Review Article

Simple calix[n]arenes and calix[4]resorcinarenes as drug solubilizing agents

Abstract

Many drug molecules have low solubility in aqueous media and, hence, poor bioavailability. The formation of a host-guest complex with some other compound which has a good solubility profile can facilitate solubilization of hydrophobic drugs. Complex formation relies upon the formation of non-covalent interactions between the host molecule and the drug guest. The use of calix[n]arenes, a well-characterized class of cyclic oligomers, has been investigated for their ability to form complexes with a variety of ionic and molecular species. This review highlights those studies which have demonstrated the potential of calix[n]arenes as host molecules in novel drug delivery systems.

Keywords: Calix[n]arene, Calix.[4]resorcinarene, Drug solubilization

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Introduction

The administration of drug molecules to the body requires them to be formulated into a suitable dosage form that may be dictated by the fundamental properties of the drug or the site of the drug target and disease being treated. It is essential for a drug to have a high degree of bioavailability so the choice of formulation can be critical if the drug is to progress from the drug discovery phase to the clinic. More specifically, many hydrophobic drugs suffer from poor bioavailability so there is a need for specific formulations to overcome this, thus enhancing the efficacy of these drugs and enabling the administration of lower dosages. This is particularly important for certain drug classes, especially cytotoxic agents which are used in cancer chemotherapy. In order for drug molecules to be administered effectively intravenously they need to be readily soluble in aqueous media. This is often problematic and complex systems of excipients are used to aid such solubility. However, many conventional excipients experience disadvantages such as instability upon dilution, viscosity implications and adverse side effects. As such novel formulation technologies are being introduced to overcome such hurdles and render drug compounds useable which would have otherwise been redundant. Amongst these technologies emerging as suitable vehicles for drug delivery are calix[n]arenes and calix.[4]resorcinarenes.

Calix[n]arenes and the closely related calix.[4]resorcinarenes area group of cyclic oligomers with characteristic structures prepared easily from the reaction of a phenolic substrate with an aldehyde, typically under acidic conditions. The synthesis, properties and potential of calix[n]arenes and calix.[4]resorcinarenes has been described.[1-3] Calix[n] arenes and calix.[4]resorcinarenes have found use in supramolecular chemistry, catalysis and separation science but they have attracted much interest for their potential use in drug design and delivery.[4-10] The compounds consist of substituted aromatic rings joined together by a bridging atom, normally the carbon within a methylene group, to form a cyclic structure typically represented as a truncated cone with an upper and lower rim (Figure 1). Substituents on these peripheral rims confer specific chemical, structural and physical properties on the molecules. Closely related series of compounds, heterocalix[n] arenes in which the phenolic residues are bridged by sulfur atoms and calix.[4]pyrroles, for example, have also been studied but not to the same extent as the parent compounds. This review will focus on the use of calix[n]arenes and calix.[4]resorcinarenes bearing functionalities on the upper and lower rims in facilitating the solubilization of drug molecules in aqueous media.
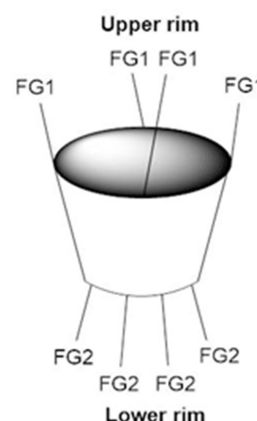

Figure 1 Representation of the idealized cone-like calix[n]arenes and calix[4] resorcinarenes.

Drug solubilization and delivery using calix[n]arene aggregates or calix[n]arenes that have been assembled into or form part of larger supramolecular structures has been reported.[11-15] For example, sulfonatocalix[n]arenes have been incorporated into larger architectures in which the hydrophobic drug molecule becomes encapsulated within a supramolecular assembly; the capsule walls of these assemblies contains the calix[n]arene.[16,17] Release of the drug molecule contained within such a complex may be triggered by an external stimulus, facilitating site-specific delivery. Such supramolecular chemistry is out with the scope of this review. The use of calix[n]arenes and calix.[4]resorcinarenes as drug delivery systems is still a relatively novel concept and as such, the number of reported studies are much fewer compared with other technologies such as cyclodextrins. However, these structures do offer a number of advantages including their ease of synthesis and modification and low toxicity. There is also the opportunity to develop formulations which enhance the site-specific delivery of drug molecules using novel formulation strategies and the development of image guided theranostics is a progression of this, combining imaging capability with site specific drug delivery. The main disadvantage of these systems is their tendency to be non-universal solubilizers since solubilization is dependent on molecular size of drug or complexation ability. Additionally, it is possible for aggregation to occur during long term storage which would hinder drug incorporation.

