and can be found in many natural complexes such as enzyme-substrate [2,3].The formation of host-guest complexes-the basis of supramolecular chemistry-especially in aqueous media is interesting not only from a mechanistic point of view, due to hydrophobic effects, but also from its possible applications, for example, in catalysis and bioreceptors [4]. Water-soluble macrocycles can encapsulate small organic compounds under physiological conditions. A principle study of host-guest interactions is of interest especially in pure water as the solvent [5].

In Supramolecular Chemistry, Preorganization and Architect of Suitable Host Molecules before Synthesis is Important. Large molecules with an internal cavity capable of including guest molecules, ability of solving in water and stable conformation of receptors are of great interests to workers in supramolecular chemistry [6,7].

Availability also accounts for the increasing attention that artificial bridged aromatic oligomers called calixarenes [8] have received over the last decades [9]. Remarkable applications of calixarene derivatives have been discovered, which include their use as efficient sensors, highly selective extractants, enzyme mimics, precursors of capsules, building blocks for nanoporous materials, and ect. [10]While most studies in calixarene chemistry has focused on molecular recognition [10].

To date, calixarenes have been extensively studied as a platform to construct a novel host compound bearing a specific function [11,12]. By selective functionalization [13] both at the phenolic OH groups (lower rim) and at the para position of the phenol rings (upper rim) we could obtain selective receptors for cations [14-19], anions [20], and neutral molecules [21-25].Some derivatives of calixarenes are flexible enough to adjust the cavity dimension and able to form inclusion compounds with neutral and biological molecules such as amino acids [26-28].

For importance of studying the biological systems, recently, chemists have been focused on host–guest binding of biomolecules and water soluble calixarenes in wide field. Host-guest interactions of calix[4]arenes in water by means of fluorescence spectroscopy were studied by shi et al. [29]. In 1993, Reinhoudt and et al., were reported the synthesis of calix[4]arene

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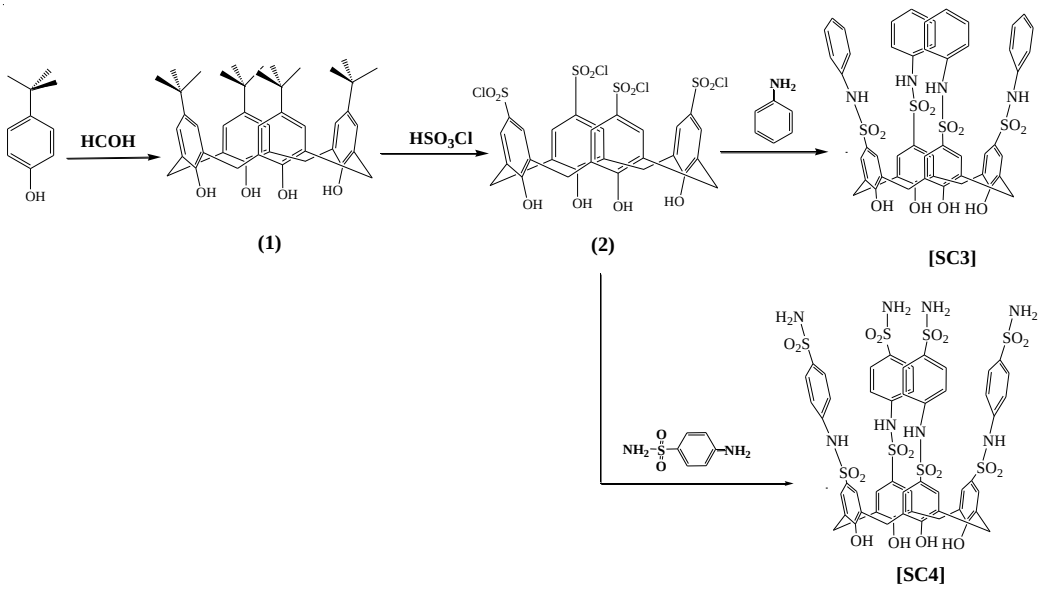
sulfonamides via direct chlorosulfonation at the upper rim of lower rim functionalized calix[4]arene, followed by reaction with an appropriate aliphatic amine , These sulfonamide Derivatives behave as hydrophobic, selective neutral anion receptors [30]. In 2004, the complexation of the sulphonamide calixarene hybrids with anions were studied by NMR titration, and association constants were determined [31]. in 2005, the synthesis of various sulfonate and sulfonamide derivatives were reported as a metallo-enzyme active sites [32].The complexation properties of sulphonated calixarenes towards small neutral organic molecules, drug molecules [33,34] and biomolecules such as amino acids, peptides [35] and protein [36] in aqueous solution have been extensively investigated by ^{1}H-NMR spectroscopy [37], calorimetric titration [38] and MALDI-MS [39].

