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Molecular recognition study of ethosuximide by the supramolecular probe, *p-t*-butyl calix(8)arene

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ABSTRACT

The supramolecule, *p-t*-Butyl calix(8)arene, forms inclusion complex with the antiseizure drug molecule, ethosuximide. This feature is explained on the basis of optical absorption spectroscopy. Here *p-t*-Butyl calix(8)arene is the host molecule and ethosuximide is the guest molecule. The stoichiometry of the host–guest complex and the binding constant has been determined using Benesi–Hildebrand plot. Based on the result obtained the structure of the inclusion complex has been proposed.

1. Introduction

Supra molecular chemistry deals with highly organized structures involving two or more individual molecules held together only by intermolecular forces [1]. Supra molecular systems involve catalysis of chemical reactions [1,2], organic synthesis [3,4], molecular recognition [1,2], bio mimetic reactions [5], drug delivery [6], and industrial applications [7]. Molecular recognition reveals multi molecular entities formed between chemical species of complementary topology through non covalent interactions such as hydrogen bonding, polar attractions, van der Waals forces, and hydrophilic–hydrophobic interactions.

Calix(*n*)arenes are considered as the third generation of supra molecule receptors after cyclodextrin and crown ethers [8,9]. By comparing with the naturally occurring host molecules such as cyclodextrin, the calix(*n*)arenes provide a well-defined conformational properties and cavities with molecular dimensions to encapsulate guest molecules. Calixarenes are cyclo oligomers formed in the condensation reaction of formaldehyde and para substituted phenol [8]. They contain 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 capable to act as molecular baskets (host) towards the guest molecules [8]. This "basket" plays a vital role in shaping the entire structural design of calixarene for its function in host–guest chemistry. Calix(*n*)arenes are used in various applications including electrochemical sensors, optical sensors, chiral recognition devices, solid phase extraction phases [10], carriers in liquid membrane transport [11]. They have been analogous to cyclodextrin in the formation of inclusion complexes [9,12] (host–guest properties, molecular recognition) with metals [13–15], neutral molecules [16], anions [17], cations [18,19], organic molecules [20–22] and act as catalysts [23–25]. Inclusion of fullerene within the calixarene annulus leads to the novel purification and useful method for the guest molecule [26,27].

Ethosuximide is a heterocyclic, antiseizure drug molecule [28]. Ethosuximide belongs to the succinimide group of new generation antiseizure drug. It is a drug of choice for the treatment of simple absence seizure [28] which is a least toxic drug among the succinimides. The principal use of antiseizure drugs, referred to AEDs, is in the prevention and the control of epileptic seizures. The ideal AED among other things should completely suppress seizures in doses that do not cause undesired central nervous system toxicity [28]. It should be well tolerated and highly effective against various type of seizures and devoid of adverse side effects on vital organs and functions. Many of the standard AEDs containing ureide structure have been clinically used for more than 30 years. As a consequence of rapid development in molecular biologic techniques for the study of neuro physiology of epilepsy, a new generation of clinically available AEDs has emerged.

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The increased exploration for potential applications of calixarenes urges the use of different physical chemical methods to evaluate the structural and material properties. Analytical techniques have been used to measure such properties include UV–visible spectroscopy which is the quickest method. In order to attain effectual molecular recognition, *p*-*t*-Butyl calix(8)arene has been used as a host molecule for this study. Although there are lot of reports on the interaction of metal ions [13–15] with calixarenes, very few reports are available on the recognition of organic molecules, particularly drug molecules [21] with these supra molecules in organic solvents.

In this aspect we are fascinated in the study of molecular recognition of drug molecules by *p*-*t*-butyl calix(8)arene. We have used the drug molecule ethosuximide as a guest and *p*-*t*-butyl calix(8)arene as a host molecule. In this current study we have determined the stoichiometry, and the binding constant of the host–guest complex formed between *p*-*t*-butyl calix(8)arene and ethosuximide.

2. Materials

The ethosuximide was obtained from Sigma chemical laboratory. *p*-*t*-butyl calix(8)arene from Aldrich chemical laboratory and the solvent dichloromethane from Merck chemical laboratory were used.

3. Experimental

10^{-4} Molar stock solution of *p*-*t*-butyl calix(8)arene and 10^{-4}molar stock solution of ethosuximide were prepared using dichloromethane as a solvent. To determine the stoichiometry of the complex formed and 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^{-2} M $([G]+[H])$.The solutions were kept in ultrasonicator 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.