Calix[n]arene Structure

The most familiar and widely studied calix[n]arenes are the calix.⁴arenes, molecules which consist of four phenolic residues bridged by methylene groups. Besides the familiar cone conformation which presents a bowl-like cavity, calix[4]arenes can exist in several other conformations (Figure 2). Conceptually the bowl-shaped cone attracts the most attention in host-guest chemistry due to the obvious presence of an interior cavity. Many other studies of significance employ substituted calix.⁶arenes and calix.⁸arenes, which consist of six or eight phenolic residues joined through methylene bridges, respectively (Figure 3). Of course, as the number of phenolic residues within the calix[n]arene core structure increases so does the number of possible conformations. The greater number of rotatable bonds in these larger oligomers can present a challenge: for example, there are four possible conformations which can be adopted by calix.⁴arenes but this increases to sixteen for calix.⁸arenes, each conformation having different properties and, hence, potential for host-guest complex formation .[18] Most studies into calix[n]arene facilitated drug solubilization have focused upon the synthesis of novel calix[n]arene derivatives bearing, for example, ionizable groups or rich functionality on either or both the upper and lower rims. Such calix[n]arenes are often amphiphilic and may self-assemble into larger networks in an aqueous environment, sometimes an advantage for solubilization of small molecules.[19] Calix[n]arenes and calix.⁴resorcinarenes with more complex functionalities that also have biological activity and potential for solubilization have been reported, glycosylated calix[n]arenes and other multivalent calix[n]arenes for example.[20-23]
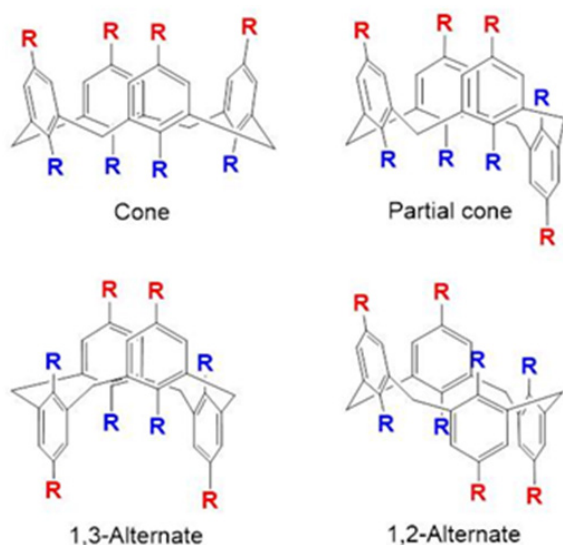

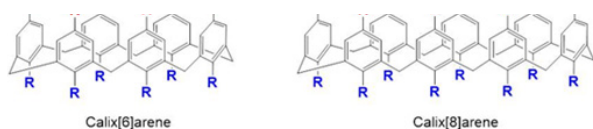**Figure 2** The four possible conformations of a calix.⁴arene.

Figure 3 The structures of a calix.⁶arene and a calix.⁸arene.

