# COMPLEXATION OF PHOSPHORYLATED CALIXARENES WITH URACILS. STABILITY CONSTANTS AND DFT STUDY OF THE COMPLEXES

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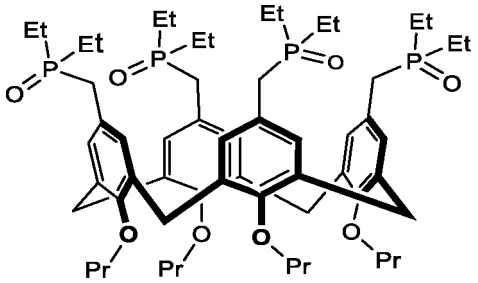
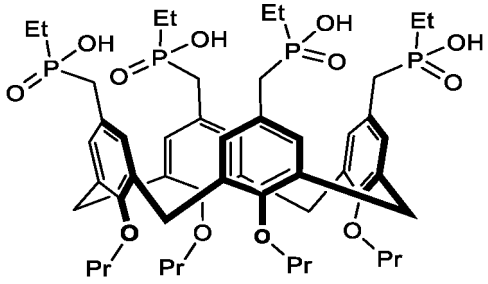
Nano-sized cup-shaped calixarenes [1] and their self-assembled supramolecular aggregates, which are able to form host-guest supramolecular complexes with bioactive substances, are promising structures for creating drug delivery nanovectors [2].

Prospective systems for drug delivery are calixarenes, functionalized on the upper or lower rim of the macrocycle by biophorichydrophilic organophosphorus groups. Phosphorus is a biologically friendly element and a number of medicines have been created on the basis of natural and synthetic organophosphorus compounds [3]. An advantage of calixarenes in the context of drug design and drug delivery is low cytotoxicity [4] and absence of immune reactions [5].

The nano-sized water-soluble cone-shaped tetrapropoxycalix[4]arenes modified on the upper rim with hydrophilic phosphine oxide groups **CPO** or phosphinic acid groups **CPA** were synthesized and their complexation with eleven uracils (2,4-dioxopyrimidines), including APIs of 5-Fluorouracil and 5-Methyluracil drugs, were investigated by HPLC and DFT calculation methods in the context of drug delivery.



**CPO**



**CPA**

Water-soluble calixarenes are usually prepared by introducing various anionic, cationic, or neutral hydrophilic substituents on the upper or lower rim of the macrocycle [6]. Four polar diethylphosphine oxide or ethylphosphinic acid groups provide high solubility of **CPO** and **CPA** calixarenes in water (> 100 mg/g).

Calixarene **CPO** was synthesized in one step by the Arbuzov reaction of chlorometylpropoxycalix[4]arene with i-PrOPEt$_2$ with 95% yield. Calixarene **CPA** was synthesized in two steps. First, isopropyl ester of calixarene ethylphosphinic acid was prepared by the Arbuzov reaction of chlorometylpropoxycalix[4]arene with (i-PrO)$_2$PEt. The next step includes interaction with trimethylbromosilane to replaced isopropyl substituents with trimethylsilyl groups by the McKenna reaction. The treatment of the received calixarenewith wet methanol caused the P-O-Si bond to break and gave calixarene phosphonic acid **CPA** with 88% yield.

The complex formation of calixarenes **CPO** and **CPA** with uracils was investigated by the HPLC method [7]. The most efficient binding of calixarene **CPO** is observed for 5-nitrouracil ($K_A$ = 18 482$M^{-1}$), the least effective is for 5-aminouracil ($K_A$ = 4484 $M^{-1}$). The most effective binding of calixarene **CPA** is observed with 5-methyluracil ($K_A$ = 18104 $M^{-1}$), and the least effective is with 1,3-dimethyluracil ($K_A$ = 1961 $M^{-1}$). The influence of hydrophobic, π,π- and H,π-interactions on the stability of the calixarene-uracil adduct is discussed.

Structures of calixarenes and their nanoadducts were optimized using a novel and efficient Grimme's RI-B97-3c DFT functional [8] that reproduces well electron dispersion effects and, on the other hand, is suitable for treating large molecules. Conformational flexibility of the structures requires analysis of a large number of conformers in order to find out and locate the one with the

lowest total energy. One of the criteria for the search of the conformation is the number of hydrogen bonds, which obviously play an important role in the formation and stabilization of the calixarene-uracilcomplexes. Another binding properties of calixarenes requiring our attention are hydrophobic, π,π- and H,π-interactions with a guest molecule. In order to decrease the conformational diversity in the model calixarene structures that mimic the experimentally studied of **CPO** and **CPA** calixarene ligands, ethyl groups were replaced with methyl substituents. It was found in themodel host-guest complexes **A,B** the uracil molecules coordinate via hydrogen bonding with the phosphorus-containing groups on the upper rim of the calixarene ligands.

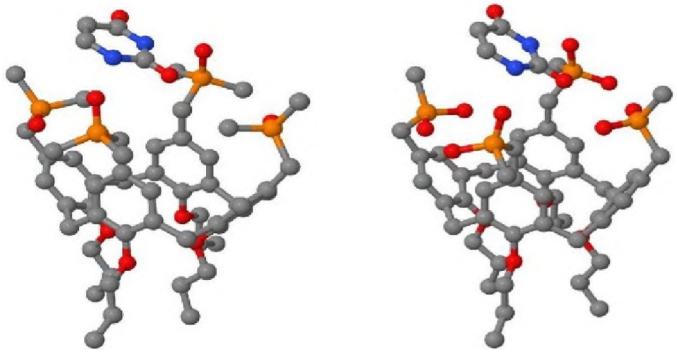



**Fig. 1** Model structures of the complexes**CPO***Uracil (**A**) and **CPA***Uracil (**B**). Hydrogen atoms are omitted for clarity

The obtained results allow proposing the water-soluble calixarenes **CPO** and **CPA** as promising compounds in the development of nanovectors for drug delivery of bio-active uracil derivatives.

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