4. Results and discussion

The molecular structure of ethosuximide is shown in Fig. 1. IUPAC name of ethosuximide is (*RS*)-3-ethyl-3-methyl-pyrrolidine-2,5-dione. It consists of a heterocyclic, pyrrolidine ring with two free carbonyl groups as functional groups at positions 2 and 5.

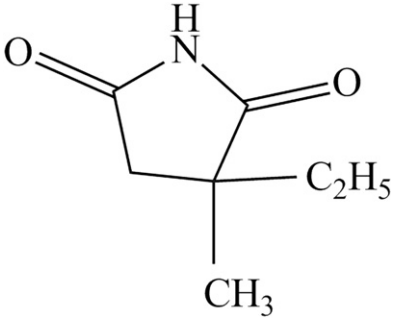

Fig. 1. Structure of ethosuximide.

The molecular structure of *p*-*t*-butyl calix(8)arene is presented in Fig. 2. *p*-*t*-butyl calix(8)arene consists of 8 *p*-*t*-butyl phenol units connected via methylene bridge in the ortho position with respect to hydroxyl groups. It contains two well defined rims, an upper rim with tertiary butyl substituent of phenolic ring, a lower rim with phenolic hydroxyl group and a central annulus [8]. Owing to the larger annulus, *p*-*t*-butyl calix(8)arene is favoured to form the inclusion complexes [29,30]. Molecular models reveal that the *p*-*t*-butyl calix(8)arene is a more flexible molecule [8,31] for molecular recognition. An X-ray crystallographic determination of *p*-*t*-butyl calix(8)arene shows that the compound exists in a pleated loop conformation, as pictured in Fig. 2. In this conformation, eight OH groups are positioned in a circular array, which is an pleated loop, is preferably constituted for circular hydrogen bonding [8]. *p*-*t*-butyl calix(8)arene assumes a pleated loop conformation in the solid state and it is the preferential conformation(8) in solution as well.

Fig. 3 depicts the optical absorption spectra of *p*-*t*-butyl calix(8)arene and ethosuximide in varying molar ratios. In the UV–visible spectrum of ethosuximide with *p*-*t*-butyl calix(8)arene, there are two prominent absorption bands at 229 and 289 nm. For this investigation, the observed absorption spectral features around 229 nm band of ethosuximide in presence of *p*-*t*-butyl calix(8)arene reflect the extend of complexation and make it possible to determine the binding constant. The change in wavelength maxima and absorbance (at wavelength maxima) at 229 nm suggests that the main contribution for the host–guest interaction is due to the polar interaction and hydrogen bonding between the host–guest molecule. In the current study the absence of any remarkable shift in the λ_{max} and also the non formation of any new band clearly rules out the formation of charge transfer complexes [32].

Job's method is generally used in the spectroscopic determination of stoichiometry of the complex formed between the host and guest molecules [32]. In Job's method of continuous variation, the change in optical density at 229 nm band under the effect of guest–host interaction (δA) is plotted (Fig. 4) against the mole fraction of *p*-*t*-butyl calix(8)arene. In the continuous variation plot the absorption minimum is at 0.2 M ratio which corresponds to the 1:4 stoichiometry of the *p*-*t*-butyl calix(8)arene (host) and ethosuximide (guest). This stoichiometry predicates the binding of four molecule of guest ethosuximide with one host molecule of *p*-*t*-butyl calix(8)arene. Generally continuous variation plot shows a maximum δA at a particular mole fraction of host which provides the stoichiometry of the complex formation i.e. absorbance value

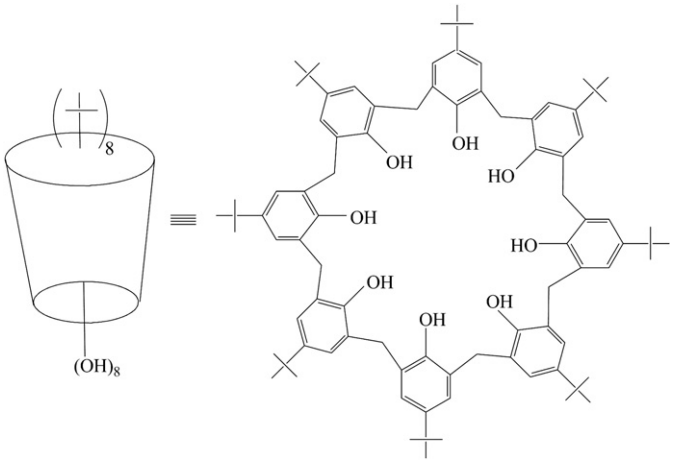

Fig. 2. Structure of *p*-*t*-butylcalix(8)arene.