Calix.⁴resorcinarenes are a related class of cyclic tetramers prepared by reacting resorcinol with an aldehyde to give a cone-like structure (Figure 4).[24] The key features of this class of compounds is that unlike the calix[n]arenes, which are prepared from the reaction of a phenol with methanal to form the methylene bridges, calix.⁴resorcinarenes

can be prepared from the reaction of resorcinol with quite complex aldehyde precursors, usually in the presence of a suitable acid catalyst. For example, a glycosylated calix.⁴resorcinarene was readily prepared from the condensation of resorcinol with a glycosylated benzaldehyde (Figure 5).[25] The calix.⁴resorcinarenes are often represented as a truncated cone functionalized on the upper and lower rims. However, a number of well-characterized conformations of calix.⁴resorcinarenes may be isolated and the distribution of these conformations depends upon the starting materials in addition to the reaction conditions used.[26,27] It is possible to lock the calix.⁴resorcinarene into a cone-like structure by adding additional methylene bridges between the phenolic oxygen atoms on adjacent aromatic rings to form a generic structure colloquially known as a cavitand (Figure 6). This obviously removes some opportunities to functionalize the upper rim of the molecule but standard aromatic chemistry can be used to add additional functional groups and the lower rim can be decorated with diverse functionalities also. The chemistry and uses of calix.⁴resorcinarenes and cavitands has been described: cavitands and analogues form the basic structural unit of a widely studied series of supramolecular assemblies which have been used as hosts for small molecular species, molecular containers (carcerands) and catalysts.[28-31]
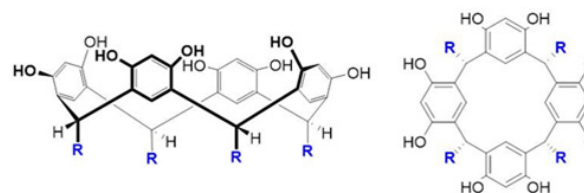

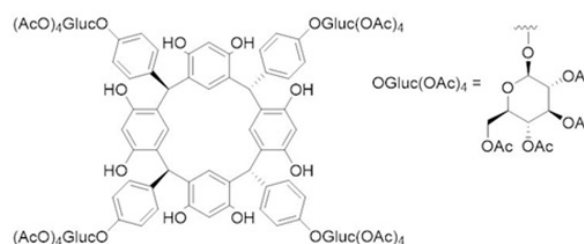**Figure 4** The structure of a calix.⁴resorcinarenes.

Figure 5 A tetraglycosylated calix.⁴resorcinarenes.

Figure 6 A simple cavitand.

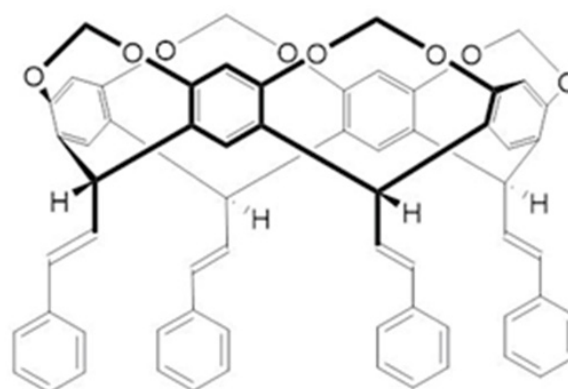Unfunctionalized calix[n]arene and calix.⁴resorcinarene molecules are typically hydrophobic in nature and insoluble in aqueous media. They must be functionalized with suitable groups in order to make them soluble and relevant for studies in drug solubilization. Shinkai et al. first reported the synthesis of water-soluble calix[n]arenes bearing sulfonate functional groups on the upper rim and alkyloxy

groups on the lower rim.[32-35] The interior cavity of calix[n]arenes and calix.[4]resorcinarenes in the cone conformation is typically hydrophobic and this can be exploited to form reversible host-guest complexes with small organic molecules *via* non-covalent interactions. In studies such as these the calix[n]arenes are often referred to colloquially as 'nano-baskets', indicating their proposed use. Many early studies into complex formation with calix[n]arenes have been undertaken in non-aqueous environments. Once in an aqueous environment water-soluble calix[n]arenes can, in some cases, enhance the solubility of hydrophobic drugs *via* a non-covalent hydrophobic interaction within the core of the calix[n]arene. Studies in aqueous environments in which there is an abundance of water molecules capable of forming hydrogen bond networks with polar functional groups present on the calix[n]arene have shown that the solubilization of specific drugs with particular structural features depends not only upon this hydrophobic interaction but also the functional groups on the upper and lower rims and the size of the calix[n]arene, whether it is a calix.[4]arene or calix.[6]arene for example. Larger molecules or those with specific functional groups, for example groups which can form hydrogen bonds, may actually form complexes with the functional groups on the upper or lower rims of the calix[n]arene rather than enter the cavity at all. Often, though, the principal consideration to be overcome is that in order to increase the binding capacity for hydrophobic molecules within the calix[n]arene the size of the cavity must be appropriate. This should then allow complexation with larger, more sophisticated drug molecules. Effectively, the hydrophobic cavity must be sufficiently deep or wide, or in a specific conformation. However, this is not the sole factor to consider and the majority of examples of calix[n]arenes which have demonstrated enhanced drug solubilization potential have ionisable substituents on the upper rim and, perhaps, the lower rim also. In some studies the solubilizing potential of calix[n]arenesis compared directly with that of cyclodextrin analogues.

