



# Host-guest complexes of local anesthetics with cucurbit[6]uril and *para*-sulphonatocalix[8]arene in the solid state



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## ABSTRACT

Here we describe the host-guest inclusion complexes of local anesthetic drugs with two macrocyclic hosts cucurbit[6]uril and *para*-sulphonatocalix[8]arene in the solid state. The anesthetic agents used in the co-crystallization with the supramolecular hosts are lidocaine, procaine, procainamide, prilocaine and proparacaine. Both macrocycles encapsulate the alkylammonium moieties of anesthetics guests into their cavities although the mechanism of complexation, host-guest stoichiometry and geometry differ depending on the nature of the supramolecular host.

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## 1. Introduction

The development of new local anesthetic formulations with prolonged anesthetic action and without toxic side effects is a current pharmaceutical challenge [1]. The anesthetic agents bind to the sodium channels of the nerve membrane stabilizing the inactivated state and thus block the initiation and propagation of nerve impulses. However, local anesthetics show a relatively short duration of action and may have adverse side effects such as cardiac and neurological toxicity, accompanied sometimes by allergic reactions. In order to improve the application and provide slow controlled release, the supramolecular encapsulation of different anesthetic drugs within macrocyclic host molecules such as cyclodextrins [2], *para*-sulphonatocalix[*n*]arenes [3] and cucurbit[7]uril [4] have been investigated. These three families of macrocyclic hosts are characterized by different chemical structures, cavity properties and size. Cyclodextrins, macrocyclic oligosaccharides, prefer binding of neutral and anionic guests via a combination of hydrophobic effect, hydrogen bonding and van der Waals interactions [5].

Cucurbiturils, composed of glycouril units linked with methylene bridges, possess nonpolarizable hydrophobic cavities accessed via two polar carbonyl-rimmed openings. Cucurbiturils are known to form very stable host-guest complexes with cationic guests due to ion-dipole interactions, hydrogen bonding and hydrophobic effect [6]. Water-soluble *para*-sulphonatocalix[*n*]arenes have electron rich hydrophobic cavities build from aromatic systems and upper rims composed of anionic sulphonate groups. They tend to complex cationic species via a combination of electrostatic interaction with ammonium groups of guests, charge-assisted hydrogen bonding and interactions involving  $\pi$  systems of the calixarene skeleton [7]. With regard to these last host molecules there exists a wide knowledge of their behaviour both at the cellular level and in vivo [8].

Here we present structural studies on the host-guest complexes between local anesthetics and two different macrocyclic hosts cucurbit[6]uril **CB6** and *para*-sulphonatocalix[8]arene **C8S**, Fig. 1. Despite rich solution studies on the complexation of anesthetics with cucurbit[7]uril [4] and its acyclic analogue [9] no solid state structural studies on the inclusion properties of cucurbiturils towards local anesthetic drugs have been undertaken so far. As for the *para*-sulphonatocalix[*n*]arenes, several crystal structures of the inclusion host-guest complexes of local anesthetics; tetracaine,

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