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Synthesis of P-Sulfonato Calix[4]Resorcinarene and its Complexation Ability with Caffeine

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Research Article

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ABSTRACT

Synthesis of novel and versatile calix[4]Resorcinarene and P-sulfonato calix[4]Resorcinarene {p-SC[4]R} in the modern field of supramolecular chemistry which is also well known as host-guest chemistry. Here P-sulfonato calix[4]Resorcinarene act as supramolecular host and caffeine act as a guest molecule. The new 1:1 stoichiometry complex formation of caffeine–{p-SC[4]R} has been investigated. The aim of this work is to explored the supramolecule "P-sulfonato calix[4]Resorcinarene" as a drug delivery vehicle for the caffeine. From the last few decades caffeine citrate (cafcit) is used for the treatment of breathing problems of inborn babies (20 mg of caffeine citrate is equivalent to 10 mg of caffeine base). Its encapsulation directly delivers the caffeine base into the body which makes the synthesised soluble supramolecule as a versatile drug delivery molecule which can enhance its activity in various aspects.

INTRODUCTION

Caffeine, 1,3,7-trimethylxanthine is a natural xanthine alkaloid having a molecular weight of 194.19 $gmol^{-1}$, and molecular formula of $C_8H_{10}N_4O_2$. Caffeine can be isolated from *Camellia sinensis Linn* commonly known as tea leaves. Energy drinks contains high level of caffeine. Caffeine is the most widely consumed drug by humans. Intake of caffeine may not be harmful. The FDA considers caffeine to be both a drug and a food additive. They recommend

a maximum intake of 400 mg a day [1]. Caffeine overdose can lead to be fatal and should be avoided. Caffeine acts as a stimulant and a Central Nervous System (CNS) and is used medically to reduce physical fatigue and to restore alertness when drowsiness occurs [2]. It increased wakefulness, thought clearance, increased attention, and regulates body coordination and increases energy level. It is an adenosine antagonist receptor. As caffeine is a natural stimulant and that is isolated from *Camellia sinensis* Linn. Commonly known as tea leaves. Caffeine is the most widely consumed drug by humans. The FDA considers caffeine to be both a drug and a food additive hence it is used in soft drinks and energy drinks.

MATERIALS AND METHODS

Research over the past few decade showed that caffeine has been extensively investigated for its therapeutic benefits. Caffeine contains Purine derivatives play a crucial role in the most of biological processes. Due to its nominal side effects it can be used pharmacologically with higher efficacy and makes it a potential biologically active compound which can be used for variety of human diseases.

To keep the positive effects of caffeine molecule in mind, the interaction of the Caffeine molecule with the versatile water soluble macrocyclic compound p-sulfonato calix[4]resorcinarene has been studied by UV spectrum and IR spectrum. Calixarenes are a well-known class of macrocyclic compounds. The calixarene family can be subdivided into two major branches, the phenol derived cyclooligomers i.e. calixarenes and the resorcinol derived cyclooligomers i.e. Calix resorcinarene. Calixarenes has a long history but from the last few decades it was emerged as versatile macrocyclic compound which act as a supramolecular host in this modern field of supramolecular chemistry or commonly known as host-guest chemistry. Calix[4]Resorcinarene is a cyclic tetramer and have bowl shaped structure of calix[4]Resorcinarenes have a concave binding cavity formed by four resorcinol units and high affinity towards various guests such as cations, anions and molecules with different sizes with various hydrophobic/ hydrophilic interactions.

Insolubility of calixarenes in water is a big concern as this property resists this molecule to act as a carrier molecule in our biological system. Shinkai and co-worker reported water soluble calixarene derivatives bearing a sulfonic acid groups at the upper rims. Sulfonato calixarenes have become a particularly important class in host-guest supramolecular chemistry because of their high solubility in water, stability and less toxicity than cyclodextrins and have a number of potential biological activities.

From the last few decades these water soluble calixarenes interacts with the different drugs becomes the most prominent and versatile drug delivery molecule, as these macromolecules after the interaction enhances the solubility of different drugs which can be used for different disease. These interaction processes may consist of the displacement of water molecules from the cavity of the p-SC[4]R by more hydrophobic drug, with the formation of hydrogen bond or other low energy interaction and an increase in van der Waals interaction between molecules.