It should be noted here that derivatization of calix[n]arenes by changing the functionality on the lower rim, especially by attaching pendant groups or the joining of two calix[n]arene units together, and their use in delivery of molecules of pharmaceutical relevance has been reported.[36] Such lower rim-functionalized molecules can form complexes with other species, with metal ions in the development of sensors for example, but have not received the same attention for drug solubilization.

Biocompatibility of Calix[n]arenes

Biological studies of the toxicity of calix[n]arenes investigated for clinical use have been reported alongside studies into drug solubilization and other applications.[37,38] These studies have shown that the calix[n]arenes are biocompatible with negligible toxicity *in vivo*. This is obviously critical if they are to be clinically useful in pharmaceutical formulations to enhance drug solubilization and facilitate delivery. A fluorescent probe derived from an aminocalix.[4]arene was shown to be no more toxic towards Chinese hamster ovary cells (CHO) and human promyelocytic leukemia (HL-60) cells than PBS buffer over a range of concentrations.[39] Para-sulfonatocalix.[4]arene-was screened for cytotoxicity against human ovarian carcinoma cell line A2780 and the corresponding cisplatin-resistant daughter line A2780cis. Results from the MTT test indicate that the calix.[4]arene is not cytotoxic.[40]

Para-Sulfonatocalix.[4]arene and substituted analogues do not give rise to haemolysis at concentrations up to 200 mM. Increased haemolysis is observed for the corresponding *para*-sulfonatocalix.[6]arene and *para*-sulfonatocalix[8]arene at the same concentration but this is much reduced for all sulfonated calixarenes at lower concentrations.[41] No haemolytic effects were observed for solid lipid nanoparticles derived from a series of amphiphilic calixarenes.[42]

The three *para*-sulfonatocalix[n]arenes showed no activation of neutrophils, even at relatively high concentrations, indicating that they do not illicit an immune response.[43]

In contrast to the minimal observed toxicity of calix[n]arenes with potential use for drug solubilization and delivery, it should also be noted here that calix[n]arenes have been developed as molecules with clinically relevant biological activity in their own right. Functionalized calix[n]arenes have been demonstrated to have antibacterial, antifungal, antiviral and anticancer activity.[37,38] They have also been used in enzyme inhibition and gene transfection studies.[44] Calix[n]arenes have also been used as a non-therapeutic residue in prodrug assemblies.[45] The use of calix[n]arenes as pharmaceutical agents in their own right is not detailed within this review but such compounds do provide opportunities for dual use.

Calix[n]arenes for drug solubilization

Within the area of drug solubilization using calix[n]arenes, it is the anionic calix[n]arenes which dominate reported studies. Such calix[n]arenes have been demonstrated to form host-guest complexes with amino acids and other biomolecules and knowledge gained from these investigations informs the pharmaceutical applications.[46-49] Sulfonated calix[n]arenes are attractive for applications in drug delivery because they are highly soluble in water and readily form host-guest complexes with hydrophobic molecules in aqueous media. The sulfonate groups on the upper rim of sulfonatocalix[n]arenes are completely ionized at pH 0.4 but most studies are conducted at pH 7.4 with few examining drug association at pH 2.0. In many cases the sulfonate groups on the upper rim play a complementary role and aid in the formation of complexes by combining ionic interactions and hydrogen bonding with other non-covalent interactions within the hydrophobic cavity. Interestingly, it has been reported that the hydrophobic cavity within *para*-sulfonatocalix.[4]arenes is not sufficiently large to accommodate small, substituted benzene derivatives. It is not surprising, therefore, that *para*-sulfonatocalix.[6]arenes and *para*-sulfonatocalix.[8]arenes have dominated drug solubility studies.