In this work, our strategy consists of the synthesis of the p-sulfonamid calix[4]arenes derivatives with aromatic amines via tetrakis (chlorosulfonyl) calix[4]arenes. These synthesized receptors based on p-sulphonamide calix[4]arene in aqueous solutions can be complexated with bimolecular guests (Scheme **1**).



Scheme 1: Synthesis of receptors.

Results and discussion

In this work, two new sulfonamide-calix[4]arenes were synthesized from 25, 26, 27, 28– tetrahydroxy 5, 11, 17, 23 -tetrakis[chlorosulfonyl] calix[4]arene (2) and two aromatic amines, aniline and sulfanilamide (Scheme **1**). First 25, 26, 27, 28– tetrahydroxy 5, 11, 17, 23 -tetrakis[chlorosulfonyl] calix[4]arene(2) was prepared by ipso-chlorosulfonasion reaction and four tert-buthyl groups substituted by SO_2Cl groups. The ipso- chlorosulfonasion reaction in CH_2Cl_2 gave chlorosulfonyl-calix[4]arene in 79% yield.

The 25, 26, 27, 28- tetrahydroxy 5, 11, 17, 23-tetrakis [phenylsulfamoyl] calix[4]arene **(SC3)** were obtained by reaction of chlorosulfonyl-calix[4]arene (2) with aniline in presence of pyridine as a base in 30% yield. This yield is 10% in presence of NEt_3 as a base. The obtained compound was purified by column chromatography and then analyzed.

25, 26, 27, 28- tetrahydroxy 5, 11, 17, 23-tetrakis [phenyl sulphanilamidesulfamoyl] calix[4]arene **(SC4)** was obtained by the same method in 13% yield by reaction of chlorosulfonyl-calix[4]arene (2) with sulfanilamide in presence of pyridine. This yield is 15% in presence of NEt_3 as a base.

The ^{1}H-NMR chemical shift of the calix[4]arene starting material : -OH (10.34 ppm), -Ar (7.05 ppm), tert-buthyl (1.21 ppm) and methylene bridge (3.54-4.24 ppm), are identical. In the ^{1}H-NMR spectra of compound 2, methylene bridge (3.87 ppm), –Ar (7.37 ppm) and –OH (9.84 ppm) were observed. It was observed that the Ar-CH_2-Ar protons were singlet in 3.87 by pinch-cone inversion.

In compound **SC3**, methylene bridge protons were observed as two peaks at 3.2 and 4.1 ppm and aniline aromatic protons are at 6.9, 7.0 and 7.1 ppm. It was observed that the –OH protons of **SC3** resonate at

9.8 ppm and the –NH- resonate at 12.9 ppm respectively (see Figure **1**) .the –NH- protons were resonate at high field because these protons are acidic protons. ^{13}C-NMR spectra were illustrating nine kind of carbon that eight of carbons appear at aromatic range. In the FT-IR spectra, the vibrations of the **SC3** appear at 1140 and 1311 cm^{-1} (SO_2NHR), 1657 and 3231 cm^{-1} (NH), 3200 cm^{-1} (OH) respectively.