Harada and co-workers studied the encapsulation of curcumin with cyclodextrin. But cyclodextrin is present inside the cell which leads to deformation of the cell structure. Recent studies shows that calixarene do not affect the structure of the cell and has numbers of medicinal applications. This studies shows that in mice, a single dose of free p-sulfonatocalixarene at doses equivalent to 2-5 g/kg in humans shows no acute toxicity. Binding of p-SC[4]R with biologically important drug molecules Lamotrigine [3]. The thermodynamic parameters. The ΔS is negative and ΔG negative value indicates that the formation of curcumin/p-SC[4]R inclusion complex. It was an exothermic and spontaneous process [4].

Based on the structure, properties, and such broad applications of these molecules, calix[4]resorcinarene along with its sulphonated product named as p-Sulphonato calix[4]resorcinarene were synthesised and studied by the help of modern spectroscopic techniques UV and IR.

Experimental work

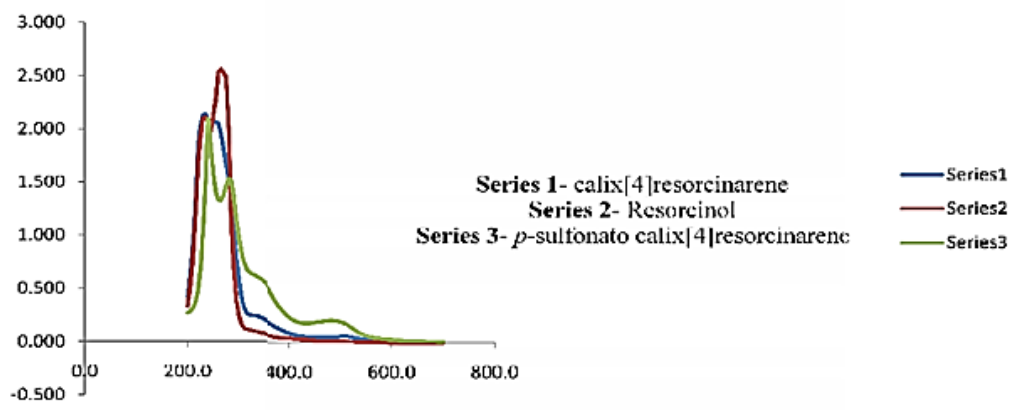
Resorcinol (11.01 g, 0.10 mol) and acetaldehyde (4.41 g, 0.10 mol) was added in 40 mL of water and then 10 mL of concentrated hydrochloric acid was carefully added. A precipitate was rapidly formed. The reaction mixture was stirred at 75˚C for 1 h, cooled in an ice bath, and filtered. The precipitate was washed for almost 15 days with a hot water and dried [5,6]. A mixture of calix[4]resorcinarene (5.44 g, 0.01 mol), a solution of 37% formaldehyde (4.1 g, 0.05 mol) and sodium sulfite (6.3 g, 0.05 mol) in distilled water (50 ml) was stirred and heated at 90-95˚C for 4 h, dilute hydrochloric acid (2 N) was added after cooling to adjust the pH to 7, followed by acetone (150 ml) to precipitate the product. The solid was filtered, washed with acetone (100 ml) and dried to get p-sulfonato calix[4]Resorcinarene [7-9]. 20 g of tea leaves was taken in a 150 ml of beaker and then 30 ml of deionised water was added. The contents in beaker gently boiled for 20 minutes. The extract was filtered and poured into the beaker and then 2 g sodium carbonate was added. The tea extract was cooled to room temperature and the tea extract was transferred from beaker to a separating funnel that is supported by a ring on a ring stand. 5 ml Dichloromethane (DCM) was added to the separating funnel and it was shaken gently in such a way to avoid emulsion and allowed the contents of the separating funnel to settle down. The two distinct mostly clear layers formed and Carefully Drain The Lower (DCM) layer. These steps were repeated for several times. 0.5 g anhydrous sodium sulphate was added to the combined DCM extract. The anhydrous sodium sulphate absorbed the small amount of water dissolved in DCM. The DCM extract was heated to remove the DCM part and to isolate the desired caffeine.

RESULTS AND DISCUSSION

UV-visible spectrum analysis

UV-Vis spectrum of Calix[4]resorcinarene, resorcinol, *p*-sulfonato calix[4]resorcinarene were overlaid over each other and were recorded in the region of 200-550 nm. The results show three different peaks 450 nm, 500 nm and a common peak at 280 nm for the common phenolic groups and aromatic region in these three phenolic compounds (Figure 1).