Sulfonatocalix[n]arenes for drug solubilization

Para-Sulfonatocalix.[4]arene, *para*-sulfonatocalix.[6]arene and *para*-sulfonatocalix.[8]arene (Figure 7) were investigated for their potential to form complexes with testosterone in aqueous media. Predictably, *para*-sulfonatocalix.[4]arene formed a weak complex and measurements indicated that the steroid had not entered the hydrophobic cavity. The solubility of testosterone was enhanced by 1:1 complex formation with *para*-sulfonatocalix.[6]arene and *para*-sulfonatocalix.[8]arene, studied across a range of pH; it was noted here that the conformation of a *para*-sulfonatocalix[n]arene in solution may affect the stability of any complex formed. In fact, the solubility enhancement exceeded that which is observed when testosterone is complexed with β-cyclodextrin, demonstrating at this stage the great potential of sulfonatocalix[n]arenes.[50,51]
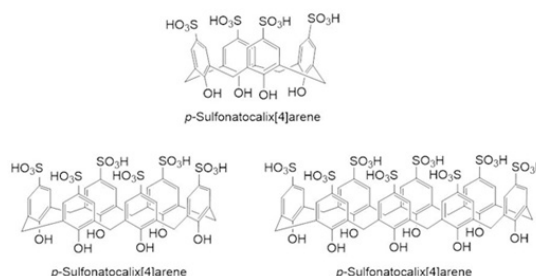

Figure 7 Para-Sulfonatocalix[n]arenes most commonly used in solubilization studies.

Sulfonatocalix[n]arenes of various sizes have thus been shown to form simple host-guest complexes with drug substances in which the drug molecule is partially inserted within the hydrophobic cavity of the calix[n]arene. Studies with the sodium salt of *para*-sulfonatocalix.[4]arene revealed that it was capable of forming a complex with topotecan, a topoisomerase I inhibitor used in the treatment of a number of different cancer types.[52] The hydrochloride salt of topotecan is soluble in aqueous media but the non-protonated form is only sparingly so, therefore careful formulation is required in order for it to be clinically appropriate. A strong stoichiometric complex was formed between topotecan and *para*-sulfonatocalix.[4]arene. Nuclear magnetic resonance (NMR) spectroscopy was used to determine the structure of the complex formed and the various non-covalent interactions which were involved, in particular. It was shown that the relatively hydrophobic quinolone-containing moiety of the complexed topotecan molecule is held within the hydrophobic cavity of the calix[n]arene whilst the more hydrophilic hydroxylated lactone portion resides outside of the cavity. Solubility of the complexed topotecan was five-fold greater than topotecan alone .[52]

Carvediol, a non-selective β-antagonist used in the treatment of hypertension is freely soluble in dimethylsulfoxide but practically insoluble in water, hampering administration. The drug molecule forms a 1:2 complex with *para*-sulfonatocalix.[4]arene and a 1:1 complex with the corresponding *para*-sulfonatocalix.[6]arene, both of which were markedly more soluble than the free drug. Additionally, there was no increase in the toxicity observed for the free drug when compared to each of the complexes in *in vivo* studies.[53] This exciting study highlights the potential of these systems to act as drug solubilizers without increasing the event of any adverse side effects.

