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Determination of association constant of host–guest supramolecular complex (molecular recognition of carbamazepine, antiseizure drug, with calix(4)arene)

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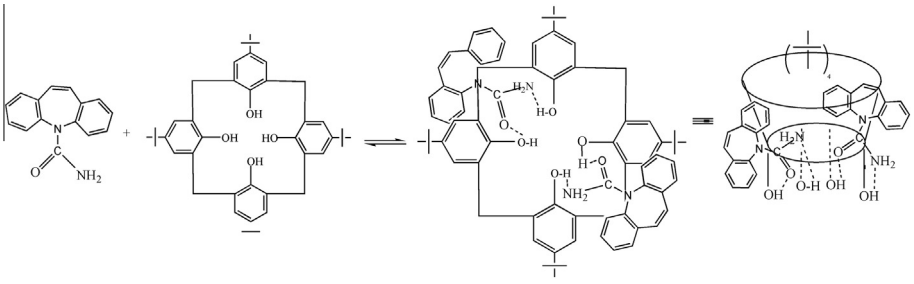
HIGHLIGHTS

- *p-t*-Butyl calix(4)arene is used as host and carbamazepine as guest molecule.
- Thermodynamic property of the host–guest, complex formed was studied.
- The stochiometry of the host–guest complex formed was 1:2.
- Dimension of the host molecule plays a vital role in forming the host–guest inclusion.

GRAPHICAL ABSTRACT



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ABSTRACT

The thermodynamic property of the host–guest, inclusion complex formed between *p-t*-butyl calix(4)arene which is a supramolecule, and the antiseizure drug, carbamazepine was studied. *p-t*-Butyl calix(4)-arene has been used as a host molecule and carbamazepine as a guest molecule. Optical absorption spectral studies were carried out to investigate the molecular recognition properties of *p-t*-butyl calix(4)-arene with carbamazepine. The stochiometry of the host–guest complexes formed and the association constant were determined. An interesting 1:2 stochiometric host–guest complex was formed. Job's continuous method of variation and Benesi–Hildebrand expression were used for the determination of binding constant and the stochiometry of the host–guest complex formed. Molecular dimension of the host molecule plays a vital role in the formation of the host–guest stochiometric complexes.

1. Introduction

The term supramolecular chemistry was coined in 1969 by Jean-Marie Lehn. Lehn defined supramolecular chemistry as the chemistry of the intermolecular bond. Supramolecular compounds are built by linking molecules with intermolecular interactions [1]. Supramolecular chemistry deals with the construction of organized molecular "arrays" with much larger length scales. In molecular chemistry, strong association forces such as covalent and ionic bonds are used to assemble atoms into discrete molecules and hold them together. In contrast, the forces used to organize and hold together supramolecular assemblies are weaker noncovalent interactions, such as hydrogen bonding, metal coordination, hydrophilic–hydrophobic interactions, van der Waals forces, pi–pi interactions and electrostatic effects. In any supramolecular assembly, a large number of intermolecular interactions are possible, but only few are actually observed. The weakness of these interactions makes it difficult to predict

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supramolecular structures and means that, in solution, supramolecular structures are not always stable over time but this flexibility also means that they are frequently favoured in important mechanisms, notably in biological reactions and in crystallization processes, where the ability to form short-lived transition states and to perform trial-and-error correction easily is essential [2]. Supramolecular chemistry include molecular self-assembly, folding, molecular recognition, host–guest-chemistry, mechanically-interlocked molecular architectures and dynamic covalent chemistry [3].

The development of supramolecular or host–guest chemistry of the crown ethers resulted in a diverse array of supramolecular structures. The last two decade, supra molecule cyclodextrins have wide range of applications in organic synthesis [4], industrial applications [5], drug delivery and in pharmaceutical industry due to their use as a complexing agent to increase the aqueous solubility of the poor soluble drug molecules and to increase their bioavailability and stability [6,7]. Three-dimensional structures, that already have a molecular cavity, are attractive building blocks in supramolecular chemistry. In this aspect calixarenes as nano-baskets have been considered as the third generation of supramolecular host compounds after cyclodextrins and crown ethers [8,9]. By comparing with the naturally occurring cyclodextrins and crown ethers the calix(n)arenes provide well defined conformational properties and cavities with molecular dimensions to encapsulate guest molecules [10]. Calixarenes have become important receptors in synthesis and applications as supramolecular platforms for molecular recognition, sensing and self-assembly, catalysis, nanotechnology, and drug discovery. The analytical applications of calixarene derivatives in fields of complexation, separation, electroanalysis, spectroscopy, chemometrics [11] and in industries [12] are well reviewed in journals. Calix(n)arenes are used as electrochemical sensors, optical sensors, chiral recognition devices, solid phase extraction phases [13], carriers in liquid membrane transport [14]. The other application includes calixarene as metalo enzyme models [15,16]. The biomedical applications of Calix(n)arene inclusion complexes includes anti-cancer, anti-mycobacterial, antiproliferativity, catalytic and inhibitory activities (including HIV as target), as well as solubility control, drug analysis, drug purification and drug supports [17–19].