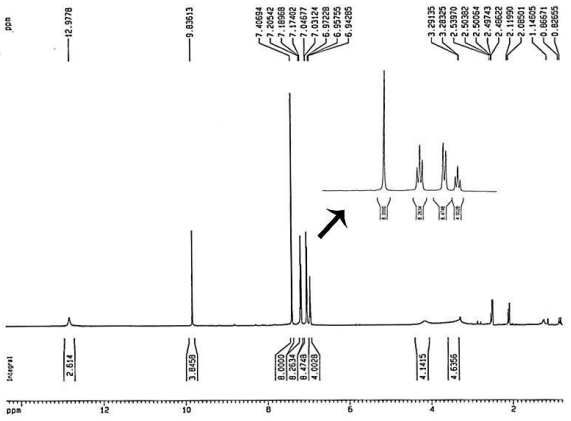


Figure 1. ^{1}HNMR of SC3:

The^{1}H-NMR spectra of **SC4** indicates the presence of 16 protons at 7.2 and 7.6 ppm for sulfanilamide rings, 8 –NH_2 protons at 7.5 ppm, 4 –OH protons at 10.5 ppm and 4 sulfonamide –NH- protons at 12.9 ppm.

^{13}C-NMR spectra were illustrating nine kind of carbon that eight of carbons appear at aromatic range. In the FT-IR spectra, the vibrations of the **SC4** appear at 1141 and 1317 cm^{-1} (SO_2NHR), 1595 and 3245 cm^{-1} (NH), 3200 cm^{-1} (OH and NH_2) respectively.

Both of the two compounds **SC3** and **SC4** dissolve in water and alcohols easily. However, these compounds are suitable for bimolecular mediums and can be complex by bio guests in aquase media.

Conclusion

In this study, two receptors based on sulfonamide calix[4]arene were synthesized. These receptors have been suitable functional groups (polar) to establish non-covalent interactions with polar molecular guests and able to forming stable host-guest complexes. According to previous experiments, these synthesized receptors are flexible enough to adjust the cavity dimension and able to form inclusion compounds with bio molecular or neutral molecules because these compounds are soluble in water and can be used to recognition of neutral molecules in aqueous solution.

Experimental

Chemicals and reagents:

All the reagents and solvents were purchased from various commercial sources and were analytical pure grade. Solvents were dried generally. Since the reactions were carried out under a dry nitrogen gas, all glassware was flame dried before use.

Characterization:

Melting points were determined with an Electro thermal 9200.ATR-FTIR spectra were obtained on a BRUKER, model: TENSOR 27 (German Co) with Specac Golden Gate ATR accessory.NMR spectra were recorded on a Bruker spectrometer with TMS as internal standard. FAB mass spectra were obtained with a Bruker Campass Data Analysis 4.0 mass spectrometer.

Synthesis:

5, 11, 17, 13-tetra(tert-butyl)-25, 26, 27, 28-tetra hydroxy calix [4] arene (p-tert-butyl calix[4]arene) (1) was synthesized according to previously described methods by Gutsche and co-workers [8]. mp=342–344 ^{o}C. ^{1}H NMR (500 MHz, $CDCl_3$, TMS) δ(ppm),1.21 (s, 36 H,$CH(CH_3)_3$), 3.51(d, 4H, $ArCH_2Ar$, J=12.8 Hz), 4.24 (d, 4H, $ArCH_2Ar$, J=12.8Hz), 7.05(s, 8H,Ar-H), 10.34 (s, 4H, 4OH); ^{13}CNMR (125 MHz, $CDCl_3$) δ(ppm) 30.5, 32.4, 34.0, 126.1, 128.2, 144.5, 146.8 ; IR, ν(cm^{-1}) = 3155.

Synthesis of 25, 26, 27, 28– tetrahydroxy 5, 11, 17, 23 - tetrakis[chlorosulfonyl] calix[4]arene(2):

5, 11, 17, 13-tetrahydroxy 25, 26, 27, 28 - tetrakis [chlorosulfonyl] calix[4]arene (2) was prepared in accordance with the previously method described by Coquiere and coworkers [32] with some modification. A mixture of p-tert- butyl calix[4]arene (1) (6.16 mmol) and anhydrous dichloromethane (160 ml) was placed in a three necked 500 ml round-bottom flask equipped with a magnetic stirrer, reflux condenser and dropping funnel. The mixture was stirred for 20 min at room temperature in an inert atmosphere of nitrogen gas. To this mixture, chlorosufonic acid (40 ml) was slowly added by syringe at a rate to keep the temperature between 0 and -10 °C. When the addition of chlorosulfonic acid was finished (2h), the solution mixture was stirred for one hour in room temperature and then was refluxed for 10 min under vigorous stirring. After cooling, dry ether was added since the suspended powder was observed