A derivative of *para*-sulfonatocalix.[4]arene bearing tetrabutyloxy groups in place of the hydroxyl groups on the lower rim was shown to form a stoichiometric complex with ascorbic acid in water.[54] Interestingly the association constant, determined by fluorescence spectroscopy, increased dramatically as the temperature of the solution increased, indicating that entropy plays a significant role in determining the degree of complexation. NMR studies demonstrated that the ascorbic acid molecule was complexed such that the hydroxylated chain was embedded within the hydrophobic cavity, leaving the unsaturated lactone moiety projected out of the cavity facilitating the formation of a hydrogen-bonded network with the sulfonate functional groups .[54]

Para-Sulfonatocalix.[6]arene was shown to form complexes with the local anaesthetics tetracaine and proparacaine in their protonated forms, which would be present *in vivo* at physiological pH.[55,56] para-Sulfonatocalix.[6]arene formed a strong, stoichiometric host-guest complex with each molecule which was confirmed by NMR and other spectroscopic studies. The association between *para*-sulfonatocalix.[6]arene and the non-protonated proparacaine was demonstrated to be considerably weaker. Indeed, studies revealed that the ionized amino groups are held closely to the calixarene cavity, highlighting the importance of ionic interactions in complex formation with calix[n]arenes in addition to any considerations of the hydrophobic effect .[55,56]

Para-Sulfonatocalix.[4]arene and *para*-sulfonatocalix.[6]arene were employed in investigations into the solubilization of the hydrophobic anticonvulsant drug carbamazepine.[57] The drug suffers from poor bioavailability and is thus an excellent investigational tool to determine if increased solubility by complex formation may enhance the clinical utility of a drug molecule. It was shown that carbamazepine forms stable complexes with both calix[n]arenes, with a 1:1

stoichiometry for the complex with *para*-sulfonatocalix.[6]arene and a 2:1 stoichiometry for the complex with *para*-sulfonatocalix.[4]arene. Dissolution studies confirmed that the differing sizes and, hence, cavity volumes of the calix[n]arenes used influenced the increased solubility of carbamazepine. Importantly the dissolution rates of the carbamazepine complexes were increased significantly as compared to the drug alone .[57] These results indicate that the novel formulations were more effective and showed great potential as drug carriers for carbamazepine.

The sodium salts of *para*-sulfonatocalix.[4]arene and *para*-sulfonatocalix.[6]arene were investigated for their ability to form a complex with the tuberculostatic drug isoniazid with the goal of developing a system for protecting the drug from the biological environment before it reached the site of action.[58] Analysis of the stoichiometric complexes formed between the sulfonated calixarenes indicated that the isoniazid molecule is held with the planar pyridine residue occupying the hydrophobic cavity within the calix whilst the hydrazine residue interacted with the sulfonate groups on the upper rim. The activity of each of the isoniazid: calixarene complexes against *Mycobacterium tuberculosis* was investigated and determined to be close to the activity of isoniazid alone.[58] These studies highlight the potential of these systems in the protection of drug molecules in their *in vivo* journey before reaching their desired site of action.

Para-sulfonatocalix[8]arene was investigated as a solubilizing agent for fluroquinolone antibiotics, more specifically norfloxacin.[59] As would be expected from its structure the solubility of norfloxacin in aqueous media is pH-dependent and it is least soluble at plasma pH of 7.4. Experiments conducted over a range of pH and in the presence of various co-solvents and surfactant demonstrated that a stoichiometric complex is formed between norfloxacin and *para*-sulfonatocalix.[8]arene with association predominantly governed by electrostatic and hydrogen bonding interactions rather than any hydrophobic effect. Interestingly the addition of bovine serum albumin to a solution containing the complex caused the norfloxacin to be released and associate with the serum protein, thus demonstrating the potential of calixarenes for the controlled release of drug molecules.[59]

