

Conformational folding of alexidine and pentamidine molecules within the bowl-shaped cavity of p-sulfonatocalix[4]arene

K. Kravets¹, M. Kravets¹, O. Danylyuk¹

¹Institute of Physical Chemistry Polish Academy of Sciences, Kasprzaka 44/52, 01-224, Warsaw, Poland

kkravets@ichf.edu.pl

This study investigates the co-crystallization of p-sulfonatocalix[4]arene (C4S) with two medically relevant guest molecules: alexidine (ALEX) and pentamidine (PT). The complexes were characterized using single-crystal X-ray diffraction and NMR spectroscopy. These techniques provided deeper insight into how the molecules engage in host-guest interactions with a common macrocyclic host. They also uncovered the conformational and binding behavior of the guests within the corresponding supramolecular complexes [1].

X-ray diffraction analysis reveals that C4S induces *U-shaped* folding of both drug molecules by accommodating their flexible aliphatic linkers within its macrocyclic cavity. In the *C4S_ALEX* complex, the hexyl chain of alexidine is inserted into the macrocycle cavity and stabilized by hydrogen bonding and *C-H...π* interactions, Figure 1a. The *C4S_PT_H2O* complex contains two guest molecules: one pentamidine adopts a partially folded conformation within C4S cavity, stabilized by *C-H...π* interactions, while a second molecule remains outside the cavity, Figure 1b.

In both complexes, the cationic groups of the guest molecules positioned outside the host cavity participate in charge-assisted hydrogen bonding with the sulfonate oxygen atoms of adjacent calixarenes and water. The macrocyclic host adopts a pinched cone shape, allowing for complementary fitting despite the differences in the structure and conformation of the guest molecules.

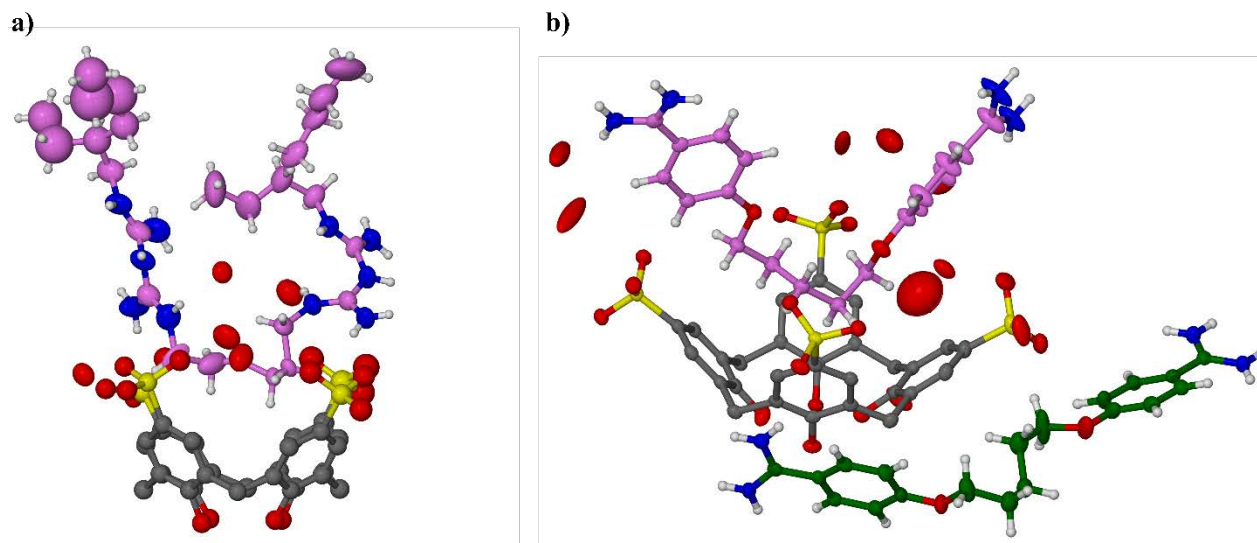


Figure 1. The asymmetric units of the (a) *C4S_ALEX* and (b) *C4S_PT_H2O* host-guest complexes. Atomic displacement parameters set at 50% probability.

[1] Kravets, K., Kravets, M., Sashuk, V., Perret, F., Maskani, W., Albertini, D., Lazar, A.-N., Zimnicka, M. M., Danylyuk, O. (2025). Alexidine and Pentamidine Fold Inside the Bowl-shaped Cavity of p-Sulfonato-calix[4]arene, *Chem. Eur. J.* **31**, e202404625.

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