Poster

Host-guest interactions guide pentamidine folding inside and outside the cavities of macrocyclic hosts

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Pentamidine is the FDA-approved anti-protozoal drug currently rediscovered as a membrane-targeting antibiotic sensitizer helping restore antibiotic activity against multidrug resistant bacteria pathogens [1]. Pentamidine belongs to the structural class of non-steroid small molecule sensitizers of C_{2h}-symmetric di-cationic structure provided by two amidinium end groups. The knowledge on the structural chemistry of the pentamidine and its complexes is limited. The search of CSD on the pentamidine structures gives only 2 hits on the diisethionate salt of pentamidine and several hits on the pentamidine host-guest complexes with carboxylated pillar[*n*]arenes recently reported by our group [2,3]. All reported up to now small-molecule crystal structures comprise pentamidine in the extended conformation. We have decided to target this cationic drug molecule using supramolecular host-guest and crystal engineering approach. The objective of this work was to study conformational and structural behaviour of highly flexible pentamidine molecule under macrocyclic confinement conditions mimicking biological confinement near the active sites of proteins and enzymes.

The simple bowl-shaped calix[4]arene framed with sulfonate groups at the upper rim effectively mediates U-shaped folding of pentamidine molecule, Fig. 1. The aqueous cocrystallization of C_4 symmetric bowl of calix[4]arene and C_{2h}-symmetric flexible guest results in the clamping down the central aliphatic chain of the pentamidine molecule by its inclusion and coiling inside the macrocyclic cavity. The amidinium cationic groups support complexation and assembly in terms of multiple charge-assisted hydrogen bonds with sulfonate groups on the adjacent macrocycles in the crystal structures. The cocrystallization of pentamidine with larger and more flexible calix[8]arene results in the host-guest mutual induced fit complexation. The calix[8]arene takes flattened *pseudo* pleated loop conformation with pentamidine guests bound in the grooves on the inside and outside surfaces of the macrocyclic host.

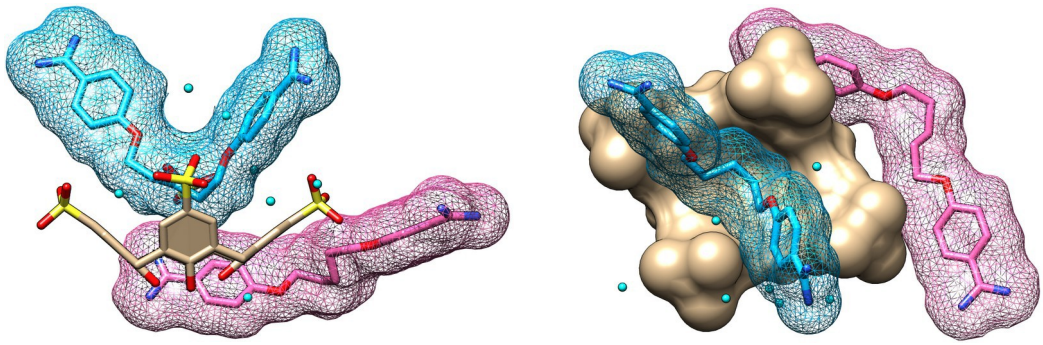

Figure 1. Crystal structure of the host-guest complex of *p*-sulfonato-calix[4]arene with pentamidine: side view and top view. Two crystallographically non-equivalent pentamidine molecules coloured in blue and pink. Water molecules in cyan.

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[2] Butkiewicz, H., Kosiorek, S., Sashuk, V., Zimnicka, M., Danylyuk, O. (2022). *Cryst. Growth Des*. **22**, 2854.

[3] Butkiewicz, H., Kosiorek, S., Sashuk, V., Zimnicka, M. M., Danylyuk, O. (2023). *Cryst. Growth Des*. **23**, 11.

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