Para-Sulfonatocalix.[4]arene, *para*-sulfonatocalix.[6]arene and *para*-sulfonatocalix.[8]arene, each with various cavity volumes dependent upon confirmation, have been investigated for their ability to solubilize a range of drug molecules with widely differing structural features and, thus, requirements for complex formation. The drug molecules used in three linked studies suffered from extremely poor solubility in water, ranging from 38 μgmL^{-1} for the diuretic furosemide, 5μgmL^{-1} for calcium channel blocker nifedipine and 230 $ngmL^{-1}$ for the anthelmintic niclosamide, which is detrimental to their bioavailability. For furosemide the solubilizing effects of each *para*-sulfonatocalix[n]arene was studied across a pH range designed to mimic the acidic gastric environment. Each of the *para*-sulfonatocalix[n]arenes studied formed a stable 1:1 complex with furosemide, with the molecule occupying the central cavity. *Para*-Sulfonatocalix.[6]arene increased the solubility of furosemide the greatest, followed by *para*-sulfonatocalix[8]arene and *para*-sulfonatocalix.[4]arene. The solubility of niclosamide was increased by complex formation with *para*-sulfonatocalix.[6]arene and *para*-sulfonatocalix.[4]arene but the experimental data indicated that the complexes with each of the calix[n]arenes investigated became insoluble at higher concentrations. The solubility of nifedipine was increased when complexed with *para*-sulfonatocalix.[8]arene and *para*-sulfonatocalix.[4]arene whereas it was decreased when challenged with *para*-sulfonatocalix.[6]arene. In each case solubilization of the drugs by the sulfonatedcalix[n]arenes investigated reflected a tangible dependence upon a number of factors, including calix[n]arene cavity

size, conformations of both the drug molecule and the calix[n]arene across a range of pH and concentration of the calix[n]arene .[60-62]

Phosphonatocalix[n]arenes for drug solubilization

The fundamental properties and chemistry of calix[n]arenes functionalized with phosphonate groups has been described.[63] They have been demonstrated to form complexes with small molecules due to non-covalent interactions, specifically those which exploit the phosphonate moieties. The sodium salts of para-phosphonatocali.[4arene, para-phosphonatocalix[6]arene, para-phosphonatocalix.8arene and a partially phosphorylated calix.4arene bearing two tert-butyl groups (Figure 8) were investigated for their ability to also solubilize furosemide, nifedipine and niclosamide. Analyses indicated that each of the phosphonatocalix[n]arenes in this series formed 1:1 complexes with the drugs investigated. The aqueous solubility of both furosemide and nifedipine was increased greatly by complexation with the partially phosphorylated calix.4arene; in the case of furosemide the phenyl residue again occupied the central cavity. Niclosamide was solubilized by complex formation with para-phosphonatocalix.4arene and para-phosphonatocalix.6arene with experimental data again indicating that the substituted aryl residue becomes embedded within the calixarene cavity; this is particularly interesting because the polar nitro group is also taken up by the cavity .[64,65]
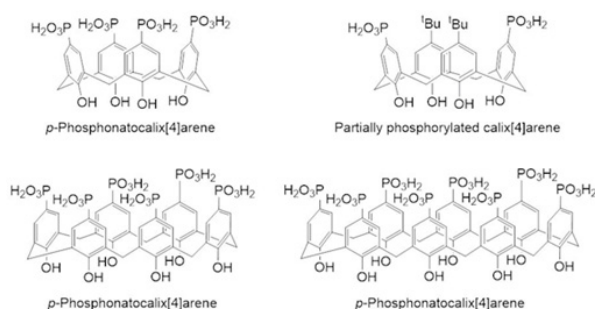

Figure 8 Para-Phosphonato calix[n]arenes used in solubilization studies.

Aminocalix[n]arenes for drug solubilization

The synthesis and properties of diverse series of calix[n]arenes that bear amino- functional groups and other basic residues has been studied .[66] This includes calix[n]arenes bearing basic functional groups on both upper- and lower-rims. However, their potential for drug solubilization has not been explored as widely as the sulfonated and phosphonated calix[n]arenes, for example. As mentioned above aminocalix[n]arenes typically have other inherent pharmacological properties which makes them attractive for further studies in nanomedicine. The key differentiator is that the aminocalix[n]arenes may be protonated to present positive charge to interacting drug molecules. Also, the hydrophilicity and, hence solubilizing potential, of the amino-substituted calix[n]arenes depends upon the interplay between several factors including: whether the amino substituent is bonded directly to the calixarene annulus, the accessibility of the charged moiety to water molecules and the aggregation behavior of amphiphilic calix[n]arenes. As with the sulfonated and phosphonated calix[n]arenes the pH of the aqueous media also plays a key role in determining solubility of aminocalix[n]arenes. For example, at neutral pH calix[n]arenes bearing both amino- and phenolic hydroxyl groups exist in the zwitter ionic form and become appreciably less soluble as pH increases.

