Impact of positive charge and ring-size on interactions of calixarenes with DNA, RNA and nucleotides

Ivana Nikšić-Franjić[a,*], Aleksandar Višnjevac[a], Benoit Colasson[b], Olivia Reinaud[b], Ivo Piantanida[a]

a) Ruđer Bošković Institute, Bijenička cesta 54 10000, Zagreb, Croatia;

b) Université de Paris, Rue des Saints Pères 45 75006, Paris, France;

**iniksicf@irb.hr*

Calixarenes were traditionally studied as supramolecular receptors for various low molecular mass cationic or anionic species, but only marginally investigated for their biological effects or applications [1]. However, systematic study revealed that cationic calixarenes can be applied as innovative DNA-transfection agents [2]. We have developed three generations of calix[6]arene-based (funnel), as well as two generations of resorcinarene-based (bowl) supramolecular systems featuring two, three or four methylimidazole-containing coordination arms grafted at the large rim, suitable to bind to variety of nucleid acid sequences [3,4].

In this work we focused on calixarenes with short, triazole-attached positively charged substituents (**2** and **4**) and their neutral analogues (**1** and **3**, Fig. 1.). Their ability to recognize specific sequences of various DNA chains was studied by thermal denaturation experiments, fluorimetric titrations, circular dichroism experiments and molecular dynamics simulations. Comparison of neutral and cationic calix[6]arene and calix[4]arene derivatives revealed that only cationic analogues non-covalently bind to ds-DNA and ds-RNA, by insertion into DNA minor groove or RNA major groove. Also, cationic analogues revealed strong and highly selective charge-dependent stabilization of AT-DNA against thermal denaturation, both neutral and cationic calixarenes bind nucleoside monophosphates with similar efficiency, by forming tweezer-like supramolecular complexes, with nucleobases inserted between aromatic pendant arms grafted to calixarene rims. Such nucleotide-calixarene complexes were monitored by emission change of calixarene as a function of nucleobase insertion, at variance to DNA/RNA complexes in which calixarene is inserted into polynucleotide groove, which do not change calixarene emission – stressing importance of the ligand insertion within calix-basket for the fluorimetric sensing.

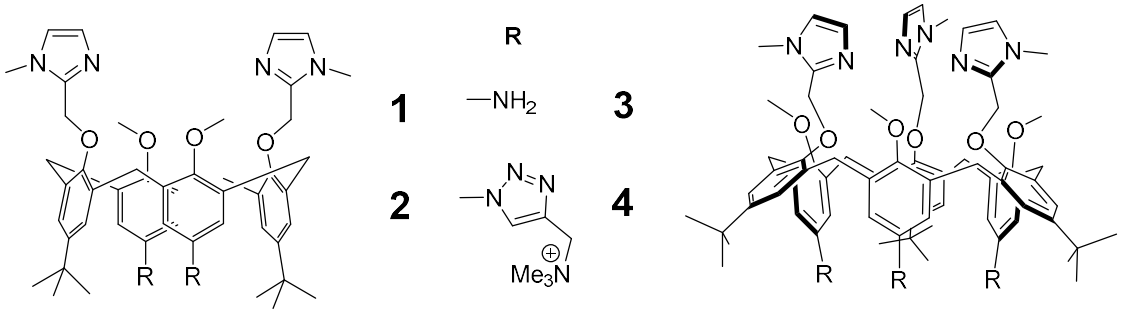

Figure 1. Molecular structures of studied cationic calixarenes **2** (as a chloride salt), **4** (as a nitrate salt) and their non-charged analogues **1** and **3**.

Thanks to Financial support from Croatian Science Foundation (IP-2020-02-3786 and IP-2018-01-5475).

[1] Baldini L.; Casnati A.; Sansone F., *Eur. J. Org. Chem.*, **2020**, *31*, 5056-5069.

[2] Bagnacani V.; Franceschi V.; Bassi M.; Lomazzi M.; Donofrio G.; Sansone F.; Casnati A.; Ungaro R., *Nat. Commun.*, **2013**, *4*, 1721-1727.

[3] Rebilly J.-N.; Colasson B.; Bistri O.; Over D.; Reinaud O., *Chem. Soc. Rev.*, **2015**, *44*, 467-489.

[4] Višnjevac A.; Gout J.; Ingert N.; Bistri O.; Reinaud O., *Org. Lett.* **2010**, *12*, 2044-2047.