Figure 1. Excel overlay plots of UV-VIS spectrums. **Note:** (——) Series 1-calix[4]resorcinarene; (——) Series 2-resorcinol; (——) Series 3-*p*-sultonato calix[4]resorcinarenc.



FT-IR spectrum analysis

The FT-IR spectrum of C[4]R, *p*-SC[4]R. The strong peaks at 1620-1640 cm^{-1} has a predominantly mixed C=O & C=C groups and 1610 cm^{-1} is indicative of symmetric aromatic stretching vibration, 650-700 cm^{-1} is C-H vibration of aromatic ring. FT-IR spectrum of calix[4]resorcinarene consisted of a broad absorption bands of OH stretching at 3400 cm^{-1} and secondary alcohol (1100cm^{-1}), C-H vibration of CH_3 group (1430-1470 cm^{-1}), C-H stretching (650-900cm^{-1}). FT-IR spectra of p-sulfonato calix[4]resorcinarene consisted of a broad band of–OH stretching at 3457 cm^{-1} while two characteristic absorption peaks at 1185, 1084 cm^{-1} indicative of–SO_3 group.

Figure 2. IR spectrum of calix[4]resorcinarene.

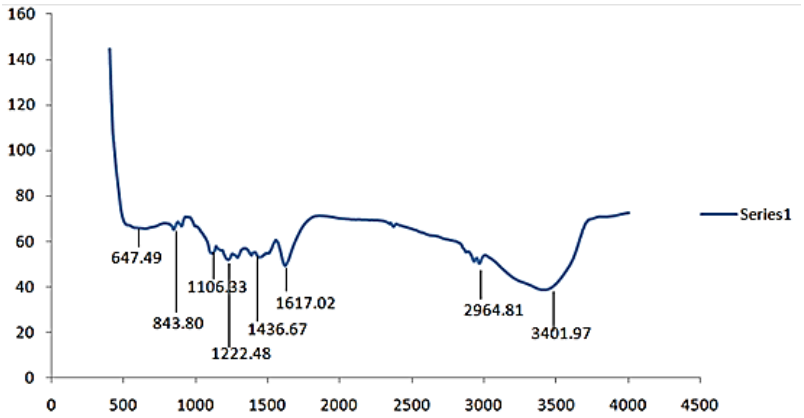
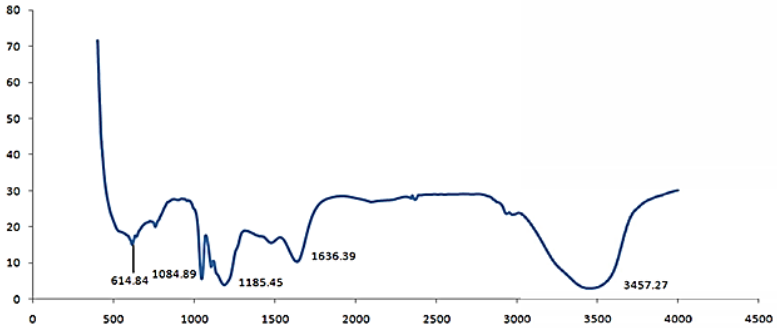


Figure 3. IR spectrum of p-sulfonato calix[4] resorcinarene.



Preparation of physical mixture

Physical mixtures were prepared by simply grinding the pure caffeine:p-SC[4]R in a molar ratio of 1:1. The mixture was crushed well for almost 30 minutes and then characterized by using UV spectroscopic method. The UV spectra of caffeine and p-SC[4]R were recorded in the region of 200–550 nm. The results showed two different peaks at 205 nm and 215 nm of pure drug caffeine, inclusion complex respectively. 10 nm slight shifts in the UV-Vis spectrum shows some interaction between the p-SC[4]R and caffeine indicates the formation of inclusion complex.

CONCLUSION

It can be concluded that calix[4]Resorcinarene, *p*-sulfonatocalix[4]Resorcinarene {p-SC[4]R} and isolation of caffeine from tea leaves has been successfully done. The new 1:1 stoichiometry complex formation of caffeine-*p*-SC[4]R has been investigated. Investigations have been done on the basis modern spectroscopic techniques like UV-VIS, FT-IR data. The aim of this work is to explored this versatile supramolecule "P-sulfonato calix[4] resorcinarene" as a drug delivery vehicle for the caffeine.

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