The potential of an aminocalix.4arene bearing tetra-alkyl ammonium residues on the upper rim and propyloxy groups on the lower rim was compared to that of β-cyclodextrin with respect to the solubilization of a series of drug molecules at pH 7.4. The aminocalix.4arene was notably better in facilitating the solubilization of lidocaine, paracetamol, ketoprofen and hydrophobic steroids, with 17β-estradiol being the most affected. However, observations suggested that aggregation of the aminocalix.4arene may be influential and the formation of stoichiometric complexes should not be assumed .[67,68]

A natural extension to the work described above is the study of calix[n]arenes which bear charged residues on both the upper and lower rims. Such amphoteric calix[n]arenes have potential for the retention and release of a complexed drug molecule by varying the pH of the aqueous environment enabling site-specific delivery, for example. A multi functionalised calix.8arene bearing anionic sulfonate residues on the upper rim and cationic tetra-alkyl ammonium groups on the lower rim self-condenses as expected through ion-ion interactions to form particulate species. However, the broad spectrum antibiotic ciprofloxacin can be accommodated within the condensed material, partially occupying the hydrophobic core of the calix.8arene and forming hydrogen bonds with groups on the upper rim. Drug release from the complex was extremely pH-dependent; little release of ciprofloxacin was observed at pH 7.4 but this increased greatly as the pH was varied either side of physiological pH. This sort of complex formation sits at the interface between supramolecular chemistry and the formation of 1:1 host-guest complexes with simple calixarenes bearing either anionic or cationic groups.[69]

Sulfonated resorcinarenes for drug delivery

The potential of calix[n]arenes in drug solubilization has been demonstrated, particularly the *para*-sulfonatocalix[n]arenes. However, use of the corresponding calix.4resorcinarene analogues has not been studied so widely despite calix.4resorcinarenes being readily prepared and modified and also the focus of many studies in supramolecular chemistry. The solubility of the immunosuppressant mycophenolate mofetil was enhanced by host-guest complex formation with the readily available *para*-sulfonatocalix.4resorcinarene (Figure 9): mycophenolate mofetil is practically insoluble in water but in the presence of *para*-sulfonatocalix.4resorcinarene a 1:2 complex was formed which was markedly more soluble. In vivo studies also indicated that the toxicity of the drug was much reduced by complex formation .[70] In a more recent report the *para*-sulfonatocalix.4resorcinarene was demonstrated to form a 1:1 complex with the common potent anticonvulsant drug lamotrigine; this was characterized using various analytical techniques and supported by molecular modelling. The complex was stabilized by hydrogen bonding and π-π interactions. The complex was also reported to display much reduced toxicity in animal studies when compared to the free drug .[71]

Conclusion

In conclusion, water-soluble calix[n]arenes and calix.4resorcinarenes have been demonstrated to improve the solubility of a variety of drug molecules in aqueous media. The reported low toxicity of the calix[n]arenes makes them attractive in comparison to other common solubilizing agents. Complex formation is not simply determined by the chemical and physical properties of the host calix[n]arene and the guest drug molecule. The various non-covalent interactions that mediate complex formation are influenced greatly by the aqueous environment, especially pH, and this may limit the potential of certain calixarenes due to the formation of aggregates and other architectures in solution. There is thus a requirement to further study and develop the range of calix[n]arenes available for drug solubilization.

Future Outlook

Calix[n]arenes and calix.⁴resorcinarenes are increasingly attracting attention in the field of nanoscience and, hence, nanomedicine. Though the number of reports of the use of derivatized calix[n]arenes and calix.⁴resorcinarenes in various situations continues to increase the full potential of simple calix[n]arenes and calix.⁴resorcinarenes for drug solubilization has not been realized. Supramolecular assemblies incorporating calix[n]arenes are attractive to study but it may be argued that the clinical application of these materials may be limited by their complexity. Simple calix[n]arenes with equal or superior solubilizing potential as compared to cyclodextrins are probably more likely to have wide clinical application. As has been highlighted in this review studies have indicated that some calix[n]arenes do exceed the potential of cyclodextrins and so further investigation is certainly justified.

Acknowledgments

None.

Conflicts of interest

None.

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