Calixarenes are cyclo oligomers formed in the condensation reaction of formaldehyde and para substituted phenol [8]. They have two well defined rims, an upper rim with para substituent of phenolic ring, a lower rim with phenolic hydroxyl group and a central annulus. Owing to this excellent skeleton with preformed cavities, the calixarenes are able to act as molecular baskets (host) towards the guest molecules [8]. This "basket" plays a vital role in shaping the entire architecture of calixarene for its function in host–guest chemistry.

Carbamazepine is a tricyclic neutral heterocyclic compound. Carbamazepine as one of the anticonvulsant drugs is widely used in the treatment of simple and complex trigeminal neuralgia, seizures, and bipolar affective disorders [17,20]. Carbamazepine is one of the two safest and most effective older AEDs for the seizure types and is chosen for monotherapy due to its high effectiveness and relatively low incidence of side effects [20]. Its tricyclic structure resembles that of psychoactive drugs imipramine, chlorpromazine and that of some structural features with the AEDs phenytoin, chlonazepam and phenylbarbitol. It belongs to iminostilbene class of antiseizure drug.

Molecular recognition is the specific binding of a guest molecule to a complementary host molecule to form a host–guest complex. The molecules are able to identify each other using noncovalent interactions such as hydrogen bonding, polar attractions, van der Waals forces, and hydrophilic–hydrophobic interactions. Molecular recognition has been defined as a process involving both binding and selection of substrate(s) by a given receptor molecule. Molecular recognition relies on geometrical complementarity based on the "key-and-lock" principle [2]. In order to study molecular recognition, some measurable property of the guest (or host) must change upon complexation. Techniques that have been used to measure such properties include NMR, UV–visible, and fluorescence spectroscopy [21]. We have adopted UV–vis spectroscopic technique for the determination of stochiometry and the association constant for the host–guest complex formed. We are enthralled in the thermodynamics of binding between the host and guest in the solution state, which is very essential to design a synthetic system that performs specific tasks. We have carried out the optical absorption studies of carbamazepine with *p-t*-butyl calix(4)arene, which is the appropriate molecule due to pre organized conformation. We have determined the association constant of the host–guest complex formed, which is the thermodynamic property and also the stochiometry of the host–guest complex formed.

2. Materials

Carbamazepine was purchased from Sigma chemical laboratory, *p-t*-butyl calix(4)arene from Aldrich chemical laboratory and the solvent Dichloromethane from Merck chemical laboratory.

2.1. Experimental

10^{-4} molar stock solution of *p-t*-butyl calix(4)arene and 10^{-4} molar stock solution of carbamazepine were prepared for this study. Dichloromethane was used as a solvent. To determine the stochiometry of the complex formed and to determine the association constant, the stock solution of host and guest were mixed in nine different [H]/([G]+[H]) ratios by the stepwise addition of (n) ml of host to ($10 - n$) ml of guest solutions (n = 1–9) keeping the total concentration as same. Two stock solutions of host and guest were mixed in nine different ratios 1:9, 2:8, 3:7, 4:6, 5:5, 6:4, 7:3, 8:2, 1:9 keeping the total concentration equal to 1×10^{-3} M ([G]+[H]).The solutions were kept in ultra sonicator for 5 min in order to make the mixture homogeneous. The optical absorption spectra were recorded using Shimadzu UV – 2450 spectrophotometer. All the experiments were performed at room temperature.

3. Results and discussion

Fig. 1 depicts the molecular structure of carbamazepine. IUPAC name of carbamazepine is 5H-Dibenz [b,f]azepine-5-carboxamide. Calixarenes are characterized by a three-dimensional basket, cup or bucket shape. Calixarenes are characterized by a wide upper rim and a narrow lower rim and a central annulus. With phenol as a starting material the 4 hydroxyl groups are intrannular on the lower rim. In calix(4)arene, 4 up-down conformations exist: cone (point group C_{2v}, C_{4v}), partial cone C_s, 1,2 alternate C_{2h} and 1,3 alternate D_{2d}. The 4 hydroxyl groups interact by hydrogen bonding and stabilize the cone conformation. This conformation is in dynamic equilibrium with the other conformations. Conformations can be locked in place with proper substituents replacing the hydroxyl groups which increase the rotational barrier. Alternatively placing a bulky substituent on the upper rim also locks a conformation. The calixarene based on *p-tert*-butyl phenol is also a cone [22]. Calixarene cavities are capable of molecular recognition [23]. Calixarenes are attractive in molecular recognition studies because of their ability to form inclusion complexes with ions and neutral molecules, so they function as ion and neutral molecule receptors. In Molecular recognition studies the