



5-Aminolevulinic acid and derivatives thereof
Properties, lipid permeability and enzymatic reactions

av

Edvin Erdtman

Akademisk avhandling

Avhandling för filosofie doktorsexamen i kemi/biofysikalisk kemi,
som enligt beslut av rektor kommer att försvaras offentligt
onsdagen den 28 april 2010 kl. 10.15,
Hörsal M, Örebro universitet

Opponent: Professor Tore Brinck
Fysikalisk kemi, Skolan för kemivetenskap,
Kungliga Tekniska Högskolan, Stockholm

Örebro universitet
Akademin för
Naturvetenskap och Teknik
701 82 ÖREBRO

Abstract

Edvin Erdtman (2010): 5-Aminolevulinic acid and derivatives thereof Properties, lipid permeability and enzymatic reactions. Örebro Studies in Life Science 6, 76 pp.

5-aminolevulinic acid (5-ALA) and derivatives thereof are widely used prodrugs in treatment of pre-malignant skin diseases of the cancer treatment method photodynamic therapy (PDT). The target molecule in 5-ALA-PDT is protoporphyrin IX (PpIX), which is synthesized endogenously from 5-ALA via the heme pathway in the cell. This thesis is focused on 5-ALA, which is studied in different perspectives and with a variety of computational methods. The structural and energetic properties of 5-ALA, its methyl-, ethyl- and hexyl esters, four different 5-ALA enols, and hydrated 5-ALA have been investigated using Quantum Mechanical (QM) first principles density functional theory (DFT) calculations. 5-ALA is found to be more stable than its isomers and the hydrolysis of the esters are more spontaneous for longer 5-ALA ester chains than shorter. The keto-enol tautomerization mechanism of 5-ALA has been studied, and a self-catalysis mechanism has been proposed to be the most probable. Molecular Dynamics (MD) simulations of a lipid bilayer have been performed to study the membrane permeability of 5-ALA and its esters. The methyl ester of 5-ALA was found to have the highest permeability constant ($P_{\text{Me-5-ALA}} = 52.8 \text{ cm/s}$). The mechanism of the two heme pathway enzymes; Porphobilinogen synthase (PBGs) and Uroporphyrinogen III decarboxylase (UROD), have been studied by DFT calculations and QM/MM methodology. The rate-limiting step is found to have a barrier of 19.4 kcal/mol for PBGS and 13.7 kcal/mol for the first decarboxylation step in UROD. Generally, the results are in good agreement with experimental results available to date.

Keywords: 5-Aminolevulinic acid, tautomerization, PDT, DFT, MM, QM/MM, Porphobilinogen synthase, Uroporphyrinogen III decarboxylase, membrane penetration, enzyme mechanism.