in the mixture. Separating was triturated several times with dry ether. (2) yield 79%; mp>250 dec; ^{1}H NMR: (500 MHz, DMSO-d6, TMS), δ(ppm), 3.87 (8H, s, $ArCH_2Ar$), 7.37 (8H, s, Ar-H) and 9.84 (4H, s, 8OH) ;^{13}C NMR: (125MHz, DMSO-d_6), δ(ppm), 151.4 (Ar-OH) , 138.3 (Ar -SO_2), 127.3 (Ar-H) , 126.4 (Ar-H), 30.4 ($ArCH_2Ar$); FAB-MS:m/z = 817.0 [$(M+H)^+$, calcd 817.5]., IR, ν(cm^{-1}) =1163, 1356 (SO_2Cl) cm^{-1}.

Synthesis of 25, 26, 27, 28- tetrahydroxy 5, 11, 17, 23-tetrakis[phenylsulfamoyl] calix[4]arene [SC3]:

To a suspension of 3 g (3.66 mmol) of 2 in 100 ml dry THF was added 5 ml aniline (3 mmol) drop wise which was distillated freshly. 1 ml of pyridine was added dropwise and the reaction mixture was stirred for 60 min at room temperature. The reaction mixture was filtered; the solvent was removed by evaporation. The crude was purified by column Chromatography with CH_2Cl_2/EtOAc to give the pure compounds as cream powder. yield 30%; mp>300 dec; ^{1}H NMR: (500 MHz, DMSO-d6, TMS), δ(ppm), 3.29 (s, 4 H, Ar CH_2Ar), 4.13 (s, 4 H, Ar CH_2Ar), 6.96 (t, 4 H, Ar-H, J=5 Hz), 7.03 (d, 8 H, Ar-H, J=4.9 Hz), 7.19 (t, 8 H, Ar-H, J=15), 7.40 (s, 8 H, ArH), 9.83 (s, 4 H, OH), 12.97 (s, 4 H, NH);^{13}C NMR: (125MHz, DMSO-d_6), δ(ppm), 159.5, 139.0, 130.3, 129.8, 129.7,129.6, 128.1, 124.5, 32.7; FAB-MS: m/z = 817.0 [$(M+H)^+$, calcd. for $C_{52}H_{36}S_4N_4O_{12}$:1036.640] ; found: *m/z* = 1028.6314, 685.4365, 413.2665.IR, ν(cm^{-1}) =1140, 1311 (SO_2NHR), 1657,3231 (NH), 3231(OH) cm^{-1}.

Synthesis of 25, 26, 27, 28- tetrahydroxy 5, 11, 17, 23-tetrakis[phenyl sulphanilamide sulfamoyl] calix[4]arene[SC4]:

To a suspension of 3 g (3.66 mmol) of 2 in 100 ml dry THF was added dropwise 3 g (19.1mmol) sulfanilamide which was dissolved in 20 ml dry THF. 1 ml of pyridine was added dropwise and the reaction mixture was stirred for 5 hours at room temperature. The reaction mixture was filtered and the solvent was removed by evaporation. The crude was purified by column Chromatography with CH_2Cl_2/EtOAc to give the pure compounds as cream powder. yield 13%; mp=240-242 °C; ^{1}H NMR: (500 MHz, DMSO-d6, TMS), δ(ppm), 3.34 (s, 4 H, Ar-CH_2-Ar), 4.16 (s, 4H, Ar-CH_2-Ar), 7.14 (s, 8 H, Ar-H), 7.23 (d, 8 H, Ar-H), 7.69 (d, 8 H, Ar-H), 7.56 (s, 8H, Ar-H),10.52(s, 4H, OH), 12.9 (s, 4H, NH));^{13}C NMR: (125MHz, DMSO-d_6), δ(ppm), 160.1, 142.2, 139.0, 130.7, 128.8,128.3, 127.9, 119.0, 32.5. FAB-MS: m/z = 817.0 [$(M+H)^+$, calcd. for $C_{52}H_{44}S_8N_8O_{20}$: 1356.840] ; found: *m/z* = 1031.5959, 862.4703, 718.9924, 413.2664.IR, ν(cm^{-1}) =1141, 1317 (SO_2NHR), 1595,3245 (NH), 3245(OH), 3505(NH_2) cm^{-1}.

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