

ANTI-FIBRILLOGENIC ACTIVITY OF THE PHTHALOCYANINE COMPLEXES:
ROLE OF THE OUT-OF-PLANE LIGANDS

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Non-controlled aggregation of proteins is connected to a large number of pathological disorders in humans such as neurodegenerative diseases and systemic amyloidosis. The accumulation of filamentous insoluble protein aggregates with the well-defined beta pleated structure (amyloid fibrils) in the intercellular space results in the dysfunction or death of the cell. Thus efficient agents able to redirect or suppress the protein fibril formation reaction are relevant in biomedical studies both for investigation of the protein aggregation processes and the development of therapeutic tools against the diseases connected with protein aggregation. Among the agents possessing anti-fibrillogenic properties the phthalocyanines - macrocyclic compounds with the planar heme-like molecules are known. Recently we have shown that phthalocyanine complexes having out-of-plane ligands and thus 3-D geometry of molecules are able to significantly affect on the pathway of fibril formation reaction [1].

In presented study we used the atomic force microscopy to investigate the products of insulin aggregation reaction in the presence of Zr and Hf phthalocyanine complexes containing out-of-plane ligands of different size and nature and this way to shed the light on the role of these ligands in anti-fibrillogenic activity of phthalocyanines.

Insulin itself forms mainly the elongated filamentous species - amyloid fibrils with diameter about 6 nm and length about 1,5-2,5 μm, both linear and branched species. The cord-like structures formed by twisted fibrils and their lateral aggregates with the height up to 15 nm are also observed. In the presence of Hf phthalocyanine containing the mid-size quinolinium styryl fragment as out-of-plane ligand (Fig.1) the number and diameter of formed fibrils is significantly reduced, only single filaments with diameter about 1-2 nm were observed in this case.

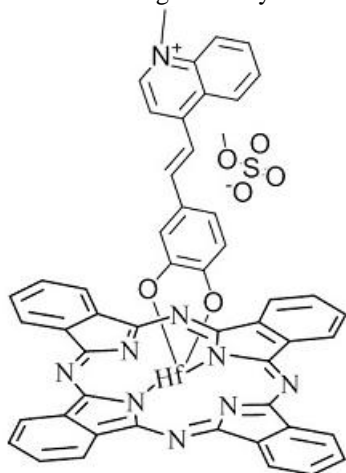


Fig.1. Structure of Hf phthalocyanine containing quinolinium styryl out-of-plane ligand.

The addition of Zr phthalocyanines with bulky dibenzoylmethane and lysine ligands to the insulin redirects the fibrillization reaction to the formation of spherical-shape oligomeric aggregates with the diameter up to 10 nm as dominant product of the reaction. The Hf phthalocyanine with small-size ligands - chlorine atoms (able to hydrolyze in aqueous media to hydroxy groups) induces the appearance of insignificant number of large size aggregates of no clear shape (diameter about 100 nm and higher), that are attributed to amorphous formations.

The diversity of the insulin aggregates caused by the presence of phthalocyanines with out-of-plane ligands of various nature and geometry shows that not only planar macroheterocyclic part of the molecule determines the protein-macrocyclic complexes binding. We could suppose that out-of-plane ligand is to the large extent responsible for the chose of the "binding site" by phthalocyanine molecule.

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